Elevated plasma Sirtuin2 level predicts heart failure after acute myocardial infarction

Meili Zheng
Beijing Chaoyang Hospital，Capital Medical University
Lei Zhao
Beijing Chaoyang Hospital，Capital Medical University
Hao Sun
Beijing Chaoyang Hospital，Capital Medical University
Mulei Chen
Beijing Chaoyang Hospital，Capital Medical University
Xinchun Yang (haiyang_beauty@163.com)
Beijing Chaoyang Hospital，Capital Medical University

Research

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Abstract

Background and Objectives: There is currently no evidence regarding the role of plasma Sirtuin2 (SIRT2) level in heart failure after acute myocardial infarction (AMI) yet. This study assessed the relationship between plasma SIRT2 level and AMI, and also investigated the association of plasma SIRT2 level with major adverse cardiovascular events (MACE) and heart failure after AMI.

Methods and Results: A total of 129 AMI patients were included in the present study. The major adverse cardiovascular events (MACE) and heart failure were recorded during hospitalization and follow-up (12 months) after discharge. According to the 75th percentile value of plasma SIRT2 level, we divided all the AMI patients into two groups: high level group (plasma SIRT2 level≥109.0pg/ml) and low level group (plasma SIRT2 level <109.0pg/ml). Compared with the low level group, the high level group had higher prercentage of Killip class≥3 (P<0.001), left ventricular ejection fraction(LVEF) <50% (P=0.007) or even <40% (P=0.012), use of breathing machine(P=0.003), and higher plasma brain natriuretic peptide (BNP) level (P=0.006). Multivariate regression analysis showed that there were higher risks of MACE (hazard ratio (HR)=11.20 [95% confidence interval (CI): 3.18-39.52, P<0.001]) and heart failure (HR=27.10 [95%CI 4.65-157.83, P<0.001]) in the high level group.

Conclusions: The present study suggested that plasma SIRT2 level is a promising biomarker to predict heart failure and MACE after AMI.

Background

Sirtuin (SIRT) is a family of NAD+-dependent histone deacetylases, regulating metabolism and aging-related diseases (e.g., diabetes, cancer, neurodegenerative and cardiovascular diseases)[1–5]. Recently, SIRT2, as a member of sirtuin family, was reported to play a significant role in cardiovascular disease. It has been previously shown that over expression of cardiac-specific SIRT2, promoting AMP-activated protein kinase (AMPK) activation, can protect heart against Ang II-induced cardiac hypertrophy and fibrosis[6], while SIRT2 can repress nuclear factor of activated T-cells (NFAT) to maintain cardiac homeostasis and ameliorate cardiac dysfunction[7]. In addition, SIRT2 gene is down-regulated in the cardiac tissue in cardiosurgical patients undergoing remote ischemic preconditioning[8], and functional genetic variants in acute myocardial infarction(AMI) patients were observed as well[9].

It is noteworthy that, SIRT2 is expressed in various metabolically relevant tissues (e.g., the heart, brain, and adipose tissue)[10], and is also detected in circulation[11]. SIRT2 plays a pivotal role in various physiological processes in maintaining metabolic homeostasis, including inflammation, oxidative stress and mitochondrial function, as well as adipocyte differentiation, fatty acid oxidation, gluconeogenesis, and insulin sensitivity. SIRT2 may enhance acetylation and activation of NF-κB p65[12, 13]and regulate expression of CXCL2 and CCL2[14] to suppress inflammatory process, while regulate acetylation of G6PD to modulate NADPH homeostasis and cell survival during oxidative stress[15]. Dysregulated SIRT2 activity has been found to be associated with inflammatory and metabolic disorders[10, 16]. Moreover, AMI, leading to the highest mortality among cardiovascular diseases, is involved in both metabolic dysfunction and inflammatory responses[17–19]. The cause of AMI patients' death is either heart failure or a malignant arrhythmia, especially heart failure, which is closely associated with inflammatory responses and contributes to long-term mortality after AMI[20, 21].

However, no study has concentrated on the role of circulating SIRT2 in AMI yet. In the present study, we investigated the relationship between plasma SIRT2 level and AMI, and evaluated the association of plasma SIRT2 level with major adverse cardiovascular events (MACE) and heart failure after AMI. Our results clarified the role of plasma SIRT2 level in AMI prognosis.

