Age, creatinine clearance, and ejection fraction (mACEF) score predicts long-term cardiac mortality in patients with hypertrophic obstructive cardiomyopathy treated non-invasively

Jun Gao[1, 2, #], Chunli Shao[3, #], Wenyao Wang[3, #], Xiangbin Meng[1, 4, #], Kuo Zhang[3], Jingjia Wang[3], Mingqi Zheng[2], Yi-Da Tang[1]

[1]Department of Cardiology, Peking University Third Hospital; Beijing-*China*
[2]Heart Center, The First Hospital of Hebei Medical University; Shijiazhuang-*China*
[3]Department of Cardiology, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College; Beijing-*China*
[4]Central China Fuwai Hospital; Central China Branch of the National Cardiovascular Center; Department of Cardiology, Zhengzhou University People's Hospital; Henan Provincial People's Hospital; Zhengzhou-*China*

Abstract

Objective: Presently, an effective model to predict long-term cardiac mortality in patients with hypertrophic obstructive cardiomyopathy (HOCM) is lacking. Therefore, the objective of this study was to evaluate the predictive value of the modified Age, Creatinine clearance, and Ejection Fraction (mACEF) score for long-term cardiac mortality in patients with HOCM.

Methods: Two hundred and ninety two patients with HOCM treated non-invasively were enrolled in this study, all of whom had intact medical information.

Results: Over a median follow-up period of 41.9 months, 28 cardiac deaths occurred. In univariate Cox regression analysis, the mACEF score was associated with long-term cardiac death [hazard ratio (HR)=1.795, 95% confidence interval (CI) 1.518–2.124, p<0.001]. Multiple Cox regression analysis identified the mACEF score as an independent risk factor for long-term cardiac death (adjusted HR=1.372, 95% CI 1.076-1.749, p=0.011). Analysis of the receiver operating characteristic (ROC) for long-term cardiac death showed that the mACEF score had a considerable predictive value (area under ROC 0.844, sensitivity 89.29%, specificity 75.00%) with an optimum cut-off value of 0.96. The study population was divided into high-risk (mACEF score ≥0.96, n=91) and low-risk (mACEF score <0.96, n=201) groups according to the optimum cut-off value. Kaplan-Meier survival analysis was performed and showed a dramatic higher rate of long-term cardiac mortality in the high-risk group than in the low-risk group (27.4% vs. 1.7%, p<0.001 by log-rank test).

Conclusion: The mACEF score has a considerable predictive value for long-term cardiac mortality in patients with HOCM treated non-invasively. A mACEF score ≥0.96 could be considered as a sign of poor prognosis in patients with HOCM.

Keywords: hypertrophic obstructive cardiomyopathy, cardiac, mortality, risk factor, prognosis

Cite this article as: *Gao J, Shao C, Wang W, Meng X, Zhang K, Wang J, et al. Age, creatinine clearance, and ejection fraction (mACEF) score predicts long-term cardiac mortality in patients with hypertrophic obstructive cardiomyopathy treated non-invasively. Anatol J Cardiol 2021; 25: 691-8.*

Introduction

Hypertrophic obstructive cardiomyopathy (HOCM) is one of the most common monogenetic heart diseases characterized by unexplained left ventricular wall hypertrophy and left ventricular outflow tract (LVOT) obstruction (occurring in approximately 37% patients with hypertrophic cardiomyopathy) (1, 2). Patients with HOCM are at increased risk of heart failure, sudden cardiac death, and atrial fibrillation with a lower life expectancy.

A rapid and effective risks stratification method plays an important role in the management of HOCM. Presently, the HCMrisk-SCD model, which is recommended by the 2014 European Society of Cardiology (ESC) guideline, is the most widely used method of sudden cardiac risk stratification in patients

#These authors were the most frequently contributors.
Address for Correspondence: Yi-Da Tang, MD, Department of Cardiology, Peking University Third Hospital, No. 49 Huayuanbei Road, Beijing-*China*
Phone: 86-10-88396171 E-mail: drtangyida@126.com

