



# Clinical, sonographic characteristics and long-term prognosis of valvular heart disease in elderly patients

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## Abstract

**Background** Valvular heart disease (VHD) is expected to become more prevalent as the population ages and disproportionately affects older adults. However, direct comparison of clinical characteristics, sonographic diagnosis, and outcomes in VHD patients aged over 65 years is scarce. The objective of this study was to evaluate the differences in clinical characteristics and prognosis in two age-groups of geriatric patients with VHD. **Methods** We retrospectively enrolled consecutive individuals aged  $\geq 65$  years from Guangdong Provincial People's Hospital and screened for VHD using transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE). Finally, 260 (48.9%) patients were in the 65–74 years group, and 272 (51.1%) were in the  $\geq 75$ -year group. Factors that affected long-term survival were explored. A multivariable Cox hazards regression was performed to identify the predictors of major adverse cardiac events (MACEs) in each group. **Results** In our population, the older group were more likely to have chronic obstructive pulmonary disease (COPD), degenerative VHD, but with less rheumatic VHD, aortic stenosis (AS) and mitral stenosis (MS). Compared with those aged 65–74 years, the older group had a higher incidence of all-cause death (10.0% vs. 16.5%,  $P = 0.027$ ), ischemic stroke (13.5% vs. 20.2%,  $P = 0.038$ ) and MACEs (37.3% vs. 48.2%,  $P = 0.011$ ) at long-term follow-up. In multivariable Cox regression analysis, mitral regurgitation, a history of COPD, chronic kidney disease, diabetes, hypertension, atrial fibrillation and New York Heart Association (NYHA) functional class were identified as independent predictors of MACEs in the older group. **Conclusion** Advanced age profoundly affects prognosis and different predictors were associated with MACEs in geriatric patients with VHD.

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## 1 Introduction

Valvular heart diseases (VHD) is a common structural

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heart disease in clinical practice and strongly associated with heart dysfunction and death.<sup>[1]</sup> Moreover, elderly patients with VHD more frequently have coexisting concomitant conditions, such as heart failure, which predispose them to a worse prognosis.<sup>[2]</sup> With the exacerbation of the aging population, VHD in the elderly will rise as a health problem and represent both a management burden and cost burden for physicians, patients, and healthcare systems.

The etiology, approach to treatment, and expected outcomes of VHD are different in the elderly compared with younger patients. Available retrospective data demonstrated

an increasing prevalence with age, predominantly as a result of degenerative pathophysiology.<sup>[1-3]</sup> Nonetheless, a direct comparison of the clinical features and major end-point events in VHD patients aged 65–74 years and  $\geq 75$  years has not been illustrated yet. The objective of this study was to evaluate the differences in clinical characteristics and prognosis in these two age-groups of geriatric patients with VHD, and determine how advanced age and comorbidities affect prognosis, including long-term major adverse cardiac events (MACEs).

## 2 Methods

### 2.1 Study design and data collection

Our study was a single-center, retrospective, observational study with a median 4-year follow-up. We enrolled consecutive hospitalized subjects aged 65 years and over with abnormal valvular structure and function which were screened by transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE) in Guangdong Provincial People's Hospital between January 1<sup>st</sup> 2010 and December 31<sup>st</sup> 2010. Younger subjects were excluded since previous studies have demonstrated that the prevalence of VHD is low in those aged  $< 65$  years.<sup>[1]</sup> Subjects with a previous diagnosis of VHD (identified by a practical cardiologist) were not all included in the echocardiographic study but their diagnostic data were collected to derive total prevalence. Exclusion criteria were (1) undergoing valvular surgery during hospitalization, (2) terminal illness such as malignant tumor, (3) clinical data were incomplete and (4) immobility or general frailty precluding attendance (as judged by the attending physician). According to the design of the present study, the population was divided into two groups: age 65–74 years and  $\geq 75$  years. For each patient, age, gender, medical history, sonographic diagnosis, and variables were collected at baseline by retrieving the electronic hospital information system (HIS).

Diseases diagnosed and recorded in the hospital information system were based on International Classification of Diseases (ICD) definitions from the World Health Organization. Our center has applied the 10th version of ICD. The medical history of hypertension, atrial fibrillation (AF), diabetes, chronic kidney disease (CKD) and chronic obstructive pulmonary disease (COPD) in the baseline were, thus, classified according to ICD-10.