Study Subjects And Methods

Study subjects

Study subjects were prospectively recruited from Beijing Chao-yang Hospital (Beijing, China). A total of 129 AMI patients (including 74 ST-segment elevation myocardial infarction [STEMI] and 55 non-ST-segment elevation myocardial infarction [NSTEMI]) with heart attack for within 12 h were enrolled in the present study. All patients successfully underwent revascularization in emergency before hospitalization. The diagnosis of AMI was carried out at the time of admission on the basis of criteria, including clinical symptoms, typical changes in electrocardiogram (ECG), elevated cardiac biomarkers (cardiac troponin-I and creatine kinase MB). The exclusion criteria were as follows: neoplasm, severe organ failure, or other infectious or inflammatory conditions. Written informed consent was obtained from all the participants. This study was conducted in accordance with the Declaration of Helsinki, and the research protocol was approved by the Ethics Committee of Beijing Chao-Yang Hospital.

Clinical conditions

For all the AMI patients data related to cardiac arrest, utilization of intra-aortic balloon pump (IABP), and breathing machine, and death during hospitalization were recorded, and the patients were followed-up for 12 months (no death happened within 12 months). The MACE included cardiac death, readmission for revascularization and heart failure. Heart failure involved death due to heart failure during hospitalization, and readmission because of heart failure after discharge.

Laboratory measurements

Baseline laboratory measurements were obtained within the first 24 h of admission. Plasma of SIRT2 levels were assayed using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems Inc., Minneapolis, MN, USA) according to the manufacturer's instructions. The coefficient of variation for the assay was < 5%. Fasting venous blood samples were collected to measure the levels of glucose, homocysteine, creatinine, and lipids (including the levels of total cholesterol, high-density lipoprotein cholesterol, and triglycerides).

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) and quartiles, while categorical variables were expressed as percentages and numbers. Comparisons between groups were performed using chi-square test for categorical variables, and two-sample t-test for comparing continuous variables in normally distributed status, as well as Kruskal-Wallis test for comparing continuous variables in non-normally distributed status. Pearson's and Spearman's correlation coefficients were used for comparing parametric and nonparametric variables, respectively. Cox proportional hazards analysis was carried out to determine the independent predictors of MACE. All the analyses were performed using SPSS 24.0 software(IBM, Armonk, NY, USA), and a 2-tailed $P < 0.05$ was considered statistically significant.

Results

Study subjects' clinical characteristics

A total of 129 AMI patients (mean age: 62.2 ± 12.7 years old, male/female 96/33) were enrolled in the present study, including 74 STEMI and 55 NSTEMI. The median value (25th, 75th percentiles) of plasma SIRT2 level was 69.0 (48.9, 109.0) pg/ml. According to the 75th percentile value of plasma SIRT2 level, we divided all the patients into high level group (plasma SIRT2 level ≥ 109.0 pg/ml) and low level group (plasma SIRT2 level < 109.0 pg/ml), and clinical

parameters between the two groups were compared (Table 1). Compared with the low level group, the high level group had significantly higher levels of C-reactive protein (CRP), blood urea nitrogen (BUN), and serum creatinine.

Table 1
Baseline Characteristics of the AMI patients with higher and lower levels of plasma SIRT2

	SIRT2 < 109.0 pg/ml (N = 96)	SIRT2 ≥ 109.0 pg/ml (N = 33)	P value
Age, years	61.9 ± 12.9	62.9 ± 12.2	0.705
Male, n(%)	73 (76.0)	23 (69.7)	0.471
STEMI, n(%)	57 (59.4)	17 (51.5)	0.431
Hypertension, n(%)	58 (60.4)	15 (45.5)	0.135
Diabetes, n(%)	34 (35.4)	13 (39.4)	0.682
Previous MI, n(%)	11 (11.5)	4 (12.1)	0.918
Previous PCI, n(%)	12 (12.5)	3 (9.1)	0.832
Current smoker, n(%)	55 (57.3)	20 (60.6)	0.739
Current drinker, n(%)	33 (34.4)	7 (21.2)	0.158
Heart rate, beats/min	78.0 [70.0–90.0]	85.0 [70.5–96.5]	0.264
Systolic blood pressure, mmHg	131.5 ± 18.2	126.7 ± 23.5	0.228
Diastolic blood pressure, mmHg	74.2 ± 13.0	74.2 ± 13.3	0.996
Body mass index, kg/m2	25.3 ± 2.3	25.6 ± 3.1	0.655
C-reactive protein, mg/L	7.45 [2.27–13.82]	13.21 [5.26–14.90]	0.033
ESR, mm/h	11.0 [5.0-19.3]	14.0 [4.8–28.3]	0.523
Leukocyte, × 109/L	8.93 [6.92–11.07]	10.21 [7.88–12.15]	0.056
Neutrophil, × 109/L	6.33 [4.73–8.61]	7.19 [5.96–9.84]	0.057
Lymphocyte, × 109/L	1.55 [1.27–2.14]	1.54 [1.27–2.14]	0.754
Hemoglobin, g/L	130.9 ± 15.3	128.2 ± 24.0	0.543
Platelets, × 109/L	205.3 ± 65.2	207.4 ± 76.9	0.879
AST, U/L	49.5 [26.3-100.8]	50.5 [28.3–199.0]	0.191
ALT, U/L	28.0 [16.0–41.0]	28.5 [21.3–90.3]	0.104
Total cholesterol, mmol/L	4.86 [4.08–5.67]	4.38 [3.74–5.32]	0.192
HDL-C, mmol/L	1.10 [0.90–1.20]	1.00 [0.80–1.10]	0.078
LDL-C, mmol/L	2.80 [2.30–3.70]	2.40 [2.10–3.50]	0.258
Triglycerides, mmol/L	1.29 [1.00-1.80]	1.43 [0.95–2.33]	0.764
Fast glucose, mmol/L	6.38 [5.19–8.18]	6.78 [5.16–9.47]	0.465
HbA1C, %	6.10 [5.80–7.10]	6.20 [5.63–8.05]	0.719