Accepted Date: 05.04.2021 **Available Online Date:** 20.09.2021

DOI:10.5152/AnatolJCardiol.2021.50322

Anatol J Cardiol 2021; 25: 691-8
DOI:10.5152/AnatolJCardiol.2021.50322

HIGHLIGHTS

- Presently, an effective model to predict long-term cardiac mortality in patients with hypertrophic obstructive cardiomyopathy (HOCM) is lacking.
- The modified age, creatinine clearance, and ejection fraction (mACEF) score has a considerable predictive value for long-term cardiac mortality in patients with HOCM treated non-invasively.
- The mACEF score might serve as a tool for stratification of long-term cardiac death risk in patients with HOCM.

with hypertrophic cardiomyopathy (HCM). The HCMrisk-SCD model was designed to save lives from sudden cardiac death (SCD) by identifying patients who were at high risk of SCD and to avoid unnecessary implantable cardioverter defibrillators in low-risk patients. SCD is one of the main causes of cardiac death in HOCM; however, other causes such as heart failure and related multiple organ failure should not to be ignored. In addition, the equation of the HCMrisk-SCD model is extremely complex with detailed medical information, including family history, Holter monitoring result, echocardiogram indices, and even cardiac magnetic resonance (CMR) image being required (3). Thus, there is an urgent need for an efficient and simple way to identity patients with HOCM at high risk of cardiac death.

The age, creatinine, and ejection fraction (ACEF) score, a simple risk assessment tool, is calculated using only three variables (4) and was first developed to predict perioperative mortality in patients undergoing elective cardiac surgery. The modified ACEF (mACEF) score was remodeled using creatinine clearance instead of creatinine (5), which provided a better predictive accuracy in cardiac operations (6-8). Actually, age, creatinine clearance rate, and left ventricular ejection fraction are the three most common prognostic markers in heart diseases. Therefore, in this study, we sought to evaluate the feasibility, effectiveness, and accuracy of the mACEF score to predict cardiac mortality in patients with HOCM on non-invasive treatment.

Methods

Ethics statement

The study was conducted in full compliance with the Declaration of Helsinki and China's regulations and guidelines on clinical practice. The Ethics Committee of Fuwai Hospital approved this study (Ethics Approval # 2015-700) with waiver of informed consent.

Study participants

This was a prospective, single-center cohort study. All the patients in this study were enrolled at the Fuwai Hospital (National Center of Cardiovascular Diseases, Beijing, China). The flowchart of inclusion and exclusion is shown in Figure 1.

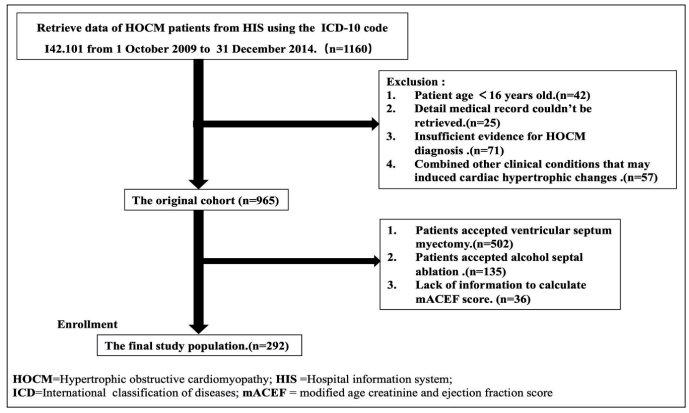

Figure 1. Flowchart of patient inclusion

A total of 965 adult patients with HOCM (age >16 years) were enrolled. Of these patients, 502 underwent ventricular septal myectomy, 135 had alcohol septal ablation (with two ICD implantations after the operation), and 36 patients lacked the data to calculate mACEF score; and all these patients were excluded. The remaining 292 patients with complete clinical information, medical history, and calculated mACEF score were enrolled in the study. All the enrolled patients were without any other cardiac or systemic diseases, inducing cardiac hypertrophic changes (such as uncontrolled hypertension or congenital heart disease, etc.).

Data collection and definitions

Clinical data were collected through the review of the medical records. Blood samples were obtained during hospitalization regularly. Cockcroft-Gault equation was used to calculate creatinine clearance (9). The mACEF was obtained from following equation: age/ejection fraction (%) + 1 point (for every 10 mL/min reduction in creatinine clearance below 60 mL/min/1.7 m^2) (10).