Follow-up started from the date of enrollment to the date of death or the endpoint of the investigation. Information was obtained by telephone interview with patients or their relatives or, for some patients, by reviewing outpatient or inpatient records.

### 2.2 Study outcomes

The prespecified primary outcomes consisted of all-cause mortality, ischemic stroke, MACEs and heart failure readmission. Ischemic stroke was defined as an episode of neurological dysfunction caused by a focal cerebral infarction, with subsequent confirmation by imaging. MACEs were defined as all-cause mortality, nonfatal myocardial infarction (MI) or revascularization. All-cause mortality was traced from hospital records, follow-up visits, and a national vital record database. Death was regarded as cardiac in origin unless obvious non-cardiac causes could be identified. Sudden death was defined as unexplained death in previously stable patients. Nonfatal MI was diagnosed according to the universal definition. The diagnosis of MI was based on signs or symptoms consistent with myocardial ischemia, electrocardiogram changes, and creatine kinase and Creatine Kinase MB Isoenzyme (mass) levels. Events compatible with the occurrence of an MI were retrospectively adjudicated by a senior cardiologist who was unaware of observed cardiac troponin T levels while evaluating the imaging records. Medical records of all patients who underwent multiple procedures or cardiac surgery or died in hospital were reviewed to ensure data accuracy. Clinical events such as death, MI, stroke, revascularization were adjudicated by the clinical event committee.

### 2.3 Echocardiography examination

Echocardiography is one of the most effective methods for the assessment of valvular structure and function, and it is widely applied for VHD screening in clinical practice. An investigating physician or cardiac sonographer undertook the clinical and echocardiographic assessment. TEE when necessary, was applied to screen all clinically significant valve abnormality. We performed echocardiography examination with trans-thoracic two-dimensional scanning from four standard transducer positions. The first examination recording was selected when the patients underwent multiple echocardiography sessions during this period. Data collection included left ventricular ejection fraction (LVEF), left atrium diameter (LAd), left ventricular internal diameter at end-diastole (LVDd), and left ventricular internal diameter at end-systole (LVSd). All patients with a diagnosis of VHD were specially identified for any of the four VHDs: aortic stenosis (AS), aortic regurgitation (AR), mitral stenosis (MS), mitral regurgitation (MR), according to the international guidelines.<sup>[4,5]</sup> Under standard echocardiographic criteria, rheumatic VHD was diagnosed on the basis of a medical history of acute rheumatic fever and/or precordial abnormalities, including the presence of a cardiac murmur.

Degenerative VHD was defined according to the echocardiographic criteria for calcific valve disease, and ischemic VHD was identified based on a medical history of ischemic heart disease. Regarding infective VHD, the Duke classification allows for standardization of its diagnosis. Congenital VHD was recognized on the basis of a medical history, and might be related to congenital abnormalities of the valve(s) or supporting evidence of other congenital conditions.

Cardiac dimensions were measured by M-mode and two-dimensional TTE according to the recommendations of the American Society of Echocardiography.<sup>[6]</sup> Left atrial dimension was taken in the parasternal long axis view in M-mode at end systole. Left ventricular ejection fraction (LVEF) was calculated using the biplane method of discs (modified Simpson's rule) in the apical 4- and 2-chamber views at end diastole. Measurements were obtained as the mean value from the apical 4- and 2-chamber views. The measurements were made in three beats in patients with normal sinus rhythm and in five beats in AF and the mean was taken for analysis.

In our study, valvular stenosis assessment was made on the basis of quantitative criteria:<sup>[7]</sup> (1) AS was defined as aortic valve thickening or calcification with a maximum aortic transvalvular velocity of 2.5 m/s; and (2) MS with a valve area of  $\leq 2.0$  cm<sup>2</sup>. Detection and gradation of valvular regurgitation was made on the basis of standard color Doppler criteria for AR (width of regurgitant color jet area half or more of the width of the left ventricular outflow tract) and MR (maximum displacement of atrial area by regurgitant color flow jet equal or greater than a third in any view).

## 2.4 Data analysis

Participants were divided by age to examine demographic and clinical characteristics. Continuous variables are expressed as the mean  $\pm$  SD or as the interquartile ranges. Categorical variables were expressed as counts and percentages. Differences between the two groups were compared using Student's *t*-test, chi-square test or Fisher's exact test for quantitative and categorical variables, respectively.