SIRT2, sirtuin2; STEMI, ST-segment elevation myocardial infarction; MI, myocardial infarction; PCI, percutaneous coronary intervention; ESR, erythrocyte sedimentation rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; HbA1C, glycosylated Haemoglobin; BUN, blood urea nitrogen; sTSH, thyroid stimulating hormone; CKMB, creatine kinase MB.

	SIRT2 < 109.0 pg/ml (N = 96)	SIRT2 ≥ 109.0 pg/ml (N = 33)	P value
BUN, mmol/L	5.65 [4.62–6.87]	6.67 [4.60-11.62]	0.038
Serum creatinine, μmol/L	75.1 [65.0-96.4]	90.0 [71.6-132.1]	0.012
Na^+, mmol/L	138.6 ± 2.5	138.0 ± 3.7	0.399
K^+, mmol/L	4.07 ± 0.39	4.23 ± 0.42	0.062
Homocysteine, μmol/L	17.0 [12.0–21.0]	16.0 [12.8–28.0]	0.42
Uric acid, μmol/L	365.5 [290.3-428.8]	401.5 [321.5-507.5]	0.064
Serum albumin, g/L	39.3 ± 3.6	38.0 ± 4.2	0.099
Free triiodothyronine, pg/ml	2.47 [2.16–2.70]	2.43 [2.11–2.68]	0.442
Free tetraiodothyronine, ng/dl	1.11 [1.00-1.23]	1.11 [1.04–1.31]	0.569
sTSH, uIU/ml	1.13 [0.74–1.91]	1.28 [0.63–2.18]	0.809
Troponin-I, ng/mL	14.6 [4.3–49.5]	17.5 [6.8-109.2]	0.337
CKMB, ng/Ml	8.00 [2.28-42.00]	12.35 [1.83–69.85]	0.696
Fibrinogen, mg/dL	293.0 [242.7-360.2]	313.4 [244.8-398.9]	0.397

SIRT2, sirtuin2; STEMI, ST-segment elevation myocardial infarction; MI, myocardial infarction; PCI, percutaneous coronary intervention; ESR, erythrocyte sedimentation rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; HbA1C, glycosylated Haemoglobin; BUN, blood urea nitrogen; sTSH, thyroid stimulating hormone; CKMB, creatine kinase MB.

Association between plasma SIRT2 level with indexes of AMI severity

The indexes of AMI severity included MACE, mortality, heart failure, utilization of IABP and breathing machine, malignant arrhythmia, cardiac arrest, Killip class, left ventricular ejection fraction (LVEF), plasma brain natriuretic peptide (BNP) level, treatment, occlusive lesions, collateral circulation, as well as SYNTAX scores and GRACE scores. Compared with the low level group (plasma SIRT2 level < 109.0 pg/ml), the high level group (plasma SIRT2 level ≥ 109.0 pg/ml) was found to have higher percentage of MACE ($P < 0.001$), heart failure ($P < 0.001$), breathing machine use ($P = 0.003$), Killip class ≥ 3 ($P < 0.001$), LVEF < 50% ($P = 0.007$) or even < 40% ($P = 0.012$), and higher BNP level ($P = 0.006$) (Table 2).

