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Value of Bax and Bcl2 expression in peripheral blood mononuclear cells for clinical prognosis of patients with chronic heart failure

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Abstract

To investigate the expression of Bax and Bcl2 protein in peripheral blood mononuclear cells (PBMC) of patients with chronic heart failure (CHF), and to analyze their value for predicting major adverse cardiovascular event (MACE) in CHF patients. A total of 154 fasting venous blood samples from CHF patients were collected in our hospital from January 2017 to June 2019, and they were divided into 2 group according to whether MACE occurred during 3 years follow-up, MACE group and No-MACE group. Levels of Bax and Bcl2 protein expression in PBMC of CHF patients using enzyme-linked immunosorbent assay (ELISA), and then evaluated the predictive power of Bax and Bcl2 expression for MACE using logistic regression analysis and ROC curve. 62 (40.26%) of 154 CHF patients occurred MACE during follow-up, and there were significant differences in age, diabetes, LVEF, LDL-C and NYHA grade between MACE group and No-MACE group. Levels of Bax protein expression in PBMC of CHF patients in MACE group were significantly higher than those in No-MACE group, while levels of Bcl2 protein expression were significantly lower than those in No-MACE group, and Bax and Bcl2 protein levels increased and decreased with NYHA grades in MACE group and No-MACE group, respectively. Results of univariate and multivariate logistic regression analysis showed that Bax (OR, 1.026; 95% CI, 1.003–1.049; $P = .027$) and Bcl2 levels (OR, 0.952; 95% CI, 0.908–0.998; $P = .041$) were independent predictive factors for MACE in CHF patients. In addition, Bax and Bcl2 levels could be used to differentiate CHF patients at risk for MACE with an AUC of 0.744 (95% CI: 0.660–0.827) and an AUC of 0.743 (95% CI: 0.667–0.819), respectively. Levels of Bax and Bcl2 protein in PBMC could be used as independent predictive factors for MACE in CHF patients.

Abbreviations: CHF = chronic heart failure, DBP = initial diastolic blood pressure, ELISA = enzyme-linked immunosorbent assay, LVEF = left ventricular ejection fraction, MACE = major adverse cardiovascular event, PBMC = peripheral blood mononuclear cells, SBP = systolic blood pressure.

Keywords: Bax, Bcl2, chronic heart failure, peripheral blood mononuclear cells

1. Introduction

Heart failure is a group of complex clinical syndromes caused by initial myocardial damage caused by various reasons, resulting in abnormal cardiac structure or function, accompanied by ventricular filling or impaired ejection function, mainly manifested as dyspnea, fatigue, limited exercise tolerance and fluid retention.[1,2] Heart failure is the end stage of various heart diseases, which not only seriously affects the daily life of patients, but also has a high mortality and disability rate.[3,4] Chronic heart failure (CHF) refers to a persistent state of heart failure that can be stable, worsening, or decompensated, which can be divided into 3 levels with no clear temporal boundaries, namely cardiac remodeling, asymptomatic cardiac insufficiency, and clinical heart failure.[5] Importantly, stroke volume and cardiac output in patients with CHF is significantly decreased with increasing severity of heart failure, significantly increasing the risk of major adverse cardiovascular events (MACE).[6,7] Therefore, early diagnosis and therapeutic measures have important clinical significance for patients with CHF.

At present, although the pathogenesis of chronic heart failure has not been fully revealed, the mechanism of cardiomyocyte apoptosis is widely accepted to play an important role in the development of CHF.[8,9] Apoptosis plays an important role in a variety of physiological processes, including embryogenesis, maintenance of normal tissue homeostasis, and aging. Both human and animal models suggest that cardiomyocyte apoptosis is associated with heart failure, and apoptosis is involved in the progression from cardiac hypertrophy to heart failure.[10,11] Furthermore, previous studies have demonstrated

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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that cardiomyocyte apoptosis plays an important role in the development of LV dysfunction in HF with reduced ejection fraction.[12,13]