Using Cox proportional hazards analyses, models with multiple adjustments were developed to estimate the associations between clinical and echocardiographic variables and MACEs, as well as the interactions between age-groups and each baseline covariate. The model included gender, diagnosis of AS, AR, MS, MR, history of AF, COPD, diabetes, hypertension, CKD, NYHA functional class, and LVEF. The Kaplan–Meier curves were constructed to compute cumulative survival for time to event and the two groups were compared by log-rank test. All statistical analyses were performed using IBM SPSS 19.0 (IBM Inc., New York, NY, USA), and a two-sided *P* value  $< 0.05$  was considered statistically significant.

## 2.5 Ethics statement

This study was approved by the institutional review committee and carried out according to the principles of the Declaration of Helsinki. All patients provided written informed consent.

## 3 Results

### 3.1 Baseline characteristics

A total of 612 patients with VHD were enrolled in the present investigation. Of these, 318 (52.0%) were in the age of the 65–74 group and 294 (48.0%) in the age  $\geq 75$  group. As provided in Figure 1, patients were excluded based on the following reasons: 31 underwent cardiac valvular surgery (29 in age of 65–74 group, 2 in age  $\geq 75$  group); 36 were diagnosed with malignant tumor (22 in age of 65–74 group, 14 in age  $\geq 75$  group) during the study period and 13 had incomplete follow-up data (7 in age of 65–74 group, 6 in age  $\geq 75$  group). Overall, 532 patients with VHD aged 65 years and over were included. Among these, 260 patients (48.9%) were the 65–74 years group and 272 patients (51.1%) were the  $\geq 75$  years group.

The mean age of the two groups was  $69.87 \pm 2.96$  years and  $80.40 \pm 4.48$  years. Patient characteristics and echocardiographic parameters are summarized in Table 1. A rela-

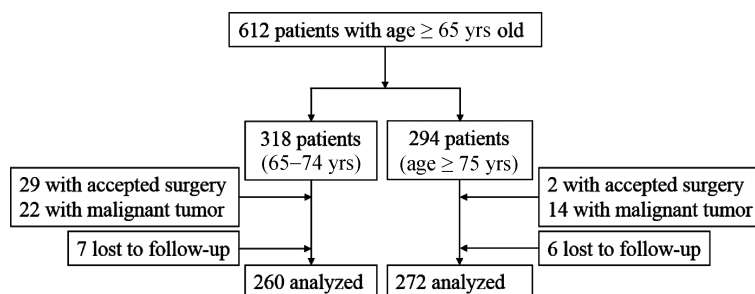


Figure 1. Flow diagram of the study population.

