Diagnostic and prognostic value of autoantibodies against β_1-adrenoreceptors in patients with heart failure following acute myocardial infarction: A 5-year prospective study

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Abstract. A number of studies have suggested that autoantibodies against β_1-adrenoreceptors (β_1R-AAbs) have an important role in pathophysiological processes of heart failure. The aim of the present study was to determine whether β_1R-AAbs are implicated in cardiac dysfunction following acute myocardial infarction (AMI) and their association with prognosis. A total of 33 cases with systolic heart failure (SHF), 49 with diastolic heart failure (DHF) and 44 with normal heart function following AMI were recruited. β_1R-AAbs were detected by ELISA and major adverse cardiac events (MACEs) were recorded during the 5-year follow-up. The positive rate of β_1R-AAbs in the SHF group (45.5%) was significantly higher compared with that in the DHF (22.4%; P<0.05) and normal (15.9%; P<0.05) groups. The area under the receiver operating characteristics curve for the diagnosis of SHF was 0.630 (95% CI: 0.514-0.747, P=0.026). During a median follow-up period of 51.0±15.4 months, the positive rate of β_1R-AAbs in the MACEs group was significantly higher compared with that in the non-MACEs group (P<0.05). Multivariate logistic regression analysis indicated that the left ventricular ejection fraction and diabetes were independent predictors of 5-year MACEs following AMI, whereas β_1R-AAbs were not. Kaplan-Meier analysis revealed that the cumulative MACEs-free survival rate was the lowest in the SHF group, followed by the DHF and normal groups (P<0.05). Therefore, β_1R-AAbs were indicated to be of value for early diagnosis of SHF after AMI but not as independent predictors for the prognosis of patients with AMI.

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Introduction

Despite major medical advances in recent decades, acute myocardial infarction (AMI) remains one of the leading causes of morbidity and mortality worldwide (1). Acute heart failure (AHF) is a common serious complication of AMI. Due to its high rate of morbidity, mortality and readmission, as well as the associated costs, AHF represents a major socioeconomic challenge (2). Therefore, accurate evaluation of cardiac function in the early stage of AMI and early treatment for AHF are crucial for improving the prognosis of patients.

An autoimmune response against the myocardium may contribute to the pathogenesis of dilated cardiomyopathy (DCM), heart failure, myocarditis, rheumatic fever, idiopathic recurrent pericarditis and atherosclerosis (3,4). Autoantibodies against β_1-adrenoreceptors (β_1R-AAbs) are amongst the most important autoantibodies to cardiovascular receptors and have been proven to be associated with myocardial enlargement and cardiac dysfunction. It is currently unclear which functional effects of β_1R-AAbs are damaging to the heart during the pathogenesis of HF. The prevalence of stimulating β_1R-AAbs in healthy individuals was determined to be low (<1%) when using the screening strategy described by Jahns *et al* (5). Under physiological conditions, the majority of cardiac antigens remain hidden from the immune system, at least within the cell. However, under pathological conditions, the cardiac antigens are more exposed on the cell surface, which stimulates the production of autoantibodies. Furthermore, these autoantibodies directed against key elements on the cell surface, particularly autoantibodies that bind to and stimulate cardiac β_1-adrenoreceptors (β_1-AR), may have an important role in the initiation and/or progression of myocardial remodeling. *In vitro*, β_1R-AAbs were indicated to have a positive chronotropic and inotropic effect on cardiomyocytes (6). In addition, Gao *et al* (7) demonstrated that β_1R-AAbs promoted apoptosis in neonatal rat cardiomyocytes. It was previously demonstrated that β_1R-AAbs have an important role in the pathophysiological

process of chronic heart failure (CHF), including DCM and ischemic cardiomyopathy (ICM) (8). Furthermore, Pei *et al* (9) observed that the positive rate of β_1R-AAbs was higher in patients with chronic and systolic heart failure (SHF), which may serve as an independent prognostic factor for sudden cardiac death (SCD) in patients with CHF, including those with DCM and ICM. In addition, it has been reported that patients with DCM positive for β_1R-AAbs had a higher incidence of serious ventricular arrhythmias and a higher incidence of SCD compared to antibody-negative patients (10). However, other studies reported no association between β_1R-AAbs and the prognosis of ICM (11,12). Furthermore, studies on the changes of β_1R-AAbs in patients with acute SHF and diastolic heart failure (DHF) are scarce and the association between β_1R-AAbs and prognosis for AMI patients remains elusive.