The B-cell lymphoma-2 (Bcl2) family is a family of proteins involved in apoptosis and anti-apoptosis, which are located in the mitochondrial membrane and function as promoters, regulators, and effectors of intrinsic apoptotic pathways.[14,15] Bcl2, an important member in the Bcl2 family, is an anti-apoptotic protein, while Bcl2-associated X protein (Bax) is a protein that promotes cell death and is a negative regulator of cell death.[16] Previous studies have shown that Bax/Bcl2-mediated cardiomyocyte apoptosis plays an important role in the development and progression of chronic heart failure.[17,18] Such as Chen C et al found that found that Paeonol alleviated the histopathological injury and suppressed the apoptosis in CHF-modeled rats, inhibited miR-21-5p expression, and upregulated SKP2 expression in vitro and in vivo, and miR-21-5p downregulated the expression of Bcl-2 and upregulated the expression of Bax.[19] However, the value of Bax and Bcl2 expression in peripheral blood mononuclear cells (PBMC) for clinical prognosis of patients with CHF is still unclear. In the present study, we designed to investigate the value of Bax and Bcl2 protein expression in PBMC for predicting MACE in CHF patients.

2. Patients and methods

2.1. Patients and ethics statement

From January 2017 to June 2019, there are 154 cases patients with CHF being prospectively recruited into the present study at Liangzhou Hospital of Wuwei City. These CHF patients must meet the following standards. Inclusion criteria: age ≥ 18 years old; according to "Chinese guidelines for the diagnosis and treatment of heart failure 2018,"[20] patients were diagnosed with chronic heart failure; disease causing chronic heart failure is clear; anti-heart failure treatment for not <1 month; informed about the content of this research and voluntarily participated in this research. Exclusion criteria: malignant disease, severe infectious disease, history of organ transplantation, acute decompensated heart failure or severe liver and kidney insufficiency; acute coronary events occurred within 1 month before enrollment, including unstable angina, acute ST-segment elevation myocardial infarction, acute non-ST-segment elevation myocardial infarction; cardiac insufficiency caused by other heart diseases, such as congenital heart disease, myocarditis, cor pulmonale and primary heart valve disease, etc; acute onset of heart failure 2 weeks before enrollment; failed to complete 3-year follow-up; severe non-cardiovascular and cerebrovascular diseases occurred during follow-up, such as malignant tumors, severe infections, severe damage to liver and kidney functions, and severe trauma diseases, etc. This study complies with the principles of the Declaration of Helsinki and was reviewed and approved by the Ethics Committee of Liangzhou Hospital of Wuwei City (Approval number LZH20200312001).

2.2. Data collection

We collected the clinical data of patients at admission, including age, gender, admission time, blood collection, initial systolic blood pressure (SBP), initial diastolic blood pressure (DBP), left ventricular ejection fraction (LVEF), medication history, medical history, hospitalization history, laboratory test data, comorbidities (hypertension) and living habit (smoking). The grade of cardiac function was assessed by the New York Heart Association (NYHA) in patients with CHF at admission. All patients were followed for 3 years and observed for the development of MACE, including cardiovascular-related death, cardiac arrest, cardiogenic shock, and complete heart block with severe haemodynamic impairment requiring pacing therapy.

2.3. Levels of Bax and Bcl2 protein assay

Peripheral blood samples were drawn from CHF patients at admission, followed by centrifugation (1000 × g, room temperature, 10 minutes) to separate blood cells and serum. We used density gradient centrifugation to analyze peripheral blood mononuclear cells (PBMC), and added cell lysate buffer (P0013C, Beyotime) after cell counts to release Bax and Bcl2 proteins. And then we used human Bcl2 associated X protein (Bax) ELISA Kit (EK12824, Signalway Antibody) to detect levels of Bax protein in lysis of PBMC, and used human B-Cell leukemia/lymphoma 2 (Bcl2) ELISA Kit (EK12835, Signalway Antibody) to detect levels of Bcl2 protein in lysis of PBMC.

