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Testing microalbuminuria improved detective ability of atrial fibrillation in hypertrophic cardiomyopathy patients

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Abstract

Atrial fibrillation (AF) is common arrhythmia in hypertrophic cardiomyopathy (HCM) patients, and indicate badly prognosis. The aim of this study was to determine the value of testing microalbuminuria (MAU) to improve the detective ability of atrial fibrillation in hypertrophic cardiomyopathy patients. The study was retrospective study. 267 patients with HCM were included from June 2013 to June 2016. Urinary albumin excretion (UAE) was detected by immunoturbidimetry method. AF was defined according to Minnesota codes. Huge atrial dimension was defined as left atrial end-systolic dimension (LAESD)≥ 50mm. 267 patients were enrolled consecutively, 37(13.9%) had AF and 47(17.6%) had MAU. The levels of UAE increased with the prevalence of AF and huge atrial dimension. In multivariate logistic analysis, age, LAESD and UAE were significantly associated with AF. Compared with patients without MAU, patients with MAU were associated with increased risk of AF

and huge atrial dimension. Combined measurements of age≥ 51.5 years, LAESD≥ 44.5mm and UAE≥ 22.6 mg/L indicated good predictive values in the presence of AF, with a specificity of 87.8% and a sensitivity of 86.5% in HCM patients. MAU might be a valuable index to evaluate the clinical status of AF in HCM patients. Testing MAU improve the detective ability of atrial fibrillation in hypertrophic cardiomyopathy patients.

Keywords: Albuminuria; Hypertrophic cardiomyopathy; Atrial fibrillation

1. Introduction

Hypertrophic cardiomyopathy (HCM) is a common heritable disease with a prevalence of 1 in 500 of the general population [1]. Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and increase the risk of cardiovascular mortality by approximately two-fold[2, 3]. MAU is defined as a urinary albumin excretion rate between 30-300mg albumin/L, and be used to evaluate left ventricular hypertrophy, generalized endothelial injury, cardiovascular and all-cause mortality [4-6]. The prevalence of MAU is significantly higher in hypertensive patients with a history of AF, and be performed in order to determine vascular end organ damage and to implement effective primary and secondary prevention measures[7, 8]. The aim of this study was to determine the value of testing microalbuminuria (MAU) to improve the detective ability of atrial fibrillation in hypertrophic cardiomyopathy patients.

2. Methods

2.1 Study design and study population

We analyzed retrospectively patients with HCM between June 2013 and November 2016. Subjects who had underwent medical history record, physical examination, 12-lead electrocardiography (ECG), 24-hour ambulatory ECGs, blood examination, coronary angiography, and cardiac magnetic resonance (CMR) were included in our study. The diagnosis of HCM was based on a maximum LV wall thickness no more less 15 mm (or no more less 13 mm with an unequivocal family history of HCM), as measured by echocardiography or CMR, excluded another cardiac or systemic diseases capable of

producing such magnitude of hypertrophy [9]. AF was defined as the Minnesota codes. The diagnosis of AF was based on a previously medical history or according to the AF documentation in ECG or 24-hour ambulatory ECGs on admission. Exclusive criteria included: patients with uncompleted clinical data, or valvular heart disease, or infection, or concomitant neoplasm, or connective tissue disease, or pregnancy or infection, or urinary tract infection, or using insulin, or incomplete disease data. Finally, 267 patients were recruited in the study.

2.2 Echocardiography

All transthoracic echocardiography was performed, according to the American Society of echocardiography's recommendation [10], using an iE 33 Color Doppler Ultrasound System (Philips Healthcare, Andover, MA). The peak velocity across the left ventricular outflow tract (LVOT) was also measured, and the peak pressure gradient was estimated using the simplified Bernoulli equation.