The aim of the present study was to observe the changes in plasma β_1R-AAbs in patients with acute SHF and DHF, and explore the association between these autoantibodies and the prognosis of patients following AMI. The results may be of value for early diagnosis and improve the prognosis of patients after AMI.

Materials and methods

Study design and population. The present study included 126 consecutive patients with AMI who were admitted to Beijing Chaoyang Hospital, Capital Medical University (Beijing, China) between July and December 2012. According to the heart function after AMI, the patients were divided into three groups: Patients with SHF (n=33), with DHF (n=49) and with normal heart function (n=44) following AMI. The diagnosis of AMI was confirmed by at least two independent professional cardiologists according to the Third Universal Definition of Myocardial Infarction (13). The diagnosis of DHF was based on the presence of heart failure symptoms, with left ventricular ejection fraction (LVEF) >40% and left ventricular end diastolic volume index (LVEDVI) <97 ml/m^2, which met at least one of the following conditions: i) Peak early diastolic transmitral velocity (E)/diastolic velocities (E') >15; ii) 8<E/E'<15 and N-terminal pro-brain natriuretic peptide (NT-proBNP) >220 pg/ml; and iii) E/E'>8 with E/late diastolic transmitral velocity (E/A)<0.5, in combination with left atrial volume index (LAVI) ≥40 ml/m^2 or left ventricular mass index ≥149 g/m^2 for males and ≥122 g/m^2 for females (14). The definition of SHF was the presence of HF symptoms, with a reduction of LVEF <40%, according to current guidelines of the European Society of Cardiology (15).

The criteria for exclusion included any of the following conditions: i) Mechanical complications after AMI, including free wall rupture, ventricular septal perforation and papillary muscle rupture; ii) cardiogenic shock; iii) cardiomyopathy and valvular heart disease; iv) severe hepatic and renal dysfunction (alanine aminotransferase ≥3 times the upper limit of normal and serum creatinine ≥3 mg/dl); v) terminal disease (e.g., terminal cancer) with an estimated survival time of <1 year; and vi) poor echocardiographic imaging results.

Routine clinical assessment. All patients enrolled in the present study underwent coronary angiography and 86 patients underwent percutaneous coronary intervention successfully, while 8 patients underwent coronary artery bypass grafting. All participants were subjected to physical examinations and answered a standardized questionnaire to assess their medical history, current illness and intake of any medications. After being admitted to the hospital, all patients received standard coronary secondary prevention (including aspirin, clopidogrel, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β-blockers and statins, unless these agents were contraindicated). All of the baseline information was carefully recorded.

Measurement of β_1R-AAbs. Blood samples were collected from the antecubital vein using tubes containing EDTA within 24 h after the patients were admitted to the Cardiac Care Unit. Within 2 h of collection, the samples were centrifuged at 2,000 x g at 4˚C for 10 min. Plasma samples were stored at -80˚C for analysis.

After blood sample collection was completed in December 2012, the β_1R-AAbs were detected in the patients' plasma using a synthetic peptide corresponding to the sequence of the second extracellular loop of the human β_1 receptor (amino acid sequence number, β_1:197-222:H-W-W-R-A-E-S-D-E-A-R-R-C-Y-N-D-P-K-C-C-D-F-V-T-N-R) by ELISA.

The peptide was synthesized using the Merrifield solid-phase method by the Biological Institute of the Chinese Academy of Medical Sciences & Peking Union Medical College. The purity of the peptides was determined by high-pressure liquid chromatography on the automatic amino acid analyzer (Beckman Instruments, Inc.). The procedures of ELISA were performed as previously described by Nagatomo *et al* (16). The corresponding curves were used to measure the sensitivity and specificity of the ELISA, for positive and negative samples. All of the samples were measured twice by ELISA to ensure the reliability of the results. The intra- and inter-assay coefficient of variation was no >5%. The optical density (OD) values were measured using a microplate reader (Molecular Devices LLC) and the positive rate was determined with positive/negative [P/N=(sample OD-blank OD)/blank OD]≥2.1 according to a widely used method (9,17,18).

Assessment of heart function. All of the patients underwent routine echocardiographic examination within 48 h after admission with the use of a ultrasound device (Vivid5; GE Healthcare). Standard transthoracic echocardiography was based on the recommendations of the American Society of Echocardiography (ASE) guidelines (19). All studies were performed by an experienced sonographer and interpreted by an experienced physician.