2.4. Statistical analysis

Data in the present study were analyzed by SPSS 19.0 software (SPSS Inc., Chicago, USA). Qualitative data are presented as counts (%), and *P* values are calculated using chi-square or Fisher exact test as appropriate. Kolmogorov-Smirnov test was used to check whether quantitative data conformed to a normal distribution, data that conformed to a normal distribution were presented as (mean ± standard deviation), and unpaired Student *t* test was used to compare differences and calculate *P* values. Quantitative data that did not conform to a normal distribution are presented as the median (interquartile range), and Mann–Whitney *U* test was used to compare differences and calculate *P* values. Receiver operating characteristic (ROC) curves were constructed and the area under the curve (AUC) was calculated to assess the performance of Bax and Bcl2 levels in distinguishing between CHF patients with and without MACE at 3 years follow-up. $P < .05$ indicated significant difference.

3. Results

3.1. Baseline data of CHF patients

A total of 154 CHF patients were divided into 2 groups according to whether MACE occurred during follow-up period, namely, MACE group (n = 62, MACE occurred) and No-MACE (n = 92, MACE not occurred). We compared the baseline data between these 2 groups, and found that there were no significant differences between the 2 groups in baseline data ($P > .05$), including gender, BMI, smoking, hypertension, SBP, DBP, TC, TG, HDL-C and BUN, while there were significant differences in age, diabetes, LVEF, LDL-C and NYHA grade ($P < .05$) (Table 1).

3.2. Expression of Bax and Bcl2 in PBMC of patients with CHF

We detected the level of Bax and Bcl2 protein in PBMC lysis of patients with CHF. As showed in Figure 1, the expression of Bax in MACE group were significantly higher than those in No-MACE group ($P < .05$) (Fig. 1A), and Bax levels rise with NYHA grades in MACE group (Fig. 1B) and No-MACE group (Fig. 1C). Similarly, the expression of Bcl2 in MACE group were significantly lower than those in No-MACE group ($P < .05$) (Fig. 2A), and Bcl2 levels decrease with NYHA grades in MACE group (Fig. 2B) and No-MACE group (Fig. 2C).

3.3. Risk factors for MACE in CHF patients

Univariate and multivariate logistic regression analysis were used to analyze independent predictive factors for MACE in CHF patients, and results showed that age (OR, 1.571; 95%

Table 1

Baseline data of chronic heart failure patients in MACE and No-MACE group [mean ± sd/n (%)].

Index	MACE (n = 62)	No-MACE (n = 92)	t/χ^2	*P*
Age (yr)	67.29 ± 6.07	58.83 ± 6.62	8.041	<.001
Male	39 (62.90)	61 (66.30)	0.188	.664
BMI (kg/m^2)	24.34 ± 1.37	24.49 ± 1.33	0.686	.494
Smoking	37 (59.68)	53 (57.61)	0.065	.798
Hypertension	35 (56.45)	51 (55.43)	0.016	.916
Diabetes	37 (59.68)	58 (63.04)	5.005	.025
SBP (mm Hg)	121.95 ± 19.75	127.00 ± 18.37	1.623	.107
DBP (mm Hg)	85.53 ± 10.60	84.39 ± 11.21	0.633	.528
LVEF (%)	56.85 ± 7.34	39.49 ± 6.93	14.887	<.001
TC (mmol/L)	4.42 ± 1.31	4.40 ± 1.32	0.209	.834
TG (mmol/L)	1.53 ± 0.41	1.52 ± 0.58	1.279	.203
HDL-C (mmol/L)	1.26 ± 0.34	1.27 ± 0.37	0.307	.270
LDL-C (mmol/L)	2.96 ± 0.21	2.84 ± 0.24	3.053	.003
BUN (mmol/L)	5.44 ± 1.19	5.46 ± 1.23	0.533	.595
NYHA				
I + II	22 (35.48)	63 (68.47)	16.305	<.001
III + IV	40 (64.52)	29 (31.52)		

BMI = body mass index, BUN = blood urea nitrogen, DBP = diastolic blood pressure, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, SBP = systolic blood pressure, TC = total cholesterol, TG = triglycerides.