**Table 1. Baseline characteristics by age-group.**

	Overall <i>n</i> = 432	65–74 years group <i>n</i> = 260	75 years group <i>n</i> = 272	<i>P</i> value
Age, yrs	75.26 ± 6.51	69.87 ± 2.96	80.40 ± 4.48	< 0.001
Male	291 (54.7%)	136 (52.3%)	155 (57.0%)	0.279
NYHA functional class				0.078
I	31 (7.2%)	22 (8.5%)	9 (3.3%)	0.014
II	179 (41.4%)	135 (51.9%)	144 (52.9%)	0.882
III	185 (42.8%)	87 (33.5%)	98 (36.0%)	0.596
IV	37 (8.6%)	16 (6.2%)	21 (7.7%)	0.590
Hypertension	358 (67.3%)	166 (63.8%)	192 (70.6%)	0.116
Atrial fibrillation	232 (43.6%)	110 (42.3%)	122 (44.9%)	0.600
Diabetes	155 (29.1%)	73 (28.1%)	82 (30.1%)	0.599
Chronic kidney disease	66 (12.4%)	29 (11.2%)	37 (13.6%)	0.392
COPD	116 (21.8%)	30 (11.5%)	86 (31.6%)	< 0.001
LVEF, %	59.75 ± 13.23	59.34 ± 13.64	60.64 ± 12.61	0.254
LAd, mm	41.49 ± 9.01	42.46 ± 9.03	40.56 ± 9.00	0.015
LVSD, mm	32.10 ± 10.66	34.13 ± 11.48	30.18 ± 9.44	< 0.001
LVDd, mm	49.51 ± 9.33	51.26 ± 10.15	47.82 ± 8.14	< 0.001
Rheumatic VHD	92 (17.3%)	58 (22.3%)	34 (12.5%)	0.003
Degenerative VHD	206 (38.7%)	63 (24.2%)	143 (52.6%)	< 0.001
Ischemic VHD	151 (28.4%)	70 (26.9%)	81 (29.8%)	0.465
Infective VHD	7 (1.3%)	6 (2.3%)	1 (0.4%)	0.063
Congenital VHD	42 (7.9%)	24 (9.2%)	18 (6.6%)	0.335
Aortic stenosis	95 (17.9%)	57 (21.9%)	38 (14.0%)	0.017
Aortic regurgitation	373 (70.1%)	172 (66.2%)	201 (73.9%)	0.051
Mitral stenosis	95 (17.9%)	61 (23.5%)	34 (12.5%)	< 0.001
Mitral regurgitation	425 (79.9%)	214 (82.3%)	211 (77.6%)	0.173
Beta-blocker	367 (69.0%)	187 (71.9%)	180 (66.2%)	0.152
ACEI/ARB	163 (30.6%)	97 (37.3%)	66 (24.3%)	0.001
Digoxin	108 (25.0%)	55 (21.2%)	53 (19.5%)	0.632
Diuretic	109 (20.5%)	43 (16.5%)	66 (24.3%)	0.027
Warfarin/ASA	234 (44.0%)	125 (48.1%)	109 (40.1%)	0.063

Data are expressed as *n* (%) or mean ± SD. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II-receptor blocker; ASA: acetylsalicylic acid (aspirin); COPD: chronic obstructive pulmonary disease; LAd: left atrium diameter; LVDd: left ventricular internal diameter at end-diastole; LVEF: left ventricular ejection fraction; LVSD: left ventricular internal diameter at end-systole; MACEs: major adverse cardiac events; NYHA class: New York Heart Association functional class; VHD: valvular heart disease.

tively definitive etiology for VHD was identified by analyzing clinical data, patient characteristics and echocardiographic information. Patients were divided into groups according to age, and the prevalence of each VHD type was shown in the different groups. Rheumatic VHD accounted for 22.3% of 65–74 years old patients and 12.5% of the advanced age group, respectively ( $P = 0.003$ ). Degenerative VHD accounted for 24.2% of 65–74 years old patients and 52.6% of the advanced age group, respectively ( $P < 0.001$ ). The prevalence of infective VHD and congenital VHD were similar after the age of 65. Three of the most prevalent comorbidities were hypertension, AF, and diabetes. There were no significant differences between the two groups with

respect to gender, NYHA functional class II–IV, LVEF, history of hypertension, AF, diabetes, CKD, AR, and MR. However, patients in the relatively younger group had higher LAd, LVSD, LVDd, higher frequency of AS, MS, and lower frequency of COPD. Further analysis of the baseline characteristics in two age groups revealed a discrepancy in the type distribution of VHD (Table 1). The 65–74 years group was akin to the advanced age group in terms of the prevalence of AR and MR.

### 3.2 Outcomes

The present investigation included a moderate number of elderly patients who presented with VHD from a single

center. Follow-up was available for 97.6% (532/545) of patients with a median duration of 52.9 months (range: 46.6 months to 58.8 months), including 260 in the 65–74 years group and 272 in the ≥ 75-year age group (Figure 1). Table 2 shows the major end-point events. In time-to-first-event analyses, there were 228 MACEs during the follow-up period. 71 patients died during the follow-up period, 26 (10.0%) in the 65–74 years group and 45 (16.5%) in the ≥ 75 years group. Compared with the 65–74 years group, the advanced age group had a higher incidence of ischemic stroke, all-cause death and MACEs. Kaplan–Meier analysis showed better long-term survival and prognosis in the 65–74 years group (Figure 2).