Left atrial diameter, left ventricular end-systolic diameter, left ventricular end-diastolic diameter and posterior wall thickness were measured using M-mode tracing. Two-dimensional (2D) imaging was performed in standard parasternal, apical four- and two-chamber views. LVEF, LAVI, LVEDVI and left ventricular end-systolic volume were measured according to the biplane Simpson's method and then indexed to body surface area. According to the ASE formula (19), LVM was calculated by 2D liner LV measurements.

E and A were determined by pulse wave Doppler imaging. E and E' of the septal wall at the level of the mitral annulus

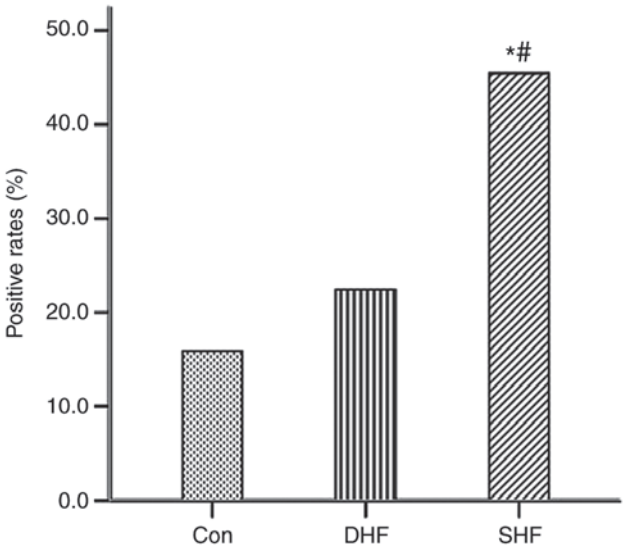

Figure 1. Positive rate of β1R-AAbs among the different groups. The β1R-AAbs positive rate following AMI was significantly higher in the SHF group compared with that in the DHF group and the normal heart function group following AMI. *P<0.05 vs. DHF group; #P<0.05 vs. normal heart function group following AMI. AMI, acute myocardial infarction; SHF, systolic heart failure; DHF, diastolic heart failure; β1R-AAbs, autoantibodies against β1-adrenoreceptors; con, control.

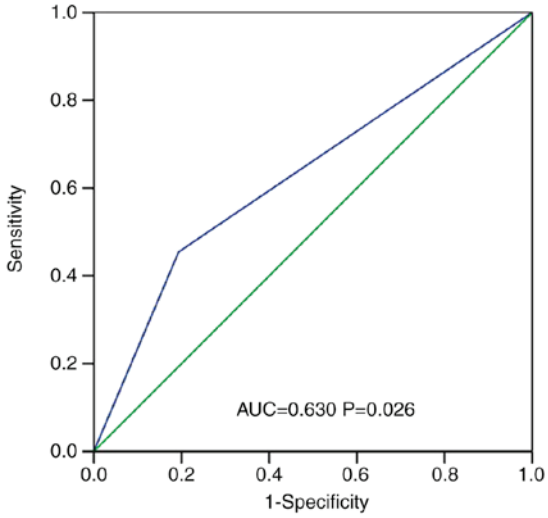

Figure 2. Diagnostic accuracy of β1R-AAbs quantified by a ROC curve. The β1R-AAbs to identify patients with systolic heart failure following acute myocardial infarction was 0.630 (95% CI: 0.514-0.747, P=0.026). ROC, receiver operating characteristic; AUC, area under ROC curve; β1R-AAbs, autoantibodies against β1-adrenoreceptors; con, control.

in the apical 4C view were recorded by pulse wave tissue Doppler. The E/A ratio and E/E' ratio were calculated.

Follow-up and endpoint events. Each patient was assigned to a designated study investigator and patients were followed up in the first and fifth year, or until the primary endpoint after initiation of the study. The patients were followed up via outpatient visits or telephone between January 2013 and January 2018. The primary endpoint events were a composite of MACEs, including AMI, stroke, rehospitalization for HF and death. All of the endpoint events were reviewed by members of an independent committee, who were unaware of the contents of the study and used pre-specified criteria.