The diagnosis of HOCM was based on the following criteria (3); wall thickness ≥15 mm in one or more left ventricular myocardial segments as measured by any imaging technique (echocardiography, cardiac magnetic resonance imaging, or computed tomography) or wall thickness 13 to 14 mm with family history, noncardiac symptoms and signs, electrocardiogram abnormalities, laboratory tests, and multimodality cardiac imaging; and patients with dynamic left ventricular outflow tract (LVOT) obstruction with an LVOT gradient ≥ 30 mm Hg at rest or during physiological provocation, such as Valsalva maneuver, standing, and exercise. Significant dynamic LVOT obstruction was documented with two-dimensional and Doppler echocardiography; or in patients in whom echocardiography was insufficient, via invasive hemodynamic catheterization with provocation. Atrial fibrillation (AF) was defined as patients with a history of paroxysmal, persistent, or permanent atrial fibrillation with documented ECG or Holter that showed AF. Ventricular tachycardia (VT) was defined as a run of ≥4 consecutive ventricular premature beats documented by ECG or Holter.

Follow-up and clinical outcomes

Follow-up began at the time of first patient clinical contact after October 01, 2009, in Fuwai Hospital. Follow-up data were collected from the record of outpatient clinic visit, phone calls, or medical records on readmission. The primary endpoint was general cardiac death. Cardiac death was defined as death because of heart failure, sudden cardiac death, cardiogenic shock, or multiorgan failure owing to cardiac causes. The unwitnessed death and death of unknown causes were also classified as cardiac death.

The patients lost to follow-up were censored at the last known contact date.

Statistical analysis

The data was analyzed using Statistical Package for the Social Sciences version 26 for MACOS and Med-Calc version 16. 8. 4. Descriptive statistics were used to summarize baseline characteristics. Categorical variables were analyzed using the chi-squared or Fisher exact tests. Normality of all variables was tested with one sample Kolmogorov-Smirnov normality test. Normally distributed continuous variables were presented as means ± standard deviation and analyzed by student's t test, and non-normal continuous variables were presented as median (lower quartile, upper quartile) and analyzed using Mann-Whitney U test. Putative risk factors of cardiac death were identified with univariate and multiple analyses with the Cox proportional hazards model to estimate hazard ratio (HR) with 95% confidence intervals (CIs). Baseline covariates identified by univariate analysis and clinical relevance were included in the multiple analysis, and an entry criterion p value of 0.1 was used. Discrimination was measured using the area under the receiver operating characteristic curve (AUROC). Comparison of ROC curve was done using DeLongs test performed by MedCalc version 16. 8. 4. Estimate of survival between high and low levels of mACEF were analyzed with the Kaplan-Meier method, and the comparison between the two groups was done using the log-rank test. A p value <0.05 was considered statistically significant.

Result

Baseline clinical characteristics

The baseline clinical characteristics are listed in Table 1. Of the total study population, 59.5% were men with a mean age of 54.86 years. The median follow-up time was 41.9 months. During follow-up, cardiac death occurred in 28 (9.5%) patients. Patients who died were found to be older with poor renal function (higher serum creatinine and lower creatinine clearance rate). These patients also had significantly higher high-sensitivity C-reactive protein (hs-CRP) and lower hemoglobin concentration. Among echocardiogram indices, LVOT gradient and left ventricular ejection fraction (LVEF) were significantly lower and the diameter of the left atrium was higher in patients with cardiac death than in those free from cardiac death. The mACEF score was also found to be significantly higher in patients with cardiac death. In addition, higher incidences of AF and worsening heart function classification [New York Heart Association (NYHA) functional class III or IV] were found in patients with cardiac death. However, the association between the presence of VT and cardiac death was not significant (chi-squared test, p=0.604).