2.3 CMRI

CMRI imaging was performed with electrocardiographic gating and breath holding on a 1.5-T scanner (Magnetom Avanto; Siemens Medical Solutions, Erlangen, Germany). Briefly[11], cine images were obtained in left ventricular two-chamber and four-chamber long-axis views, LVOT view, and LV short-axis views by a true fast imaging by steady-state precession (TrueFisp) sequence. CMR images were analyzed by an experienced radiologist on a workstation (Siemens Medical Systems, Erlangen, Germany). Endocardial and epicardial contours of the left ventricular myocardium, except papillary muscles, were traced at end diastole and end-systole on each LV short-axis cine image by radiologist. Left atrial end-systolic dimension (LAESD), Left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), left ventricular ejection fraction (LVEF), stroke volume, cardiac output, and LV mass (LVM) were then calculated in a standard fashion. LVM was derived by multiplying left ventricular myocardial volume measured at end diastole with the specific gravity of myocardium (1.05 g/ mL). All parameters were indexed to body surface area, except LVEF. Huge atrial dimension was defined as left atrial end-systolic dimension (LAESD) ≥50mm.

2.4 Blood sample and urine albumin excretion (UAE)

Venous blood and urine sample were collected on the morning and followed a standardized sample collection and testing procedure, within 2 days of echocardiography and 1 week of

CMR examination. All samples were measured within 2 hours of blood collection as routine sample analysis in our hospital laboratory, by medical technologists who were unaware of any clinical information about the studied patients. UAE was detected by immunoturbidimetry method using Hitachi 7180 automatic biochemical analyzer system with less 15% relative deviation. Abnormal UAE (MAU) was defined as 30-300mg albumin/L urine[7]. The glomerular filtration rate (eGFR) (ml/min/1.73 m^2) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. Plasma levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) were also measured using an electrochemiluminescent immunoassay (Elecsys proBNP II assay; Roche Diagnostics, Mannheim, Germany).

2.5 Statistical analysis

Continuous variables are expressed as mean ± SD. Categorical variables are shown as frequencies (percentages). Differences of continuous variables were evaluated with the independent Student's t test, Mann-Whitney U test, or Kruskal-Wallis H test (as appropriate). Comparisons among different groups were performed using the 2 Mantel-Haenszel test for trend in the distribution of AF and LAESD≥ 50mm. Pearson's correlation test or Spearman's correlation test was used to examine correlations between two variables. Univariable and stepwise multivariate logistic regression analyses (*p* value threshold to enter 0.05; to remove, 0.10) were used to determine factors associated with AF. The area under the curve (AUC) and optimal cutoff values of age, LAESD and UAE in predicting AF were identified using receiver-operating characteristic (ROC) curve analysis. The sensitivity, specificity, and positive and negative predictive values were calculated for selected age, LAESD and UAE cutoff points. A 2-tailed *p* value <0.05 was considered as statistically significant. Statistical analysis was performed with the statistical package SPSS 20.0 (SPSS Inc, Chicago, Illinois) and GraphPad 7.0 (GraphPad Software Inc. La Jolla, CA, USA).

3. Results

3.1 Clinical feature of HCM patients

Of 267 patients, there were 142(53.1%) males, 37(13.9%) with AF, and 47(17.6%) with MAU. The median level of UAE was 8.75mg/l (IQR 4.81 to 16.56) (**Table1**). Greater UAE levels were found in those who had atrial fibrillation (AF) (17.1[IQR 7.33-26.62] VS 8.16[IQR 4.72-13.94], *p*<0.001) and ACEI/ARB therapy (12.02[IQR 7.19-20.60] VS

7.85[IQR 4.71-15.74], p = 0.016) (**Table2**). UAE levels correlated positively with NT-pro-BNP (r = 0.142, p = 0.020), LVEF (r = -0.225, p = 0.001), LAESD (r= 0.174, p=0.004), LVESV index (r = 0.124, p = 0.044), and LVEDV index (r = 0.227, p = 0.001) (**Table3**). The prevalence of AF (p for trend= 0.002) and huge atrial dimension(≥50mm) (p for trend= 0.026) increased significantly with the ascending UAE tertiles (**Figure1**).