Statistical analysis. Values are expressed as the mean ± standard deviation of continuous variables, while categorical variables are expressed as numbers and percentages. Continuous variables were compared with the Kruskal-Wallis test and Dunn's test was used as a post-hoc test following the Kruskal-Wallis test for comparing between two groups. Pearson's χ^2 test was used for categorical variables. Receiver operating characteristics (ROC) curves were constructed to evaluate the sensitivity and specificity of all detection methods and evaluate their ability to diagnose SHF after AMI. The association between the risk of MACEs and the cardiovascular risk factors was assessed by univariate and multivariate logistic regression. The results are expressed as the univariate odds ratio (OR) with 95% CI and the OR was then adjusted for age, sex, hypertension, dyslipidemia, obesity, diabetes and smoking to assess the interdependence of the autoantibodies and traditional cardiovascular risk factors. The effects of these predictors on incidence for MACEs over 5 years were analyzed using Kaplan-Meier survival curves. All tests were two-tailed and P<0.05 was considered to indicate a statistical significance. All statistical analyses were performed using IBM SPSS Statistical software for Windows 22.0 (IBM Corp.).

Results

Clinical, hemodynamic and medical characteristics at baseline. The baseline characteristics of the patients of the present study are provided in Table I. The heart rate was faster in patients with SHF after AMI compared with that in patients with DHF of normal heart function after AMI (P<0.001). Renal function was worse in patients with SHF compared with that in the other two groups (P<0.05). Patients with SHF after AMI were more likely to have diabetes (P=0.003). As expected, left ventricular function was more impaired in patients with SHF. A higher level of NT-proBNP and a lower LVEF value were present in patients with SHF (P<0.05). Regarding the other characteristics, there were no differences in age, sex, systolic blood pressure, hypertension, hyperlipidemia, smoking, type of AMI, revascularization, cTnI and medication among the three groups (P>0.05).

β_1R-AAbs for early diagnosis of SHF after AMI. The positive rates of β_1R-AAbs were 15/33 (45.5%) in the SHF group, 11/49 (22.4%) in the DHF group and 7/44 (15.9%) in the group with normal heart function after AMI. The positive rates of β_1R-AAbs were significantly higher in patients with SHF compared with those in patients with other diagnoses (P<0.05), but there was no significant difference between the DHF and normal heart function groups (P>0.05), as presented in Fig. 1.

Univariate and multivariate logistic regression was used to assess whether β_1R-AAbs acted synergistically with other factors, including age, sex, hypertension, dyslipidemia, obesity, diabetes and smoking. β_1R-AAbs positivity was significantly associated with an increased incidence of SHF after AMI on univariate analysis (OR3.472; 95% CI: 1.474-8.179, P=0.004), and this association was also statistically significant following adjustment for the traditional cardiovascular risk factors mentioned above (OR=4.791; 95% CI: 1.765-13.000, P=0.002).

Table I. Baseline data of the study population.

Variable	Normal	DHF	SHF	P-value
Age (years)	63.3±7.9	66.9±11.1	67.9±13.6	0.063
Male sex	34 (77.3)	30 (61.2)	22 (66.7)	0.246
BMI (kg/m^2)	25.5±2.9	25.5±2.4	25.9±2.9	0.749
Heart rate (bpm)	73.4±11.0	71.3±11.9	87.2±16.4[a,b]	<0.001
SBP (mmHg)	123.3±17.4	133.3±24.6	128.5±27.1	0.198
Risk factors				
Hypertension	23 (52.3)	34 (69.4)	25 (75.8)	0.073
Hyperlipidemia	13 (29.5)	8 (16.3)	9 (27.3)	0.282
Diabetes	4 (9.1)	19 (38.8)	12 (36.4)	0.003
Smoking	19 (43.2)	21 (42.9)	13 (39.4)	0.936
Type of AMI				
STEMI	27 (61.4)	30 (61.2)	20 (60.6)	0.362
Anterior	15	19	13	
Inferior	4	3	2	
Inferior+right ventricle	6	5	3	
Inferior+posterior	3	3	2	
NSTEMI	17 (38.6)	19 (38.8)	13 (39.4)	0.362
Revascularization				
PCI	32 (72.7)	35 (71.4)	19 (57.6)	0.306
CABG	1 (2.3)	3 (6.1)	4 (12.1)	0.214
Medication				
Aspirin	43 (97.7)	48 (98.0)	30 (90.9)	0.070
β-blockers	31 (70.5)	32 (65.3)	24 (72.7)	0.752
ACEI/ARB	19 (43.2)	30 (61.2)	18 (54.5)	0.216
Statin	37 (84.1)	45 (91.8)	27 (81.8)	0.362
Heart function				
LVEF (%)	61.0±10.6	57.6±7.7	35.1±7.6[a,b]	<0.001
NT-ProBNP (mg/dl)	160.3±149.8	1510.3±2028.5[c]	4092.0±4250.5[a,b]	<0.001
Blood parameters				
Cr (μmol/l)	83.2±14.7	93.2±36.8	104.9±41.8[a]	0.014
UA (μmol/l)	317.8±81.7	308.2±105.8	333.0±115.4	0.572
cTnI (ng/ml)	21.7±36.0	35.5±71.9	45.8±67.6	0.468