Table 2
Comparation of AMI severity in patients with higher and lower levels of plasma SIRT2

	SIRT2 < 109.0 pg/ml	SIRT2 ≥ 109.0 pg/ml	P value
MACE, n(%)	5 (5.2)	17 (51.5)	< 0.001
Death, n(%)	2 (2.1)	4 (12.1)	0.06
Heart failure, n(%)	2 (2.1)	14 (42.4)	< 0.001
IABP use, n(%)	9 (9.4)	8 (24.2)	0.054
Breathing machine use, n(%)	3 (3.1)	7 (21.2)	0.003
Malignant arrhythmia, n(%)	7 (7.3)	5 (15.2)	0.32
Cardiac arrest, n(%)	4 (4.2)	4 (12.1)	0.224
Killip class ≥ 3, n(%)	7 (7.3)	12 (36.4)	< 0.001
LVEF < 50%, n(%)	20 (20.8)	15 (45.5)	0.007
LVEF < 40%, n(%)	6 (6.3)	8 (24.2)	0.012
LVEDD, mm	47.5 ± 4.8	49.6 ± 8.6	0.099
BNP, pg/mL	161.0 [70.5–339.0]	302.0 [103.5-851.5]	0.006
Drug therapy, n(%)	5 (5.2)	2 (6.1)	0.804
PCI, n(%)	83 (86.5)	26 (78.8)	0.438
CABG, n(%)	8 (8.3)	5 (15.2)	0.423
Occlusive lesions, n(%)	55 (57.3)	18 (54.5)	0.738
Collateral circulation, n(%)	8 (8.3)	3 (9.1)	0.893
SYNTAX score, points	19.0 [12.0–26.0]	24.0 [15.8–31.8]	0.082
GRACE score, points	158.0 [138.5-181.5]	183.0 [138.0-208.0]	0.089

SIRT2, sirtuin2; MACE, major adverse cardiovascular event; IABP, intra-aortic ballon pump; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; BNP, brain natriuretic peptide; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

Relationships between plasma SIRT2 level and clinical parameters

Plasma SIRT2 level was noted to be associated with leukocyte and neutrophil (r = 0.209, P = 0.018 for leukocyte; r = 0.217, P = 0.014 for neutrophil), and also correlated with erythrocyte sedimentation rate (ESR) and CRP (r = 0.215, P = 0.025 for ESR; r = 0.265, P = 0.004 for CRP). Additionally, plasma SIRT2 level was also correlated with renal function (r = 0.183, P = 0.039 for serum creatinine; r = 0.279, P = 0.001 for renal dysfunction) and heart rate (r = 0.199, P = 0.024). However, plasma SIRT2 level was not associated with patient's age, gender, the levels of blood glucose and lipid, cardiac Troponin-I, creatine kinase MB (CKMB), as well as GRACE and SYNTAX scores (Table 3).

Table 3
Association between Plasma Sirtuin 2 and Clinical Parameters in AMI

	r	P value
Gender (1 = male, 2 = female)	0.070	0.430
Age	-0.053	0.550
Body mass index	-0.037	0.732
ESR	**0.215**	**0.025**
C-reactive protein	**0.265**	**0.004**
Leukocyte	**0.209**	**0.018**
Neutrophil	**0.217**	**0.014**
Lymphocyte	-0.061	0.494
Hemoglobin	0.013	0.883
Platelets	0.039	0.658
Fast glucose	0.026	0.772
HbA1C	0.026	0.774
Total cholesterol	-0.051	0.570
HDL-C	-0.124	0.162
LDL-C	-0.019	0.830
Triglycerides	0.02	0.825
Homocysteine	0.126	0.181
Uric acid	0.101	0.255
Heart rate	**0.199**	**0.024**
Systolic blood pressure	-0.039	0.658
Diastolic blood pressure	0.065	0.462
BUN	0.126	0.156
Serum creatinine	**0.183**	**0.039**
Renal dysfunction	**0.279**	**0.001**
Serum albumin	-0.069	0.441
Troponin-I	0.127	0.152
CKMB	0.100	0.278
GRACE score	0.115	0.194
SYNTAX score	0.060	0.496
Current smoking	-0.008	0.924

AMI, acute myocardial infarction; ESR, erythrocyte sedimentation rate; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; BUN,blood urea nitrogen; CKMB, creatine kinase MB.

	r	P value
Current drinking	0.014	0.871

AMI, acute myocardial infarction; ESR, erythrocyte sedimentation rate; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; BUN,blood urea nitrogen; CKMB, creatine kinase MB.