Table 1 Baseline characteristics of all 267 HCM patients

Variable	Overall population
UAE (mg/L)	8.75(4.81-16.56)
MAU (%)	47 (17.6%)
Age (years)	49.9±11.1
Men	142(53.1%)
Body mass index (kg/m^2)	25.6±3.4
Heart rate (bpm)	70.9±11.1
SBP (mmHg)	117.6±17.7
DBP (mmHg)	72.9±10.3
Hypertension	89(33.3%)
Diabetes mellitus	18(6.7%)
Hypercholesterolemia	82(30.7%)
Current smokers	88(33.0%)
NYHA classification III or IV	125(46.8%)
Family history of HCM	48(18.4%)
Atrial fibrillation	37(13.9%)
Medications	
β-Blockers	207(77.5%)
ACEI/ARB	42(15.7%)
CCB	55(20.6%)
Risk factors for SCD	
Family history of SCD	21(7.9%)
Syncope	76(28.5%)

Non-sustained VT	27(10.1%)
NT-proBNP (fmol/ml)	1248(695.1-2233.4)
Cardiac troponin I (ng/ml)	0.019(0.007-0.041)
Serum creatinine (umol/l)	72.7±14.1
eGFR (ml/h)	101.5±27.9
Albumin (g/l)	43.2±4.1
Echocardiographic parameters	
LVOT gradients at rest (mmHg)	90.4±27.0
Cardiovascular magnetic resonance	
IVS thickness (mm)	23.0(19.0-26.0)
LVEF (%)	71.2(68.0-77.0)
LAESD (mm)	41.8±7.9
LVEDV index (ml/m^2)	68.2±15.1
LVESV index (ml/m^2)	20.7±8.4
LVSV index (ml/m^2)	47.5±10.6
Cardiac index (L/min/m^2)	3.1(2.7-3.6)
Left ventricular mass index (g/m^2)	82.7(63.7-107.8)
LGE	213(79.8%)

Data are expressed as mean ± SD, median (interquartile range), or number (percentage).

HCM hypertrophic cardiomyopathy, SBP systolic blood pressure, UAE urine albumin excretion, MAU microalbuminuria, DBP diastolic blood pressure, HT hypertension, DM diabetes mellitus, NYHA New York Heart Association, ACEI angiotensin-converting enzyme inhibitor, ARB angiotensin receptor blocker, CCB calcium channel blocker, SCD sudden cardiac death, VT ventricular tachycardia, NT-pro-BNP N-terminal pro-B-type natriuretic, eGFR glomerular filtration; LVOT left ventricular outflow tract, IVS interventricular septum, LVEF left ventricular ejection fraction, LAESD left atrial end-systolic dimension, LVEDV index left ventricular end-diastolic volume index, LVESV index left ventricular end-systolic volume index, LVSV index stroke volume index, and LGE late gadolinium enhancement.

Table2. The level of UAE according to clinical variables of all 267 patients with HCM

Variable	UAE (mg/l)				*p* Value
	n	Present	n	Absent	
Men	142	7.70(4.70-15.58)	125	10.20(5.14-16.91)	0.098
Hypertension	89	9.52(4.98-20.66)	178	8.50(4.72-15.27)	0.305
Diabetes mellitus	18	8.76(4.74-18.3)	249	8.63(4.80-16.29)	0.793
Hypercholesterolemia	82	8.31(4.72-16.67)	185	8.83(5.09-16.49)	0.704
Current smokers	88	8.34(5.26-19.69)	179	8.76(4.71-15.1)	0.728
NYHA classification III or IV	125	7.65(4.57-13.86)	142	9.39(5.22-17.16)	0.206
Family history of HCM	48	9.50(4.67-14.12)	219	8.63(4.98-17.10)	0.975
Atrial fibrillation	37	17.1(7.33-26.62)	230	8.16(4.72-13.94)	<0.001
Family history of SCD	21	11.89(4.05-19.00)	246	8.62(4.93-15.54)	0.493
Syncope	76	8.62(5.19-14.96)	191	8.76(4.79-17.10)	0.532
Resting LVOTG ≥ 30mmHg	234	8.76(4.93-17.00)	33	8.15(3.84-13.85)	0.375
Non-sustained VT	27	11.67(6.51-17.44)	240	8.37(4.72-16.33)	0.216
Systolic anterior motion II/III	140	8.72(5.01-16.90)	127	8.75(4.72-15.31)	0.532
Huge atrial dimension (LAESD≥50mm)	44	11.3(6.5-26.4)	223	8.34(4.69-15.1)	0.016
LEG	213	9.13(5.16-17.19)	54	9.19(3.79-12.57)	0.054
Medications					
β-Blockers	207	8.60(4.71-15.31)	60	10.62(5.52-17.88)	0.292
ACEI/ARB	42	12.02(7.19-20.60)	225	7.85(4.71-15.74)	0.016
CCB	55	11.38(5.17-20.88)	212	8.34(4.80-14.86)	0.124