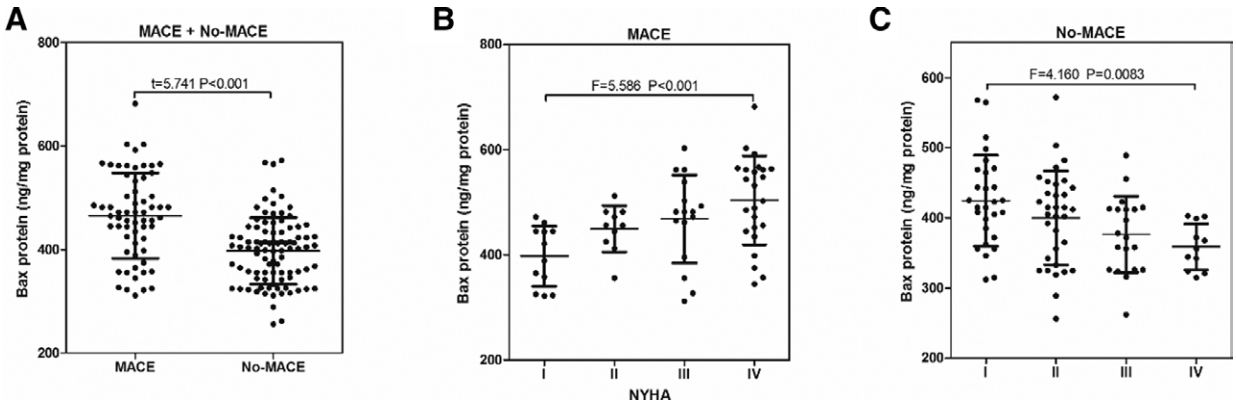

Figure 1. Expression of Bax protein in PBMC of patients with CHF. A-C, ELISA kit was used to detected the expression of Bax protein in PBMC of CHF patients in MACE + No-MACE group (A), MACE group (B), or No-MACE group (C). CHF = chronic heart failure, ELISA = enzyme-linked immunosorbent assay, MACE = major adverse cardiovascular event, PBMC = peripheral blood mononuclear cells.

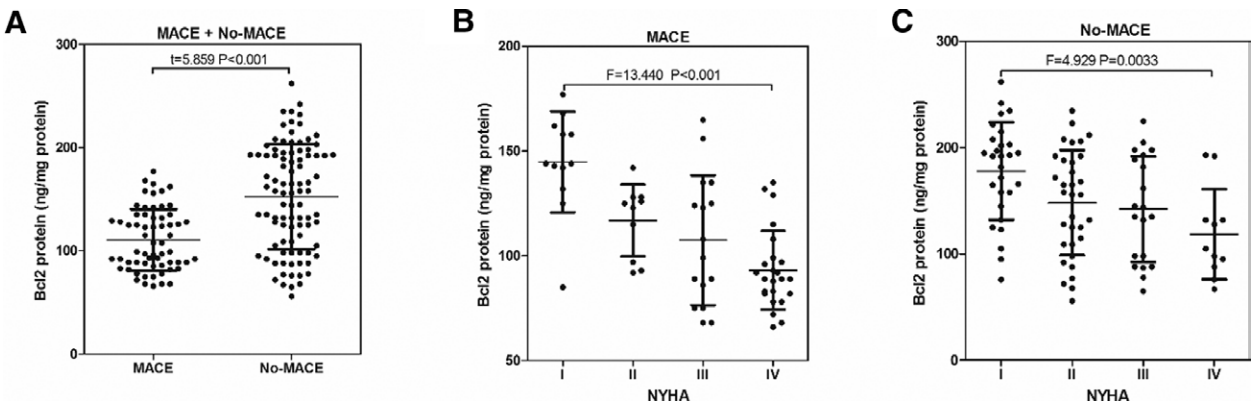

Figure 2. Expression of Bcl2 protein in PBMC of patients with CHF. A-C, ELISA kit was used to detected the expression of Bax protein in PBMC of CHF patients in MACE + No-MACE group (A), MACE group (B), or No-MACE group (C). CHF = chronic heart failure, ELISA = enzyme-linked immunosorbent assay, MACE = major adverse cardiovascular event, PBMC = peripheral blood mononuclear cells.