Modified age, creatinine clearance, and ejection fraction score and cardiac death

The association of clinical indices with cardiac death was calculated using univariate Cox regression (left part of Table 2). The mACEF score was found to be associated with long-term cardiac mortality (unadjusted HR=1.795; 95% CI 1.518–2.124; p<0.001). Other 13 variables were also identified as putative risk factors for long-term cardiac mortality according to univariate Cox regression analysis. Beside age, serum creatinine, and LVEF, which were the components of the formula of mACEF; all putative factors were put into the multivariate Cox regression analysis. The mACEF score remained an independent predictor for long-term cardiac mortality in HOCM (HR=1.372; 95% CI 1.076–1.749; p=0.011; right part of Table 2). In addition, hs-CRP (HR=1.122; 95% CI 1.041–1.210; p=0.003), presence of atrial fibrillation (HR=3.185; 95% CI 1.396–7.265; p=0.006), and NYHA heart function classification III-IV (HR=1.563; 95% CI 1.108–2.205; p=0.011) were also found to be independent risk factors of long-term cardiac death.

Predictive value of the modified age, creatinine clearance, and ejection fraction score

ROC curve was performed to evaluate the predictive value of the score. As a result, the mACEF score demonstrated an excellent predictive value with AUROC of 0. 844 (95% CI 0.797–0.883; sensitivity 89.29%; and specificity 75.0%), and the optimum cut-off value was 0.96 (Fig. 2). AUROC of hs-CRP, atrial fibrillation, and NYHA heart function classification III-IV was 0.764, 0.639, and 0.687, respectively. The predictive value of mACEF score was significantly higher than that of AF and NYHA heart function III-IV. Although statistically significance difference was not found, AUROC of mACEF was numerically higher than that of hs-CRP (0.844 vs. 0.764, p=0.215) (Fig. 3).

Survival analysis of the modified age, creatinine clearance, and ejection fraction score in long-term cardiac death

The study population was divided into high-risk (mACEF score ≥0.96, n=91) and low-risk (mACEF score <0.96, n=201) groups according to the optimum cut-off value. The Kaplan-Meier survival analysis was performed and showed a dramatic higher rate of long-term cardiac death in the high-risk group than in the low-risk group (27.4% vs. 1.7%, p<0.001 by log-rank test, Fig. 4).

Discussion

This study was the first to validate the use of mACEF score in HOCM and found a significant association between mACEF score and cardiac mortality during long-term follow-up. Our findings suggested that the mACEF score could be considered as an effective tool for risk stratification in HOCM.

Anatol J Cardiol 2021; 25: 691-8
DOI:10.5152/AnatolJCardiol.2021.50322

Table 1. Baseline characteristics of the study population stratified by cardiac death