[a]P<0.05, SHF vs. normal group; [b]P<0.05, SHF vs. DHF group; [c]P<0.05, DHF vs. normal group. Values are expressed as n (%), mean ± standard deviation. SHF, systolic heart failure; DHF, diastolic heart failure; BMI, body mass index; SBP, systolic blood pressure; NSTEMI, non-ST-segment elevation acute myocardial infarction; PCI, percutaneous transluminal coronary intervention; CABG, coronary artery bypass grafting; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor antagonist; LVEF, left ventricular ejection fraction; NT-ProBNP, N-terminal-pro brain natriuretic peptide; Cr, creatinine; UA, uric acid; cTnI, cardiac troponin I.

ROC curve analyses indicated that β_1R-AAbs exhibited good accuracy for the diagnosis of SHF after AMI, with an area under the curve of 0.630 (95% CI: 0.514-0.747, P=0.026), as presented in Fig. 2.

Prognostic value of β_1R-AAbs for MACEs during 5-year follow-up. During the mean follow-up period of 51.0±15.4 months, 4/126 (3.2%) patients were lost in the fifth year. MACEs were observed in 19/30 β_1R-AAbs-positive patients (63.3%) and in 38/92 β_1R-AAbs-negative patients (41.3%); the difference between these two groups was statistically significant (P=0.036). On univariate analysis, antibody-positive status was a predictive factor for MACEs in patients following AMI (OR=2.455; 95% CI: 1.048-5.747, P=0.039). The univariately predictive variables for MACEs of patients with different heart function after AMI are provided in Table II. On multivariate logistic regression analysis, LVEF and diabetes were identified as independent predictors of 5-year primary endpoints following AMI, but β_1R-AAbs-positive status was not an independent predictive factor, as presented in Table II.

The adjusted Kaplan-Meier curves for MACEs in patients following AMI are depicted in Fig. 3. Patients with SHF had the worst 5-year prognosis among the three groups (P<0.001; Fig. 3A). The 5-year prognosis was significantly worse in patients with diabetes compared with that in patients without diabetes (P<0.05; Fig. 3B). No significant difference was

observed in the 5-year prognosis between the antibody-positive and -negative groups (P>0.05; Fig. 3C).

Discussion

The present single-center prospective study evaluated the diagnostic and prognostic value of autoantibodies that bind to and stimulate the human β_1-AR in acute SHF, DHF and normal heart function patients following AMI. The most important results were as follows: First, the positivity rates of β_1R-AAbs were higher in patients with SHF after AMI compared with those in patients with DHF and normal heart function after AMI, but there was no difference between the DHF and normal groups. Furthermore, β_1R-AAbs may be a factor for identifying patients with acute SHF after AMI. In addition, positivity for β_1R-AAbs appeared to be associated with MACEs, but was not an independent predictor for the prognosis of AMI patients, while a decreased LVEF and diabetes were determined to be independent predictors.

Over the past 30 years, the autoimmune mechanisms involved in cardiovascular disease have attracted extensive attention. In 1989, Limas *et al* (20) discovered a substance in the serum of patients with DCM that was able to inhibit ligand binding to a β-AR distributed on myocardial cells of rats, which was suspected to be an antibody. This substance was later proven to be a β_1R-AAb. β_1R-AAbs have been reported to be a common target for CHF caused by several autoantibody-associated diseases, including DCM, Chagas disease and atrial fibrillation (21-23). Previous studies by our group indicated that, in patients with CHF arising from different causes, the positive rates of β_1R-AAbs were all significantly higher compared with those of healthy subjects and were associated with the severity of CHF (24,25). In an animal study, Matsui *et al* (26) used synthetic peptides corresponding to the sequence of the second extracellular loop of either the human β_1R or M_2R to immunize rabbits monthly for 1 year, and these peptides induced a marked enlargement of the ventricles with thinning of the walls, identical to the changes of DCM in humans. These results suggested that the levels of β_1R-AAbs did not depend on the diseases leading to HF, but rather on the pathogenesis of HF itself. Based on the above-mentioned results, the changes of β_1R-AAbs in patients with acute SHF and DHF were investigated by our group, which have been rarely reported to date, to the best of our knowledge. The mechanism of β_1R-AAbs induction is currently unknown, but it may either be due to the molecular mimicry between AR and specific antigens or induced by exposure of autoantigens to the immune system (27). Furthermore, it is unknown whether certain patients have immune disorders or genetic defects that make them more likely to produce β_1R-AAbs, all of which require further investigation.