CI, 1.203–2.052; *P* = .001), LVEF (OR, 1.864; 95% CI, 1.272–2.731; *P* = .001), Bax levels (OR, 1.026; 95% CI, 1.003–1.049; *P* = .027) and Bcl2 levels (OR, 0.952; 95% CI, 0.908–0.998; *P* = .041) were independent predictive factors for MACE in CHF patients (Table 2).

3.4. Bax and Bcl2 for predicting MACE in CHF patients

Among 154 patients with CHF, 62 (40.26%) patients with CHF occurred MACE during 3-years followed-up, and we used ROC curve to analyze the value of Bax and Bcl2 levels in PBMC for prediction of MACE in CHF patients. The results of ROC curve

Table 2

Univariate and multivariate logistic regression analysis of independent predictive factors for MACE in chronic heart failure patients.

	Univariate		Multivariate	
Index	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Age	1.229 (1.147–1.316)	<.001	1.571 (1.203–2.052)	.001
Gender	1.160 (0.592–2.274)	.665		
BMI	1.089 (0.566–2.096)	.798		
Smoking	0.919 (0.722–1.169)	.491		
Hypertension	1.042 (0.545–1.994)	.901		
Diabetes	0.475 (0.247–0.916)	.026	0.206 (0.020–2.135)	.186
SBP	0.986 (0.969–1.003)	.107		
DBP	1.010 (0.980–1.040)	.525		
LVEF	1.334 (1.223–1.454)	<.001	1.864 (1.272–2.731)	.001
TC	1.117 (0.398–3.134)	.833		
TG	15.446 (0.225–158.045)	.204		
HDL-C	0.026 (0.000–16.663)	.269		
LDL-C	10.122 (2.106–48.647)	.004	53.493 (0.023–125729.846)	.315
BUN	0.665 (0.149–2.963)	.592		
NYHA	0.308 (0.157–0.603)	.001	0.675 (0.081–5.625)	.716
Bax	3.589 (2.125–6.059)	<.001	1.026 (1.003–1.049)	.027
Bcl2	0.106 (0.043–0.259)	<.001	0.952 (0.908–0.998)	.041

BMI = body mass index, BUN = blood urea nitrogen, CI = confidence interval, DBP = diastolic blood pressure, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, OR = odds ratio, SBP = systolic blood pressure, TC = total cholesterol, TG = triglycerides.

analysis showed that Bax or Bcl2 levels could be used to differentiate patients at risk for occurring MACE. And ROC curve of Bax with an AUC of 0.744 (95% CI: 0.660–0.827), Bcl2 with an AUC of 0.743 (95% CI: 0.667–0.819), Bax combined with Bcl2 with an AUC of 0.777 (95% CI: 0.705–0.849) (Fig. 3). At the same time, When the Bax level of 443.5 ng/ ml was used as the cutoff value to distinguish the MACE of CHF patients, and the sensitivity of Bax level in the diagnosis of MACE in patients with CHF is 78.25% and the specificity is 79.35%. Similarly, when the Bcl2 level of 144.5 ng/ ml was used as the cutoff value to distinguish the MACE of CHF patients, and the sensitivity of Bcl2 level in the diagnosis of MACE in patients with CHF is 65.43% and the specificity is 88.71%.