### 3.3 COX regression analysis

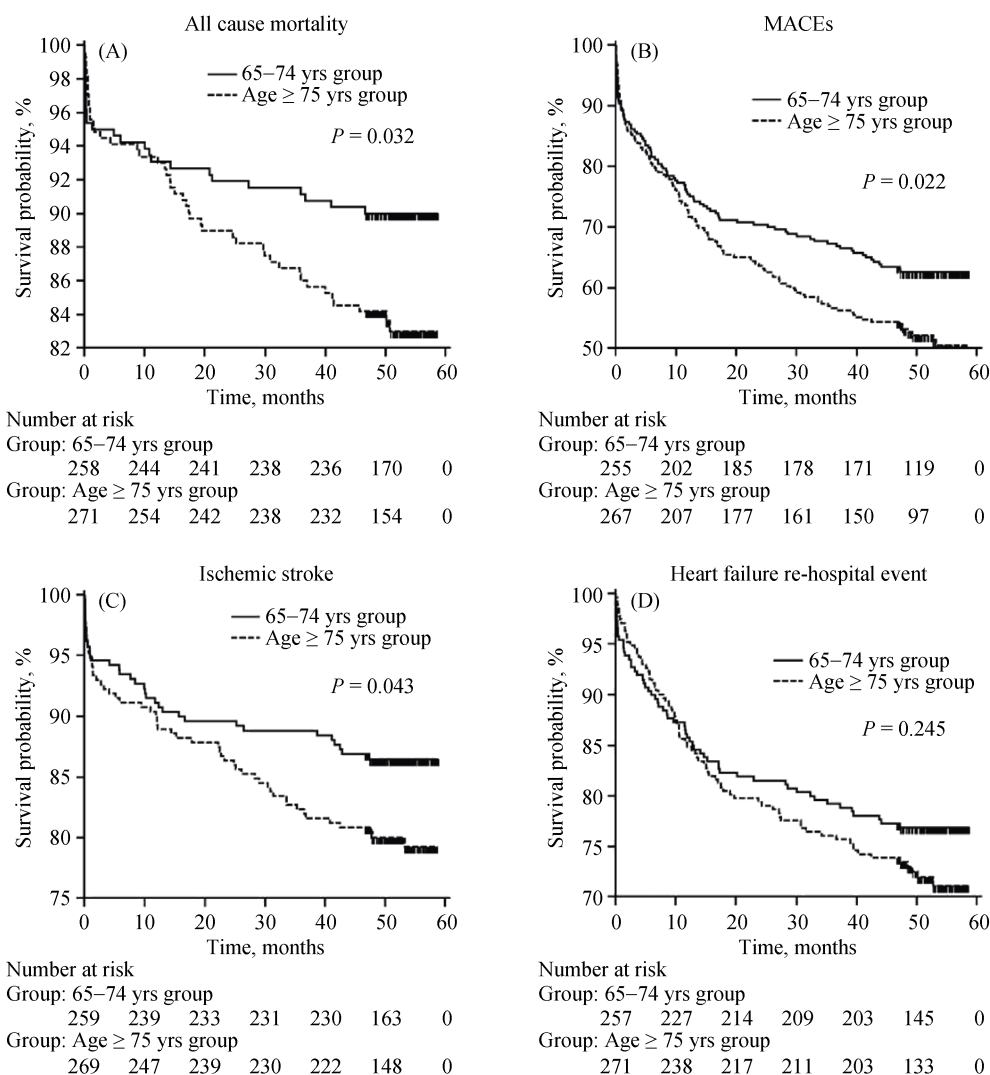
Age-stratified multivariable Cox regression analysis re-

vealed that NYHA functional class, use of beta-blocker, a history of diabetes, AF, hypertension and CKD were the independent risk factor associated with MACEs in both age groups of patients. Restricting this analysis to older subjects, there was an association with NYHA functional class (HR = 1.456, 95% CI: 1.147–1.848,  $P = 0.002$ ), diagnosis of MR (HR = 1.719, 95% CI: 1.078–2.743,  $P = 0.023$ ), a history of

**Table 2. Major outcomes during follow-up.**

	65–74 years group <i>n</i> = 260	75 years group <i>n</i> = 272	<i>P</i> value
Ischemic stroke	35 (13.5%)	55 (20.2%)	0.038
Heart failure readmission	60 (23.1%)	76 (27.9%)	0.199
All-cause death	26 (10.0%)	45 (16.5%)	0.027
MACEs	97 (37.3%)	131 (48.2%)	0.011

Data are presented as *n* (%). MACEs: major adverse cardiac events.