Abbreviations as in Table 1

Table3 Correlation between UAE and other continuous variables in all 267 HCM

Variable	UAE	
	r	*p* value
Age (years)	0.076	0.215
Body mass index (kg/m^2)	0.079	0.199
Heart rate (bpm)	0.054	0.375
SBP (mmHg)	0.075	0.223
DBP (mmHg)	0.072	0.242
Albumin (g/l)	0.115	0.060
NT-pro-BNP (fmol/ml)	0.142	0.020
Cardiac troponin I (ng/ml)	0.108	0.079
Serum creatinine (umol/l)	0.031	0.619
eGFR (ml/h)	-0.008	0.897
Echocardiographic parameters		
LVOT gradients (mmHg)	-0.021	0.728
Cardiovascular magnetic resonance		
IVS thickness (mm)	0.036	0.560
LVEF (%)	-0.225	<0.001
LAESD (mm)	0.174	0.004
LVESV index (ml/m^2)	0.124	0.044
LVEDV index (ml/m^2)	0.227	<0.001
LVSV index (ml/m^2)	0.006	0.928
Cardiac index (L/min/m^2)	0.053	0.385
Left ventricular mass index (g/m^2)	0.077	0.212

Abbreviations as in Table 1

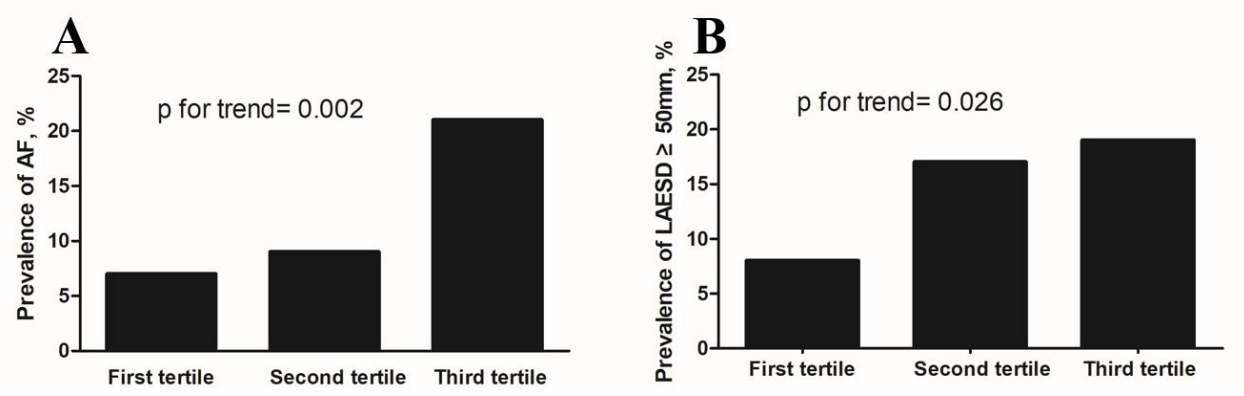

Figure1. Prevalence of AF and huge atrial dimension were associated with the increasing levels of UAE. Prevalence of AF (**Figure1A**) and huge atrial dimension (**Figure1B**) increased with the ascending MAU tertiles. AF= atrial fibrillation; MAU= microalbuminuria

3.2 Clinical data associated with AF

The variables associated with AF determined by univariate logistic regression are shown in Table4. Multivariate analysis demonstrated that only age (OR=1.052,95%CI=1.014-1.091, p=0.006), LAESD (OR=1.095, 95%CI=1.044-1.150, p=0.001), and UAE (OR=1.013,95%CI=1.001-1.024, p=0.036) were independent factors for AF (**Table4**). Compared with without MAU, patients with MAU were associated with increased risk of AF (OR=3.63,95%CI=1.70-7.77, p< 0.001) and huge atrial dimension (OR=13.9,95%CI=6.56-29.4, p< 0.001) (**Figure2**).