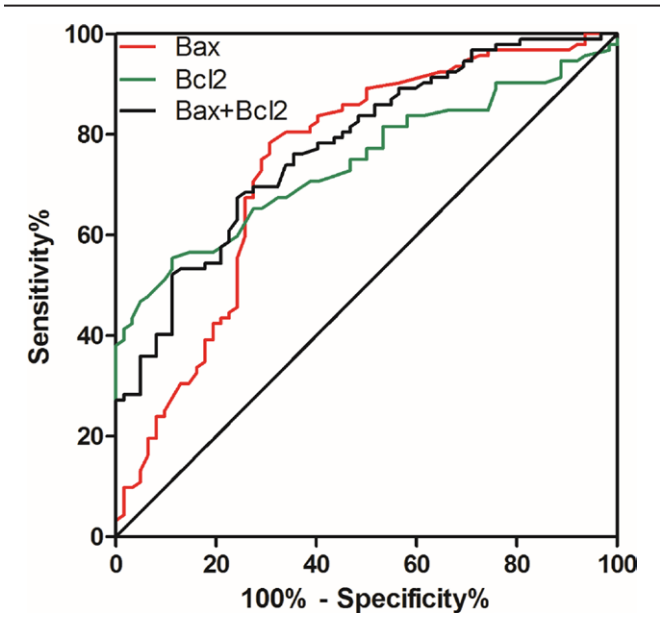

Figure 3. ROC curve of Bax or Bcl2 expression in PBMC for prediction of MACE in CHF patients. MACE = major adverse cardiovascular event, PBMC = peripheral blood mononuclear cells.

4. Discussion

Epidemiological statistics show that the incidence of heart failure in China is increasing year by year, with an annual incidence of 0.28% for people aged ≥ 25, 1.03% for people aged ≥ 65, and 1.66% for people aged ≥ 80. It is estimated that there are 2.97 million/ year new-onset heart failures and 12.05 million heart failure patients over the age of 25 nationwide.[21,22] Importantly, about 50% of heart failure patients in China die 5 years after diagnosis, the survival rate is lower than that of many types of cancer, and the mortality rate caused by heart failure has increased by 6 times in the past 40 years.[23] Major adverse cardiovascular event (MACE) is the main direct cause of death in CHF patients, so independent predictors that predict the occurrence of MACE in CHF patients have important implications for preventing MACE in CHD patients.[24,25] Clearly, all types of heart failure are characterized by an increased amount of cell death, which is divided into apoptosis, programmed death, and autophagy.[26,27] Therefore, factors related to apoptosis are considered to be involved in the development of heart failure.

In this study, we found that levels of Bax protein expression in PBMC of CHF patients in MACE group were significantly higher than those in No-MACE group, while levels of Bcl2 protein expression were significantly lower than those in No-MACE group, and Bax and Bcl2 protein levels increased and decreased with NYHA grades in MACE group and No-MACE group, respectively. And the present result is similar to a previous study by Liu W, et al,[18] and Liu W, et al found that compared with healthy people, the expression of Bax mRNA were significantly increased and Bcl2 mRNA were significantly decreased in PBMC of CHF patients.[18] In addition, Liu W, et al also found Bax mRNA was negatively and BCL2 mRNA expression was positively associated with cardiac function in CHF patients.[18]

Further analysis, Bax is an important pro-apoptotic protein of the Bcl2 apoptosis regulatory protein family, and Bcl2 is an important anti-apoptotic protein of the Bcl2 apoptosis regulatory protein family.[28] In healthy cells, Bax is mainly present in the cytoplasm, and when stimulated by death, Bax initiates conformational activation, migrates to mitochondria, and becomes embedded in the mitochondrial outer mold, where it binds to relevant factors to initiate the apoptotic program.[29,30] And Bcl2 inhibits the pro-apoptotic effect of Bax by forming a dimer with Bax, thereby exerting an anti-apoptotic effect.[31] Previous study has shown that apoptosis is associated with heart failure in both human and animal models, and that apoptosis is involved in the progression from

cardiac hypertrophy to heart failure.[32] Moreover, cardiomyocyte apoptosis plays an important role in the development of left ventricle dysfunction in heart failure with reduced ejection fraction, and cardiomyocyte loss is a well-defined feature of heart failure with reduced ejection fraction.[33,34] Therefore, the present results suggest that the protein levels of Bax and Bcl2 in PBMC of CHF patients are related to the occurrence of MACE.