Univariate and multivariate Cox analysis of predictors of MACE and heart failure

Univariate Cox regression analysis showed that elder, renal dysfunction, higher plasma SIRT2 level, greater SYNTAX and GRACE scores, malignant arrhythmia, cardiac arrest, Killip class ≥ 3, LVEF < 50% or < 40%, BNP > 500 ng/L, in addition to application of IABP and breathing machine were associated with higher risks of MACE and heart failure. The GRACE scores were calculated using patient's age, heart rate, systolic blood pressure, creatinine, Killip class, ST-segment deviation, elevated cardiac enzyme level, and cardiac arrest at the time of admission; for this purpose, we included GRACE and SYNTAX scores, gender, body mass index (BMI), diabetes, plasma SIRT2 level, BNP > 500 ng/L, as well as utilization of IABP and breathing machine in the multivariate Cox regression analysis. Higher plasma SIRT2 level and GRACE score were associated with higher risk of MACE (for plasma SIRT2 level:hazard ratio (HR) = 11.20 [95% confidence interval (CI): 3.18–39.52, P < 0.001]; for GRACE score: HR = 1.03 [95%CI 1.02–1.05, P < 0.001]) and heart failure (for plasma SIRT2 level: HR = 27.10 [95%CI 4.65-157.83, P < 0.001]; for GRACE score: HR = 1.03 [95%CI 1.01–1.05, P = 0.009]), while use of breathing machine was associated with higher risk of MACE (HR = 12.16 [95%CI 2.37–62.26, P = 0.003]) and heart failure (HR = 11.45 [95%CI 1.80-72.97, P = 0.010]) (Table 4, Fig. 1).

Table 4
Univariate and multivariate Cox regression analysis for predictors of MACE and Heart failure

	MACE				Heart failure			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR(95%CI)	P value	HR(95%CI)	P value	HR(95%CI)	P value	HR(95%CI)	P value
Age	1.05 (1.01–1.09)	0.009			1.031 (0.988–1.076)	0.158		
Male	0.66 (0.28–1.57)	0.345	3.05 (0.71–13.06)	0.134	0.63 (0.23–1.73)	0.368	7.97 (1.06–59.98)	0.044
Heart rate	1.02 (1.00-1.04)	0.045			1.02 (1.003–1.05)	0.023		
Body mass index	0.997 (0.840–1.182)	0.97	1.00 (0.84–1.19)	0.999	0.997 (0.817–1.218)	0.98	1.06 (0.87–1.29)	0.585
Renal dysfunction	6.38 (2.76–14.75)	< 0.001			8.33 (3.09–22.42)	< 0.001		
Hypertension	0.82 (0.35–1.89)	0.634			0.53 (0.20–1.42)	0.207		
Diabetes	1.47 (0.64–3.40)	0.369	1.59 (0.42–6.10)	0.498	1.77 (0.66–4.71)	0.255	1.68 (0.30–9.45)	0.559
SIRT2	1.007 (1.005–1.009)	< 0.001			1.008 (1.005–1.010)	< 0.001		
SIRT2 ≥ 109.0 pg/ml	12.45 (4.59–33.83)	< 0.001	11.20 (3.18–39.52)	< 0.001	25.89 (5.87-114.12)	< 0.001	27.10 (4.65-157.83)	< 0.001
SYNTAX score	1.03 (1.01–1.06)	0.007	0.991 (0.944–1.040)	0.7	1.033 (1.004–1.062	0.027	0.96 (0.89–1.03)	0.26
GRACE score	1.04 (1.03–1.05)	< 0.001	1.03 (1.02–1.05)	< 0.001	1.04 (1.02–1.05)	< 0.001	1.03 (1.01–1.05)	0.009
Malignant arrhythmia	5.76 (2.34–14.19)	< 0.001			4.11 (1.32–12.78)	0.015		
Cardiac arrest	6.16 (2.26–16.78)	< 0.001			4.85 (1.38–17.12)	0.014		

MACE, major adverse cardiovascular event; SIRT2, sirtuin2; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; BNP, brain natriuretic peptide; IABP, intra-aortic ballon pump.

	MACE				Heart failure			
Killip class ≥ 3	15.69 (6.51–37.80)	< 0.001			15.24 (5.47–42.43)	< 0.001		
LVEF < 50%	3.17 (1.37–7.34)	0.007			7.03 (2.43–20.32)	< 0.001		
LVEF < 40%	5.61 (2.25–14.01)	< 0.001			9.64 (3.51–26.50)	< 0.001		
LVEDD	1.05 (0.98–1.13)	0.192			1.11 (1.03–1.20)	0.005		
BNP > 500 ng/L	5.19 (2.24–12.02)	< 0.001	1.09 (0.28–4.18)	0.904	5.24 (1.96–14.04)	0.001	1.56 (0.28–8.80)	0.615
IABP use	5.09 (2.14–12.10)	< 0.001	0.26 (0.04–1.70)	0.16	7.83 (2.83–21.62)	< 0.001	0.97 (0.10–9.30)	0.982
Breathing machine use	18.19 (7.63–43.37)	< 0.001	12.16 (2.37–62.26)	0.003	23.32 (8.35–65.16)	< 0.001	11.45 (1.80-72.97)	0.01

MACE, major adverse cardiovascular event; SIRT2, sirtuin2; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; BNP, brain natriuretic peptide; IABP, intra-aortic ballon pump.