	Free from cardiac death (n = 264)	Cardiac death (n = 28)	Total (n = 292)	*P*-value
Demographics				
Male, n (%)[c]	160 (60.6)	14 (50.0)	174 (59.5)	0.190
Age, years [d]	53.57±13.28	61.11±12.05	54.86±13.74	<0.001 [a]
BMI [d]	25.65±3.93	24.30±3.71	25.52±3.92	0.080
Systolic BP, mm Hg[d]	126.14±19.64	122.48±19.90	125.8±19.6	0.360
Diastolic BP, mm Hg[d]	76.39±11.67	74.07±9.94	76.18±11.56	0.320
mACEF score [e]	0.78 (0.63, 0.96)	1.48 (1.01, 4.14)	0.80 (0.64, 1.02)	<0.001 [a]
Presence of				
Hypertension, n (%)[c]	122 (46)	14 (50)	136 (46)	0.840
Diabetes, n (%)[c]	21 (8)	1 (4)	22 (7.5)	0.710
Hyperlipidemia, n (%)[c]	106 (40)	11 (41)	117 (40)	0.998
VHD, n (%)[c]	39 (14.77)	8 (28.57)	47 (16)	0.100
Family history of HOCM, n (%)[c]	17 (6.44)	1 (3.57)	18 (6)	1.000
Smoking, n (%)[c]	126 (48)	12 (43)	138 (47)	0.690
Alcohol consumption, n (%)[c]	84 (32)	7 (25)	91 (31.1)	0.530
Atrial fibrillation, n (%)[c]	40 (15)	12 (43)	52 (17)	<0.001 [a]
Ventricular tachycardia, n (%)[c]	13 (4.9)	1 (3.5)	14 (4.7)	0.604
NYHA III or IV, n (%)[c]	15 (6)	13 (54)	28 (9.5)	<0.001 [a]
Medicine				
Calcium antagonist, n (%)[c]	125 (47.34)	10 (35.71)	135 (46.23)	0.320
β-blocker [c]	185 (70.75)	22 (78.57)	207 (70.2)	0.400
ACEI/ARB [c]	93 (35.2)	9 (32.14)	102 (34.9)	0.870
Lab test				
Hemoglobin, g/L [d]	134.74 ± 18.53	121.07 ± 20.74	133.42 ± 19.15	<0.001 [a]
Creatinine, umol/L [b]	72.2 (62.9, 84.0)	81.46 (71.3, 120.8)	73.07 (63.3, 84.2)	<0.001 [a]
CCR, mL/min [e]	98.32 (78.70, 116.97)	63.36 (41.29, 79.74)	94.26 (73.41,115.53)	<0.001 [a]
hs-CRP, mmol/L [e]	1.49 (0.77, 3.20)	6.49 (2.29, 12.44)	1.66 (0.78, 3.81)	<0.001 [a]
TC, mmol/L [e]	4.34 (3.75, 5.15)	4.13 (3.68, 4.99)	4.29 (3.74, 5.12)	0.440
HDL-C, mmol/L [e]	1.07 (0.89, 1.27)	1.02 (0.83, 1.15)	1.07 (0.87, 1.26)	0.120
LDL-C, mmol/L [e]	2.65 (2.02, 3.26)	2.59 (1.86, 3.17)	2.65 (2.02, 3.25)	0.560
Echocardiography				
LOVT, at rest, mmHg [e]	60 (39, 88)	50 (19, 66)	58 (38, 85)	<0.001 [a]
LVEF, % [e]	70 (65, 75)	63 (56, 70)	70 (65, 75)	<0.001 [a]
LV end-diastolic diameter, mm [d]	42.08 ± 6.42	45.39 ± 9.15	42.40 ± 6.78	0.010
LA diameter, mm [e]	39 (35, 43)	45 (39, 47)	40 (35, 44)	0.002 [a]
Ventricular septum thickness, mm [e]	19 (16, 23)	18 (16, 20)	19 (16, 23)	0.120
IVS > 30 mm [c]	21 (7.95)	2 (7.14)	23 (7.8)	0.610

[a] *P*<0.05 was considered to be statistically significant.
[b] SI conversion factors: to convert creatinine to mmol/L, divided by 1000.
[c] Categorical variables were analyzed with chi-squared or Fisher exact tests.
[d] Normally distributed continuous variables were presented as means ± standard deviation and analyzed using student's t test.
[e] Non-normally distributed continuous variables were presented as median (lower quartile, upper quartile) and analyzed using Mann-Whitney U test.
BMI - body mass index; CHD - coronary heart disease; VHD - valvular heart disease; HOCM - hypertrophic obstructive cardiomyopathy; NYHA - New York Heart Association functional class; mACEF - modified age, creatinine, and ejection fraction; hs-CRP - high-sensitivity C-reactive protein; ACEI - angiotensin-converting enzyme inhibitor; ARB - angiotensin receptor blocker; CCR - creatinine clearance rate; TC - total cholesterol; HDL-C - high density lipoprotein cholesterol; LDL-C - low density lipoprotein cholesterol; LA - left atrial; LV - left ventricle; LVOTG - left ventricle outflow tract gradient; LVEF - left ventricle ejection fraction