Furthermore, results of univariate and multivariate logistic regression analysis in the present study showed that Bax and Bcl2 levels in PBMC of CHF patients were independent predictive factors for MACE in CHF patients, and Bax and Bcl2 levels could be used to differentiate CHF patients at risk for MACE with an AUC of 0.744 and an AUC of 0.743, respectively, confirming their high diagnostic value.

In conclusion, our results in the present study showed that Bax and Bcl2 protein expression in PBMC is related to the occurrence of MACE in CHF patients, and levels of Bax and Bcl2 protein in PBMC could be used as independent predictive factors for MACE in CHF patients.

4.1. Limitation

It should be pointed out that as a single-center observational study, this study has its limitations, such as the sample size of this study is still very small, and the results of the study need to be further verified by multi-center large sample size. In addition, PBMCs are composed of multiple types of cells, and the detailed mechanisms require further analysis.

Author contributions

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Software: Zhenwen Yang, Tianlu Wang.
Supervision: Tianlu Wang.
Validation: Yong Zhang.
Writing – original draft: Yong Zhang.
Writing – review & editing: Yong Zhang.

References

[1] Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145:e895–e1032.
[2] Crespo-Leiro MG, Metra M, Lund LH, et al. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018;20:1505–35.
[3] Truby LK, Rogers JG. Advanced heart failure: epidemiology, diagnosis, and therapeutic approaches. JACC Heart Failure. 2020;8:523–36.
[4] Roger VL. Epidemiology of heart failure: a contemporary perspective. Circ Res. 2021;128:1421–34.
[5] McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42:3599–726.
[6] Szyguła-Jurkiewicz B, Zakliczyński M, Owczarek A, et al. Low health-related quality of life is a predictor of major adverse cardiovascular events in patients with chronic nonischemic heart failure. Kardiochir Torakochirurgia Pol = Pol J Cardio Thorac Surg. 2014;11:283–8.
[7] Zhang J, Liu W. Cardiac cycle time-corrected electromechanical activation time greater than 15% is an independent risk factor for major adverse cardiovascular events in chronic heart failure outpatients. Pak J Med Sci. 2022;38(3Part-I):456–61.
[8] Gao G, Chen W, Yan M, et al. Rapamycin regulates the balance between cardiomyocyte apoptosis and autophagy in chronic heart failure by inhibiting mTOR signaling. Int J Mol Med. 2020;45:195–209.
[9] Deng H, Ouyang W, Zhang L, et al. LncRNA GASL1 is downregulated in chronic heart failure and regulates cardiomyocyte apoptosis. Cell Mol Biol Lett. 2019;24:41.
[10] Sun ZL, Chen MH, Guo YN, et al. LncRNA XIST is elevated in patients with chronic heart failure and has a regulatory role in cardiomyocyte function. J Biol Regul Homeost Agents. 2021;35:677–82.
[11] Hsieh CC, Li CY, Hsu CH, et al. Mitochondrial protection by simvastatin against angiotensin II-mediated heart failure. Br J Pharmacol. 2019;176:3791–804.
[12] Shi B, Huang Y, Ni J, et al. Qi Dan Li Xin pill improves chronic heart failure by regulating mTOR/p70S6k-mediated autophagy and inhibiting apoptosis. Sci Rep. 2020;10:6105.
[13] Feng Y, Yan B, Cheng H, et al. Knockdown circ_0040414 inhibits inflammation, apoptosis and promotes the proliferation of cardiomyocytes via miR-186-5p/PTEN/AKT axis in chronic heart failure. Cell Biol Int. 2021;45:2304–15.
[14] Ashkenazi A, Fairbrother WJ, Leverson JD, et al. From basic apoptosis discoveries to advanced selective BCL-2 family inhibitors. Nat Rev Drug Discov. 2017;16:273–84.