Table4 Logistic regression between AF and significant variables from univariate analysis

Variable	Univariable		Multivariate	
	OR (95%)	p	OR (95%)	p
Age	1.059(1.023-1.097)	0.001	1.052(1.014-1.091)	0.006
Sex	1.235(0.616-2.474)	0.552		
Body mass index	1.024(0.924-1.136)	0.652		
ACEI/ARB	0.436(0.193-0.987)	0.046		
LVEF	0.970(0.928-1.013)	0.166		
LAESD	1.106(1.056-1.158)	0.000	1.095(1.044-1.150)	0.001
LVEDV index	1.022(1.000-1.045)	0.053		
LVESV index	1.040(1.003-1.079)	0.033		

UAE	1.016(1.005-1.027)	0.000	1.013(1.001-1.024)	0.036
NT-pro BNP	1.000(1.000-1.000)	0.036		

Abbreviations as in Table 1.

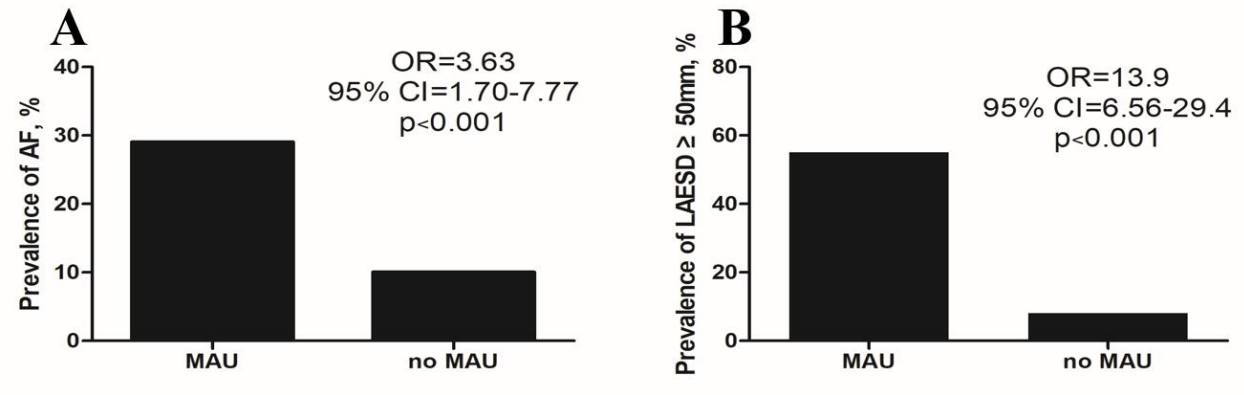

Figure2. Prevalence of AF and huge atrial dimension were associated with the prevalence of MAU. Compared with without MAU, patients with MAU were associated with increased risk of AF (OR=3.63,95%CI=1.70-7.77, p< 0.001) (**Figure2A**) and huge atrial dimension (OR=13.9,95%CI=6.56-29.4, p< 0.001) (**Figure2B**). AF= atrial fibrillation; MAU= microalbuminuria.

3.3 ROC curve analysis

ROC curve analysis was performed to evaluate the predictive efficiency of age, LAESD, and UAE as determinants of AF (**Figure3**). The optimal cutoff value of age was 51.5 years, with a sensitivity of 64.9% and a specificity of 61.3%. The optimal cutoff value of LAESD was 44.5mm, with a sensitivity of 64.9% and a specificity of 70.9%. The optimal cutoff value of UAE was 22.6mg/L, with a sensitivity of 37.8% and a specificity of 87.8%. Combining the 3 variables, the comprehensive efficiency of prediction concomitant AF in HCM patients was enhanced, with an AUC of 0.788 (95%CI 0.711-0.865; p< 0.001). Compared with age and LAESD alone or combination, the UAE≥ 22.6 mg/L yielded a high specificity of 87.4% in prediction the presence of AF, whereas the association of age≥ 51.5 years, or LAESD≥ 44.5mm, or UAE≥ 22.6 mg/L generated a high sensitivity of 86.5% (**Table5**)