Table 2. Univariate and multiple Cox regression analyses for cardiac death

	Univariate analysis		Multiple analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age	1.085 (1.049–1.122)	<0.001 [a]		
Hemoglobin	0.964 (0.964–0.982)	<0.001 [a]	0.99 (0.968–1.014)	0.420
Creatinine	1.021 (1.013–1.028)	<0.001 [a]		
CCR, ml/min	0.96 (0.946–0.975)	<0.001 [a]		
hs-CRP	1.153 (1.086–1.225)	<0.001 [a]	1.122 (1.041–1.21)	0.003 [b]
LOVTG, at rest	0.98 (0.966–0.994)	<0.001 [a]	0.983 (0.966–1.000)	0.054
LVEF	0.954 (0.936–0.973)	<0.001 [a]		
LA diameter	1.006 (0.996–1.016)	0.220		
LV end-diastolic diameter	1.055 (1.011–1.102)	0.010 [a]	1.013 (0.965–1.062)	0.606
BMI	0.907 (0.82–1.003)	0.053	0.981 (0.876–1.098)	0.738
mACEF score	1.795 (1.518–2.124)	<0.001 [a]	1.372 (1.076–1.749)	0.010 [b]
Presence of				
VHD	0.392 (0.172–0.894)	0.030 [a]	1.534 (0.507–4.643)	0.449
Atrial fibrillation	4.198 (2.016–8.740)	<0.001 [a]	3.185 (1.396–7.265)	0.006 [b]
NYHA III or IV	7.667 (3.634–16.174)	<0.001 [a]	1.563 (1.108–2.205)	0.010 [b]

[a] $P \leq 0.1$ in univariate analysis was used as an entry criterion probability value for including in multiple analysis.
[b] $P < 0.05$ was considered to be statistically significant in multiple analysis.
BMI - body mass index; NYHA - New York Heart Association functional class; mACEF - modified age, creatinine, and ejection fraction; hs-CRP - high-sensitivity C-reactive protein; CCR - creatinine clearance rate; LA - left atrial; LV - left ventricle; LVOTG - left ventricle outflow tract gradient; LVEF - left ventricle ejection fraction; VHD - valvular heart disease

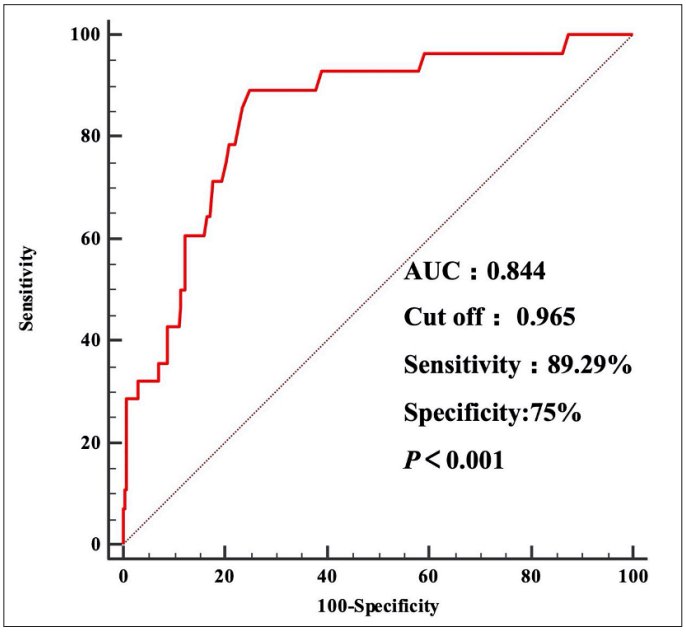

Figure 2. Receiver operating characteristic curve of the modified age, creatinine clearance, and ejection fraction score in predicting long-term cardiac death

The ACEF score was originally designed to assess the operative mortality in elective cardiac surgery with an accuracy similar or superior to pre-existing scores (additive or logistic EuroSCORE) (4). The model follows a concept of the "Occam's razor," which means "simplification" using only three factors, including age, LVEF, and preoperative creatinine. Subsequently, the ACEF score was applied to various clinical conditions (7, 11-13), and updated into different models to provide better predictive accuracy (5, 6, 14, 15). The modified ACEF (mACEF) score was remodeled from the original ACEF score by using the creatinine clearance rate as a semi-continuous variable instead of serum creatinine (5). The reason for this modification was not only because creatinine clearance rate represents a better estimate of underlying renal function but has also been previously shown to improve the predictive accuracy of cardiac risk models (16).

Reduced LVEF indicates loss of contractility and has been determined to be associated with worsening outcomes in patients with HCM (17). The age, represents the ageing of the body, was commonly used as a predictor of heart disease. In this study, age was found to be strongly associated with cardiac death. Previous studies had suggested renal function, when evaluated with creatinine clearance rate, was an independent predictor of adverse cardiac outcomes (18, 19). When the serum creatinine clearance was calculated using the Cockcroft-Gault equation, mathematical coupling and a co-linearity bias were introduced into the mACEF model because age in the mACEF model was counted twice, once alone and once when calculating the creatinine clearance. Therefore, we believed that the high predictive value of mACEF score in cardiac death because of HOCM would benefit from the "mutual reinforcement" between age and creatinine clearance rate.