Previous studies on β_1R-AAbs have focused on patients with chronic SHF (11,28,29), but this has remained to be assessed in acute SHF, to the best of our knowledge. The present study demonstrated that the positive rates of β_1R-AAbs were higher in patients with SHF following AMI compared with those with DHF and normal heart function, while there was no difference between the DHF and normal function groups. In the present study, systolic cardiac insufficiency after AMI was considered as acute cardiac insufficiency, characterized by the decrease in LVEF due to AMI. The results suggested that β_1R-AAbs may participate in the pathogenesis of acute SHF and cause myocardial damage and decreased heart function. However, this is a hypothesis and it is not clear whether the autoantibodies in heart disease are due to an improper autoimmune response following heart injury, or if there is an increase in primary autoantibodies without obvious cause or damage to the heart. To the best of our knowledge, the present study was the first to demonstrate that the presence of stimulating β_1R-AAbs affects the development of acute SHF.

Previous studies on β_1R-AAbs mainly focused on chronic SHF, but there are no reports on β_1R-AAbs in DHF during the early stages of AMI. In the present study, the level of β_1R-AAbs in patients with DHF in the early stage of AMI was examined. The results demonstrated that the rate of β_1R-AAbs positivity in the DHF group was not significantly different from that in the normal heart function group, suggesting that β_1R-AAbs were not involved in the occurrence and development of DHF. The reason may be that DHF is a compensatory condition in which the left ventricle may increase in size to obtain normal ventricular filling and cardiac volume. Its characteristics are decreased left ventricular volume and increased end-diastolic pressure, with normal or slightly decreased LVEF (30). β_1R-AAbs appear to mainly affect the myocardial structure and function, leading to a decrease in, rather than just pressure changes.

The mechanisms by which β_1R-AAbs affect cardiomyocytes, resulting in adverse cellular effects, are complex and remain to be fully elucidated. Low concentrations of β_1R-AAbs were also determined in healthy subjects as a product of natural immunity. Under pathological conditions, functional β_1-ARs are easily accessible targets localized on the cell surface and the harmful potential of autoantibodies depends on the significance of their targeting function (31). β_1R-AAbs have been indicated to activate adenylate cyclase and then moderately elevate second messenger cyclic AMP (32). In addition, it was observed that β_1R-AAbs, similar to isoproterenol receptor agonists, activate protein kinase A to phosphorylate several phosphoproteins in the cells (33). Prolonged overstimulation of β_1-ARs may lead to deterioration in heart function and the underlying mechanism is considered to be the induction of apoptosis by T-lymphocytes (34). β_1R-AAbs exerted pro-apoptotic effects with increased generation of phenyl glycidyl ether. Comparatively, xamoterol is a true β_1-AR agonist, mimicking the effects of autoantibodies on atrial apoptosis in rats (35). Furthermore, β_1R-AAbs may prolong the action potential duration and increase the L-type Ca^{2+} current from the extracellular compartment to the cytosol (36). Ca^{2+} overload may be induced by permanent β_1-AR stimulation and a continuous receptor-associated signaling cascade, leading to cell apoptosis and death (37). The above-mentioned processes are biologically plausible mechanisms by which β_1R-AAbs may lead to acute SHF following AMI. β_1R-AAbs may exert an 'agonist activity' on their target receptors, leading to myocardial damage and cardiac dysfunction.

The prognostic value of β_1R-AAbs was also assessed, particularly for DCM. Störk *et al* (11) indicated that stimulation of β_1R-AAbs was an independent risk factor for all-cause and cardiovascular mortality risk in DCM over a follow-up period of >10 years. In line with this, another study reported that higher levels of β_1R-AAbs had a negative impact on the prognosis of patients with DCM (38), as they were associated

Table II. Univariate and multivariate predictors of 5-year major adverse cardiac events.