Discussion

In the present study, we, for the first time, assessed to the role of plasma SIRT2 level in AMI patients. We found that plasma SIRT2 level is an appropriate biomarker to predict heart failure and MACE after AMI. The results showed that, compared with AMI patients with lower plasma SIRT2 level, those cases with higher plasma SIRT2 level had worse cardiac function and higher risk of MACE during hospitalization and in the follow-up after discharge.

Previous studies demonstrated that SIRT2 is a protective factor in cardiovascular disease and also showed that expression levels of SIRT2 protein were down-regulated in cardiomyocytes treated with phenylephrine or isoproterenol[7], as well as in hypertrophic hearts of mice[6] or even in hearts of T1DM rats[22]. Sirt2-KO markedly exaggerated cardiac hypertrophy and fibrosis, as well as causing decreases of cardiac ejection fraction and fractional shortening in aged mice and Ang II-infused mice[6]; besides, overexpression of SIRT2 attenuated agonist-induced cardiac hypertrophy in cardiomyocytes[7]. Moreover, SIRT2 mediates hypertension-induced vascular remodeling[23]. In cardiosurgical patients undergoing remote ischemic preconditioning, SIRT2 gene is down-regulated in the cardiac tissue[8]. Functional genetic variants within the SIRT2 gene promoter were found in AMI patients[9]. It was previously reported that SIRT2 plays a substantial role in cardiovascular disease. In addition, SIRT2 has been detected in the circulation[11], however, there is no evidence about the role of circulating SIRT2 in AMI. In the present study, we noted that circulating SIRT2 is an acceptable biomarker for AMI, and the higher plasma SIRT2 level was associated with poorer AMI prognosis, especially for worse cardiac function.

In the present study, plasma SIRT2 level was found to be correlated with counts of leukocytes and neutrophils, as well as levels of ESR and CRP, which are consistent with the results of previously conducted studies. Moreover, the results of present research unveiled that plasma SIRT2 level was mainly correlated with the indexes of heart failure after AMI, while

that wasn't correlated with myocardial enzyme or severity of coronary artery stenosis (evaluated by SYNTAX score). We also found that in AMI patients, higher plasma SIRT2 level was associated with worse cardiac function. Inflammatory response is a key risk factor for heart failure after AMI[24].Overexpression of SIRT2 suppresses inflammatory responses and reactive oxygen species–induced macrophage cytotoxicity[25–27]. Inflammatory responses in AMI patients were also associated with malignant arrhythmia[28, 29], and higher plasma SIRT2 level was noted to have higher percentage of malignant arrhythmia and cardiac arrest in the present study.

Additionally, SIRT2 was reported to be associated with renal inflammatory injury, in which SIRT2 showed an anti-inflammatory effect through regulating p65 binding to the promoters of CXCL2 and CCL2[14]. In the current study, plasma SIRT2 level was correlated with renal function in AMI, which might be due to the inflammatory responses in AMI patients.

The present study contains a number of limitations: 1) The period of follow-up was short, therefore, long-term follow-up studies need to be conducted to further analyze the association between plasma SIRT2 level and AMI. 2) This is a study with small sample size; large sample size should be carried out to verify our findings.

Conclusion

Taken together, previous studies demonstrated that SIRT2 plays a significant role in cardiovascular diseases, and we therefore can conclude that SIRT2 might be involved in cardiovascular diseases through regulating metabolic and inflammatory pathways. Our findings revealed that plasma SIRT2 level is a proper biomarker to predict heart failure and MACE after AMI.

Declarations

Ethics approval and consent to participate

The research protocol was approved by the Ethics Committee of Beijing Chao-Yang Hospital.

Consent for publication

We consent to transfer the copyright to the publisher.

Availability of data and materials

The data used to support the findings of this study are available from the corresponding author upon request.

Competing interests

The authors declare that there is no conflict of interest.

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Authors' contributions

Meili Zheng and Lei Zhao analyzed the results and wrote the paper; Hao Sun completed the plots and linguistic modification; Mulei Chen and Xinchun Yang designed the study.