In this study, family history of HCM in the study population was lower than in those in previous studies (20, 21) because

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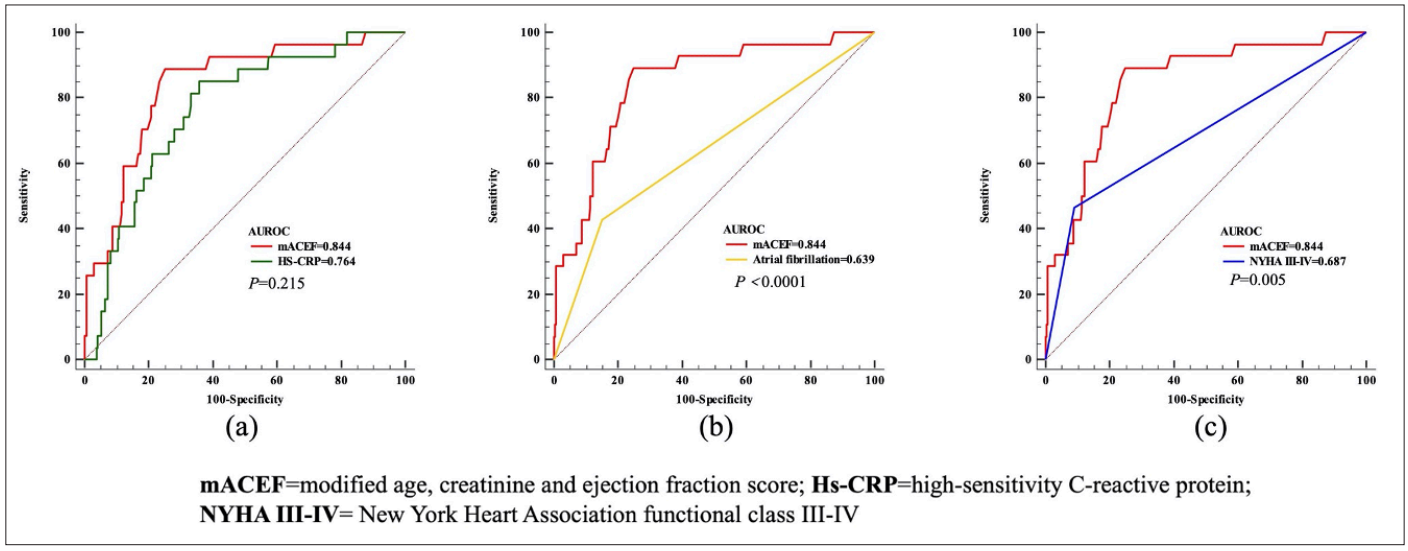

Figure 3. Pairwise comparison of receiver operating characteristic curves between the modified age, creatinine clearance, and ejection fraction score and other independent risk factors. (a) Comparison between mACEF and high-sensitivity C-reactive protein; (b) comparison between mACEF and atrial fibrillation; (c) comparison between mACEF and New York Heart Association heart function classification III-IV

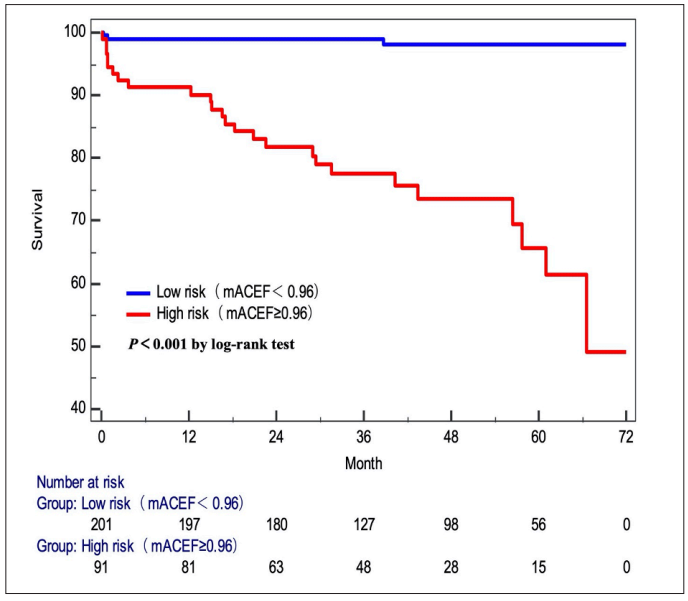

Figure 4. Kaplan-Meier curve for long-term cardiac mortality in high and low risk groups