	Univariate			Multivariate		
Factor	OR	95% CI	P-value	OR	95% CI	P-value
β_1R-AAbs	2.455	1.048-5.747	0.039	0.877	0.248-3.094	0.838
Heart rate (bpm)	1.027	1.001-1.054	0.042	0.987	0.950-1.206	0.509
Diabetes	2.776	1.219-6.321	0.015	2.641	1.105-6.311	0.029
LVEF (%)	0.950	0.921-0.979	0.001	0.951	0.922-0.981	0.001
NT-proBNP (mg/dl)	1.000	1.000-1.001	0.005	1.036	0.984-1.022	0.150
Cr (μmol/l)	1.016	1.003-1.028	0.015	0.996	0.978-1.015	0.706

β_1R-AAbs, autoantibodies against β_1-adrenoreceptors; LVEF, left ventricular ejection fraction; NT-ProBNP, N-terminal-pro brain natriuretic peptide; Cr, creatinine; OR, odds ratio.

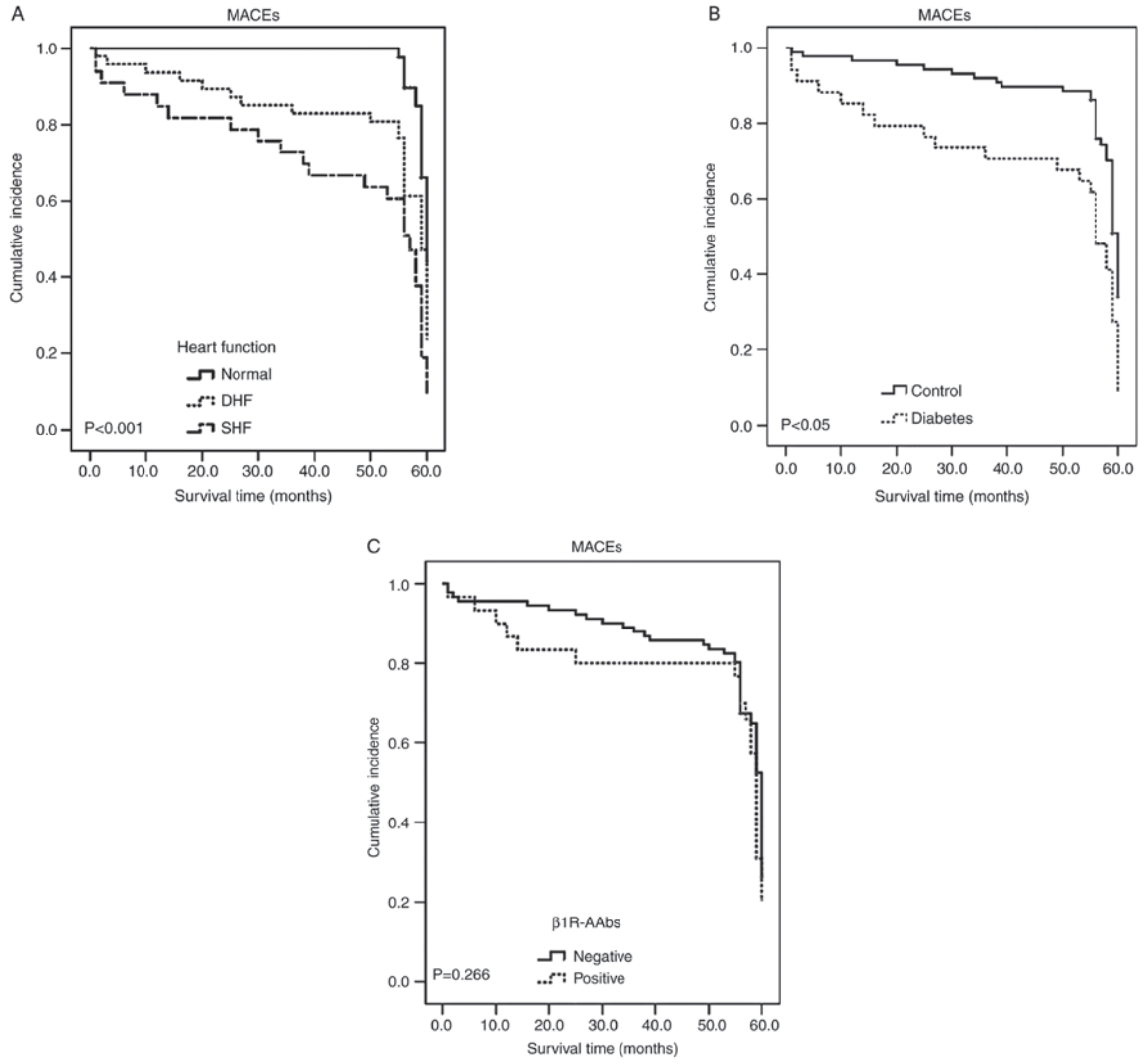

Figure 3. Kaplan-Meier curves for MACEs in patients with AMI. (A) Comparison of SHF, DHF and normal heart function groups. The patients with SHF had the worst 5-year prognosis among the three groups. (B) Comparison of diabetic and non-diabetic patients with SHF, DHF and normal heart function. The patients with diabetes had a worse prognosis than those without diabetes. (C) Comparison of antibody-positive and antibody-negative patients with AMI. The antibody status had no significant impact on the 5-year prognosis. SHF, systolic heart failure; DHF, diastolic heart failure; β1R-AAbs, autoantibodies against β1-adrenoreceptors; AMI, acute myocardial infarction; MACEs, major adverse cardiac events.

with a higher risk of ventricular arrhythmias and SCD. It has also been reported that the survival rate of patients with CHF significantly deteriorated if β_1R-AAbs >10 U/ml (39). Although β_1R-AAbs are more common in patients with DCM, they may

also be detected in patients with ICM. By contrast, they were not associated with the prognosis of patients with ICM. In the present study, lower LVEF and the presence of diabetes in patients following AMI were determined to be independent predictors of 5-year prognosis, but β_1R-AAbs were not independent predictors for MACEs during the 5-year follow-up of these patients. In addition, for the 40 patients with ICM (5 of whom tested positive for stimulated β_1R-AAbs), the presence of stimulated β_1R-AAbs was not associated with an increased risk of all-cause mortality or cardiovascular-associated mortality during a 10-year follow-up (11), which was expected, as the prognosis of patients with ICM may be affected by other factors, including LVEF, rather than immunological risk factors. However, since the number of patients in the present study was small, it cannot be excluded with certainty that β_1R-AAbs do not influence the prognosis in ICM.