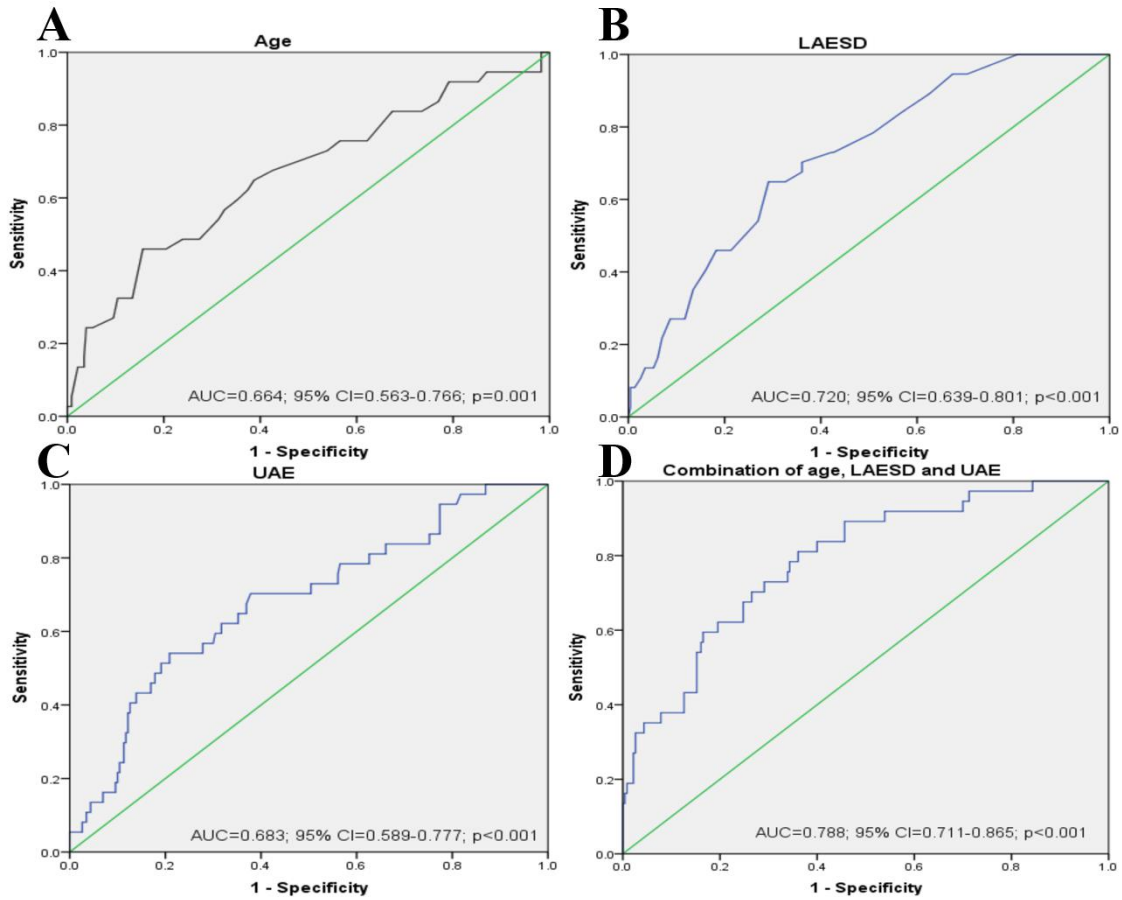

Figure3. ROC curves of age (**Figure3A**), LAESD (**Figure3B**), UAE (**Figure3C**) and the combination of the 3 variables **(Figure3D**) to predict AF in HCM patients. ROC indicates receiver-operating characteristic; LAESD left atrial end-systolic dimension; UAE urinary albumin excretion.