patients could seldom recall their past family medical history in the prior generation. VT was observed in 15 patients but was not associated with cardiac mortality, the probable reason of which might be the selection bias in the study population. In this study, patients with HOCM with a high risk of sudden cardiac death and those who had undergone septal myectomy, alcohol septal ablation, and ICD implantation were excluded. This might explain why VT was not associated with cardiac mortality. We also found that the LVOT gradient was higher in patients who survived, which could be related to reduced left ventricular function. In this study LVEF, LV end-diastolic diameter, and LA diameter, though in the normal range, were found to be significantly different between patients who survived and those who suffered cardiac death. It is comprehensible that lower LVEF and higher LV end-diastolic diameter suggest poor left ventricular systolic function. LA pressure is the output of LV diastolic function. Previous studies have shown that atrial enlargement is strongly related to LV hypertrophic and systolic function (22).

In previous studies on HCM, Maron et al. (20) and Zhu et al. (23) have reported long-term cardiac mortality of 4.0% (0.53 per 100 person-year) and 6.1% (1.67 per 100 person-year), which was lower than that in the present study (9.5%, 2.1 per 100 person-year). The difference may be attributed to the study population. Patients in our study were treated with medicine only to avoid the bias caused by surgical/interventional procedures. It is known that patients with HOCM treated conservatively have a higher long-term mortality (24, 25). This study was the first one to identify mACEF as an independent risk factor of long-term cardiac mortality in patients with HOCM treated conservatively. In addition, the presence of AF, NYHA heart function III-IV, and increasing concentration of hs-CRP were also identified as independent risk factors of HOCM, which was in accordance with previous reports (23, 26). The results of our study also showed that the mACEF score, in the setting of HOCM treated non-invasively, had a better prediction ability than other risk factors. Hence, the mACEF score could play a role as a stratifying tool to identify patients with HOCM patients at high risk of long-term cardiac mortality with an mACEF score ≥0.96 considered to be an adverse prognostic sign.

Study limitations

This was a single center, retrospective study. Patients with HOCM treated non-invasively were enrolled, which might introduce bias and limit the generalizability. Validation of our results in other patient populations and larger sample sizes is needed. Despite the limitations, this study offers a simple indicator for risk stratification for patients with HOCM in clinical practice.

Conclusion

The mACEF score showed a strong predictive ability for long-term cardiac mortality in HOCM with non-invasive treatment. An mACEF score ≥ 0.96 could be considered as a sign of poor prognosis in patients with HOCM.

Acknowledgment: We would like to thank all my colleagues for their assistance, especially Yue-yue Xi and Shuang Gao. A special acknowledgment to Kyle Chisholm, for the helpful language polishing on this manuscript.

Institutional and financial support: This work was supported by National key research and development program (2020YFC2004700), National Natural Science Foundation of China (81825003, 91957123), CAMS Innovation Fund for Medical Sciences (CIFMS 2016-I2M-1-009) and Beijing Municipal Commission of Science and Technology (Z171100000417021).

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Author contributions: Concept – J.G.; Design – J.G.; Supervision – J.G., M.Z., Y.T.; Fundings – J.G.; Materials – J.G., C.S., W.W., X.M., K.Z., J.W., M.Z., Y.T.; Data collection &/or processing – J.G., C.S., K.Z., J.W.; Analysis &/or interpretation – W.W.; Literature search – J.G., C.S., W.W., X.M., K.Z., J.W., M.Z., Y.T.; Writing – J.G., C.S., W.W., X.M., K.Z., J.W., M.Z., Y.T.; Critical review – C.S., W.W., M.Z., Y.T.

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