Several limitations should be taken into account when interpreting the results of the present study. First, as in all case-control studies, there was a possibility of selection bias. Furthermore, the results may be biased, as the sample size of the present study was small. An analysis with a larger sample size is required to confirm the present results. In addition, while the association between β_1R-AAbs and SHF after AMI was biologically reasonable, it should be pointed out that the association was not necessarily causal. Further studies are required to elucidate the causal role of these autoantibodies in SHF. In addition, using β_1R-AAbs alone as a diagnostic factor may be not accurate. In the future, β_1R-AAbs will be combined with other diagnostic factors to further comprehensively predict the occurrence of HF after AMI. Finally, only serum β_1R-AAbs were detected. Further studies on the biological activities of autoantibodies, as well as their receptors, in the plasma and myocardium are required.

In conclusion, the present study indicated that levels of β_1R-AAbs were significantly increased in patients with acute SHF after AMI. However, the presence of β_1R-AAbs was not an independent prognostic factor of MACEs in patients following AMI. In conclusion, β_1R-AAbs may be of value for early diagnostic of SHF in patients after AMI, but they are not independent prognostic factors in such patients.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding authors on reasonable request.

Authors' contributions

XW was responsible for drafting the manuscript and revising it critically for important intellectual content, and made substantial contributions to analysis of data. MH and SH were responsible for performing the study and the data analysis. YZ and XX were responsible for collection of patient and laboratory data, data interpretation and revision of the manuscript regarding content. YW and CD performed the ELISA for β_1R-AAbs. JZ and HW performed the echocardiographic examination. JL and DH were responsible for patient follow-up. MC and LZ conceived and designed the study and were responsible for performing data collection, analysis and interpretation. WZ and LX have substantial contributions to conception and design of our study, analysis and interpretation of data, and giving final approval of the version to be published. All authors read and approved the final version of the manuscript for publication.

Ethics approval and consent to participate

The present study was performed in compliance with the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee and the Prescription and Therapeutic Committee of Beijing Chao-Yang Hospital, Capital Medical University (Beijing, China). All the patients provided written informed consent prior to enrolment.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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