[15] Deng H, Yue JK, Zusman BE, et al. B-cell lymphoma 2 (Bcl-2) and regulation of apoptosis after traumatic brain injury: a clinical perspective. Medicina (Kaunas). 2020;56:300.
[16] Teijido O, Dejean L. Upregulation of Bcl2 inhibits apoptosis-driven BAX insertion but favors BAX relocalization in mitochondria. FEBS Lett. 2010;584:3305–10.
[17] Wang L, He Y, Zhang Y, et al. Effects of active components of Fuzi and Gancao compatibility on Bax, Bcl-2, and caspase-3 in chronic heart failure rats. Evid Based Complement Alternat Med. 2016;2016:7686045.
[18] Liu W, Ru L, Su C, et al. Serum levels of inflammatory cytokines and expression of BCL2 and BAX mRNA in peripheral blood mononuclear cells and in patients with chronic heart failure. Med Sci Monitor. 2019;25:2633–9.
[19] Chen C, Liu S, Cao G, et al. Cardioprotective effect of paeonol on chronic heart failure induced by doxorubicin via regulating the miR-21-5p/S-phase kinase-associated protein 2 axis. Front Cardiovasc Med. 2022;9:695004.
[20] Heart Failure Group of Chinese Society of Cardiology of Chinese Medical Association, Chinese Heart Failure Association of Chinese Medical Doctor Association, Editorial Board of Chinese Journal of Cardiology. Chinese guidelines for the diagnosis and treatment of heart failure 2018. Zhonghua Xin Xue Guan Bing Za Zhi. 2018;46:760–89.
[21] Wang H, Chai K, Du M, et al. Prevalence and incidence of heart failure among urban patients in China: a national population-based analysis. Circ Heart Fail. 2021;14:e008406.
[22] Hao G, Wang X, Chen Z, et al. Prevalence of heart failure and left ventricular dysfunction in China: the China Hypertension Survey, 2012-2015. Eur J Heart Fail. 2019;21:1329–37.
[23] Zhang Y, Zhang J, Butler J, et al. 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;23:868–75.
[24] Abdin A, Anker SD, Butler J, et al. "Time is prognosis" in heart failure: time-to-treatment initiation as a modifiable risk factor. ESC Heart Fail. 2021;8:4444–53.
[25] Cohen JB, Schrauben SJ, Zhao L, et al. Clinical phenogroups in heart failure with preserved ejection fraction: detailed phenotypes, prognosis, and response to spironolactone. JACC Heart Fail. 2020;8:172–84.
[26] Moe GW, Marín-García J. Role of cell death in the progression of heart failure. Heart Fail Rev. 2016;21:157–67.
[27] Cho GW, Altamirano F, Hill JA. Chronic heart failure: Ca(2+), catabolism, and catastrophic cell death. Biochim Biophys Acta. 2016;1862:763–77.
[28] Qi B, Cao L, Wang L, et al. Study on apoptosis and expression of P53, bcl-2, Bax in cardiac myocytys of congestive heart failure induced by ventricular pacing. J Tongji Med Univ = Tong Ji Yi Ke Da Xue Xue Bao. 2001;21:202–5.
[29] Spitz AZ, Gavathiotis E. Physiological and pharmacological modulation of BAX. Trends Pharmacol Sci. 2022;43:206–20.
[30] Wu X, Deng Y. Bax and BH3-domain-only proteins in p53-mediated apoptosis. Front Biosci. 2002;7:d151–6.
[31] Socha DS, Zhao X, Bodo J, et al. Decreased BIM expression in BCL2-negative follicular lymphoma: a potential mechanism for resistance to apoptosis. Hum Pathol. 2021;107:1–8.
[32] Abbate A, Biondi-Zoccai GG, Bussani R, et al. Increased myocardial apoptosis in patients with unfavorable left ventricular remodeling and early symptomatic post-infarction heart failure. J Am Coll Cardiol. 2003;41:753–60.
[33] Sabbah HN, Sharov VG, Goldstein S. Cell death, tissue hypoxia and the progression of heart failure. Heart Fail Rev. 2000;5:131–8.
[34] Fiedler LR, Maifoshie E, Schneider MD. Mouse models of heart failure: cell signaling and cell survival. Curr Top Dev Biol. 2014;109:171–247.