Table5. Accuracy of age, LAESD and UAE in Prediction the Presence of AF in HCM Patients

Variables	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Age ≥ 51.5 years	64.9%	61.3%	21.2%	91.6%%
LAESD≥ 44.5mm	64.9%	70.9%	26.4%	92.6%
UAE ≥ 22.6 mg/L	37.8%	87.8%	32.6%	89.7%
Age≥ 51.5 years and LAESD≥44.5mm and UAE≥ 22.6 mg/L	62.2%	80.4%	33.3%	92.9%
Age≥ 51.5 years or LAESD≥ 44.5mm or UAE≥ 22.6 mg/L	86.5%	41.3%	19.2%	95.0%

LAESD left atrial end-systolic dimension; UAE urinary albumin excretion; AF atrial fibrillation; HCM hypertrophic cardiomyopathy.

4. Discussion

MAU has been demonstrated to have significantly higher in patients with history atrial fibrillation AF in hypertension patients[7]. In the present analysis, it is the first time to show that AF is associated with an increased prevalence of MUA in HCM patients, and this association was independent of traditional risk factors predisposing to AF. Combined measurements of age≥ 51.5 years, LAESD≥ 44.5mm and UAE≥ 22.6 mg/L indicated good predictive values in the presence of AF, with a specificity of 87.4% and a sensitivity of 86.5% in HCM patients.

MAU is the predictor of AF in patients with hypertensive [7], and represents an indirect window to monitor the status of the whole vasculature[7]. Early vascular and early renal end organ damage might be associated with the occurrence of AF. As presented in our study, it has the same conclusion in HCM patients. There were two mechanism to explain the relationship between MAU and AF in HCM patients. First, an association of AF with CRP, vascular cell adhesion molecules and decreased cardiac nitric oxide production was reported[13-15]. Endothelial dysfunction as reflected by MAU might induce atrial ischaemia thereby favouring the occurrence of AF [16]. Secondly, the irregularity of pulse waves due to AF might further impair the capillary filter thereby promoting vascular damage [7]. AF enhances the magnitude and frequency of the tensile stress imposed on the arterial wall and also increases systolic flow-induced shear stress[7]. As indicated in our study, the prevalence of huge atrial dimension was associated with the increasing levels of UAE and the prevalence of MAU. The irregularity of ventricular cycle length during AF augments pulmonary wedge pressure and right atrial pressure and decreases cardiac output[17]. MAU was accompanied by increased cardiac stress plasma markers such as BNP levels[18, 19], which caused a rise in urinary albumin in excretion through enhance glomerular permeability to albumin, but not inhibition of the tubular re-absorption of albumin[20]. Taken together, we speculated that AF might be either considered as a cause of end organ damage or as a result from prolonged vascular damage, both indicated by MAU.

The study shows an association of renal and cardiac end organ damage and further supports the hypothesis that MAU is an indicator of a generalized damage to the heart and the vasculature. AF was a significant risk factor for prognosis of HCM patients. Although ECG is the golden standard for the diagnosis of AF, the ambulatory ECG monitoring is not currently sufficient to allow widespread use in HCM patients for AF detection. The practical

consequences of these data are that screening for MAU should be performed in every HCM patients in particular with AF or huge atrial dimension. Our study indicated that age, LAESD, and UAE was independently associated with the presence of AF in HCM patients.

There are some limitations in our study. This is a retrospective study with some inherent limitation. First, this was a cross-sectional, retrospective and single-center study, which does not allow one to conclude whether MAU is a cause or a consequence of AF. Second, as a retrospective study, we had to exclude those patients without records of MAU, which could affect the results to some extent. Finally, the conclusions were based on the one-time measurement of UAE. And all patients' urine sample were collected on the morning and followed a standardized sample collection and testing procedure.

5. Conclusion

MAU might be a valuable index to evaluate the clinical status of AF in HCM patients. The simple dipstick urine analysis should be performed in any high-risk patients in order to improved detective ability of atrial fibrillation in hypertrophic cardiomyopathy patients.

Author Contributions

Xiaowei Jiang were responsible for designing the study, analysing and interpreting the data, and revising the manuscript prior to submission. Min Yan were involved in the drafting and revising the manuscript prior to submission.

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and does not contain protected health information.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

All data are freely available with reasonable requirements from authors.

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