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References

1. Bonkowski MS, Sinclair DA. Slowing ageing by design: The rise of nad(+) and sirtuin-activating compounds. *Nature reviews. Molecular cell biology*. 2016;17:679-690
2. Winnik S, Auwerx J, Sinclair DA, Matter CM. Protective effects of sirtuins in cardiovascular diseases: From bench to bedside. *Eur Heart J*. 2015;36:3404-3412
3. Yamamoto H, Schoonjans K, Auwerx J. Sirtuin functions in health and disease. *Molecular endocrinology*. 2007;21:1745-1755
4. Donmez G, Outeiro TF. Sirt1 and sirt2: Emerging targets in neurodegeneration. *EMBO Mol Med*. 2013;5:344-352
5. Matsushima S, Sadoshima J. The role of sirtuins in cardiac disease. *Am J Physiol Heart Circ Physiol*. 2015;309:H1375-1389
6. Tang X, Chen XF, Wang NY, Wang XM, Liang ST, Zheng W, et al. Sirt2 acts as a cardioprotective deacetylase in pathological cardiac hypertrophy. *Circulation*. 2017;136:2051-2067
7. Sarikhani M, Maity S, Mishra S, Jain A, Tamta AK, Ravi V, et al. Sirt2 deacetylase represses nfat transcription factor to maintain cardiac homeostasis. *J Biol Chem*. 2018;293:5281-5294
8. Zitta K, Meybohm P, Gruenewald M, Cremer J, Zacharowski KD, Scholz J, et al. Profiling of cell stress protein expression in cardiac tissue of cardiosurgical patients undergoing remote ischemic preconditioning: Implications for thioredoxin in cardioprotection. *J Transl Med*. 2015;13:34
9. Yang W, Gao F, Zhang P, Pang S, Cui Y, Liu L, et al. Functional genetic variants within the sirt2 gene promoter in acute myocardial infarction. *PLoS One*. 2017;12:e0176245
10. Gomes P, Fleming Outeiro T, Cavadas C. Emerging role of sirtuin 2 in the regulation of mammalian metabolism. *Trends Pharmacol Sci*. 2015;36:756-768
11. Berggrund M, Enroth S, Lundberg M, Assarsson E, Stalberg K, Lindquist D, et al. Identification of candidate plasma protein biomarkers for cervical cancer using the multiplex proximity extension assay. *Mol Cell Proteomics*. 2019;18:735-743
12. Yuan F, Xu ZM, Lu LY, Nie H, Ding J, Ying WH, et al. Sirt2 inhibition exacerbates neuroinflammation and blood-brain barrier disruption in experimental traumatic brain injury by enhancing nf-kappab p65 acetylation and activation. *J Neurochem*. 2016;136:581-593
13. Rothgiesser KM, Erener S, Waibel S, Luscher B, Hottiger MO. Sirt2 regulates nf-kappab dependent gene expression through deacetylation of p65 lys310. *J Cell Sci*. 2010;123:4251-4258
14. Jung YJ, Lee AS, Nguyen-Thanh T, Kim D, Kang KP, Lee S, et al. Sirt2 regulates lps-induced renal tubular cxcl2 and ccl2 expression. *J Am Soc Nephrol*. 2015;26:1549-1560
15. Wang YP, Zhou LS, Zhao YZ, Wang SW, Chen LL, Liu LX, et al. Regulation of g6pd acetylation by sirt2 and kat9 modulates nadph homeostasis and cell survival during oxidative stress. *EMBO J*. 2014;33:1304-1320
16. German NJ, Haigis MC. Sirtuins and the metabolic hurdles in cancer. *Curr Biol*. 2015;25:R569-583
17. Weil BR, Neelamegham S. Selectins and immune cells in acute myocardial infarction and post-infarction ventricular remodeling: Pathophysiology and novel treatments. *Front Immunol*. 2019;10:300
18. Lim GB. Acute coronary syndromes: Supplemental oxygen in myocardial infarction. *Nat Rev Cardiol*. 2017;14:632
19. Synetos A, Papanikolaou A, Toutouzas K, Georgiopoulos G, Karanasos A, Drakopoulou M, et al. Metabolic syndrome predicts plaque rupture in patients with acute myocardial infarction. An optical coherence study. *Int J Cardiol*. 2016;209:139-141
20. Ye F, Winchester D, Jansen M, Lee A, Silverstein B, Stalvey C, et al. Assessing prognosis of acute coronary syndrome in recent clinical trials: A systematic review. *Clin Med Res*. 2019;17:11-19

21. Davis WT, Montrief T, Koyfman A, Long B. Dysrhythmias and heart failure complicating acute myocardial infarction: An emergency medicine review. *Am J Emerg Med*. 2019;37:1554-1561
22. Yuan Q, Zhan L, Zhou QY, Zhang LL, Chen XM, Hu XM, et al. Sirt2 regulates microtubule stabilization in diabetic cardiomyopathy. *Eur J Pharmacol*. 2015;764:554-561
23. Hashimoto-Komatsu A, Hirase T, Asaka M, Node K. Angiotensin ii induces microtubule reorganization mediated by a deacetylase sirt2 in endothelial cells. *Hypertens Res*. 2011;34:949-956
24. Nahrendorf M, Frantz S, Swirski FK, Mulder WJ, Randolph G, Ertl G, et al. Imaging systemic inflammatory networks in ischemic heart disease. *J Am Coll Cardiol*. 2015;65:1583-1591
25. Kim MJ, Kim DW, Park JH, Kim SJ, Lee CH, Yong JI, et al. Pep-1-sirt2 inhibits inflammatory response and oxidative stress-induced cell death via expression of antioxidant enzymes in murine macrophages. *Free Radic Biol Med*. 2013;63:432-445
26. Eskandarian HA, Impens F, Nahori MA, Soubigou G, Coppee JY, Cossart P, et al. A role for sirt2-dependent histone h3k18 deacetylation in bacterial infection. *Science*. 2013;341:1238858
27. Pais TF, Szego EM, Marques O, Miller-Fleming L, Antas P, Guerreiro P, et al. The nad-dependent deacetylase sirtuin 2 is a suppressor of microglial activation and brain inflammation. *EMBO J*. 2013;32:2603-2616
28. Kobayashi Y. How to manage various arrhythmias and sudden cardiac death in the cardiovascular intensive care. *J Intensive Care*. 2018;6:23
29. Frangogiannis NG. The inflammatory response in myocardial injury, repair, and remodelling. *Nat Rev Cardiol*. 2014;11:255-265

Figures

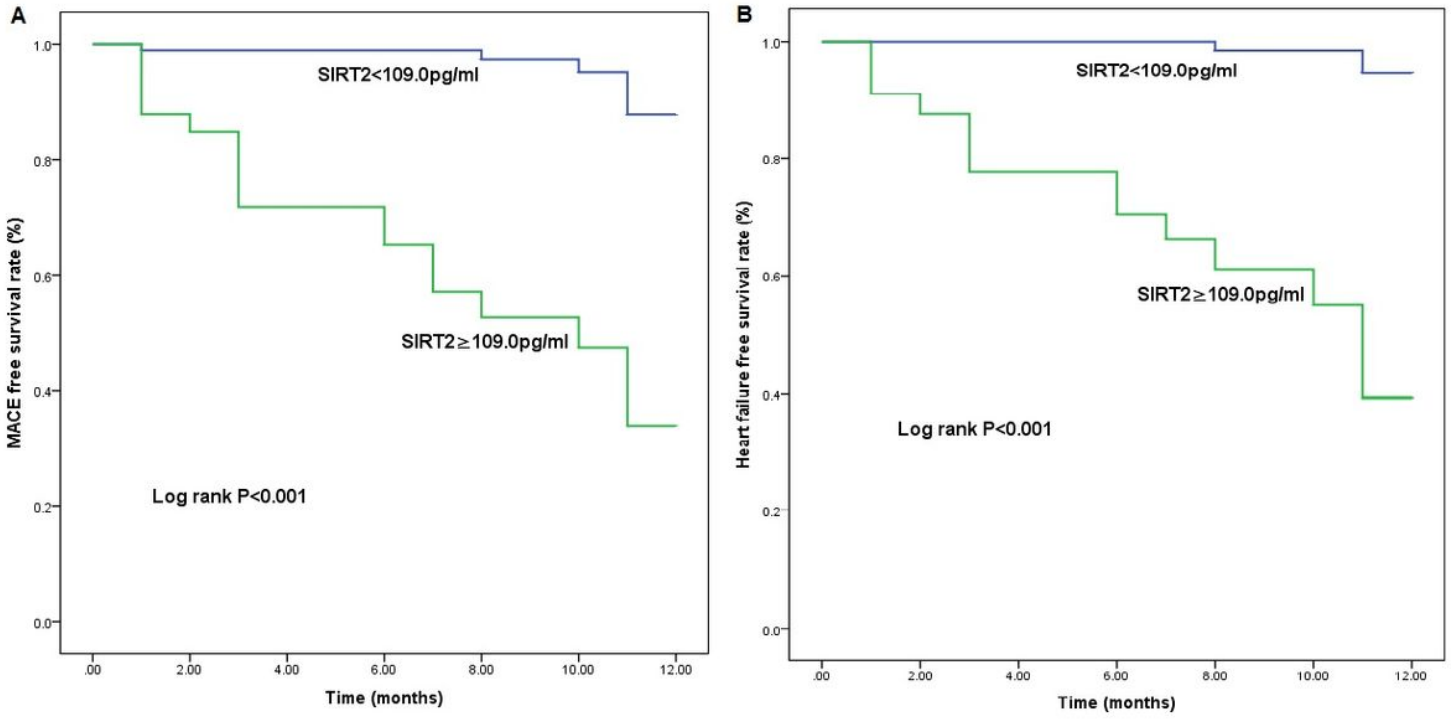

Figure 1

Kaplan-Meier curves in patients with acute myocardial infarction (AMI) with individual levels of sirtuin2 (SIRT2) during follow-up. MACE, major adverse cardiovascular events.