**Figure 2. Kaplan–Meier plots of time to events.** (A): All-cause mortality (log-rank  $P = 0.032$ ); (B): MACEs (log-rank  $P = 0.022$ ); (C) ischemic stroke (log-rank  $P = 0.043$ ); (D): heart failure re-hospitalization (log-rank  $P = 0.245$ ). MACEs: major adverse cardiac events

**Table 3.** Cox regression analysis of risk factors associated with MACEs.

	Hazard ratios (CI) (65–74 years old)	<i>P</i> value	Hazard ratios (CI) (≥ 75 years)	<i>P</i> value	<i>P</i> interaction
Male	1.291 (0.863–1.932)	0.214	1.145 (0.807–1.623)	0.448	0.626
Mitral stenosis	1.586 (1.026–2.450)	0.038	1.215 (0.739–1.999)	0.442	0.362
Aortic regurgitation	1.573 (1.003–2.466)	0.048	1.288 (0.857–1.937)	0.223	0.218
Mitral regurgitation	0.859 (0.520–1.419)	0.554	1.719 (1.078–2.743)	0.023	0.031
Aortic stenosis	1.095 (0.681–1.761)	0.709	1.045 (0.636–1.720)	0.861	0.873
Atrial fibrillation	1.797 (1.205–2.679)	0.004	1.787 (1.266–2.523)	0.001	0.879
Hypertension	1.648 (1.052–2.584)	0.029	2.048 (1.332–3.149)	0.001	0.289
Diabetes	2.083 (1.389–3.123)	< 0.001	1.939 (1.366–2.753)	< 0.001	0.761
Chronic kidney disease	2.072 (1.240–3.462)	0.005	1.578 (1.013–2.459)	0.044	0.438
COPD	1.641 (0.960–2.807)	0.070	1.702 (1.199–2.416)	0.003	0.811
LVEF < 50%	1.159 (0.715–1.880)	0.549	0.881 (0.552–1.404)	0.593	0.086
NYHA class	1.841 (1.422–2.383)	< 0.001	1.456 (1.147–1.848)	0.002	0.652
Beta-blocker	3.349 (1.829–6.132)	< 0.001	2.536 (1.659–3.877)	< 0.001	0.685
ACEI/ARB	1.433 (0.960–2.139)	0.079	1.024 (0.687–1.525)	0.908	0.751
Digoxin	1.812 (1.167–2.814)	0.008	0.814 (0.515–1.287)	0.378	0.027
Diuretic	1.802 (1.128–2.879)	0.014	1.442 (0.986–2.110)	0.059	0.427
Warfarin/ASA	1.278 (0.858–1.904)	0.228	1.383 (0.980–1.952)	0.065	0.798

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II-receptor blocker; ASA: acetylsalicylic acid; COPD: chronic obstructive pulmonary diseases; LVEF: left ventricular ejection fraction; MACEs: major adverse cardiac events; NYHA: New York Heart Association functional class.

hypertension (HR = 2.048, 95% CI: 1.332–3.149,  $P = 0.001$ ), diabetes (HR = 1.939, 95% CI: 1.366–2.753,  $P < 0.001$ ), COPD (HR = 1.702, 95% CI: 1.199–2.416,  $P = 0.003$ ), AF (HR = 1.787, 95% CI: 1.266–2.523,  $P = 0.001$ ), CKD (HR = 1.578, 95% CI: 1.013–2.459,  $P = 0.044$ ) and use of beta-blocker (HR = 2.536, 95% CI: 1.659–3.877,  $P < 0.001$ ) (Table 3). To gain further insights into the hazard ratios for the events, we tested for interactions between age and the baseline variables. For MACEs, interactions between age-group and MR and between age-group and use of digoxin were statistically significant.

## 4 Discussion

### 4.1 Main findings

Our study is a retrospective, hospital-based, echocardiographic study that directly compared the clinical profile and the long-term outcomes between patients aged 65–74 years and 75 years with VHD. Our study indicated a notable age-related difference in baseline variables in patients aged  $\geq 65$  years, and patients aged  $\geq 75$  years had a worse prognosis compared with the 65–74 years group, regardless of the risk profile.

The principal findings of the study were: (1) clinical characteristics, etiology, comorbidities and echocardiographic features varied among patients over 65 years old, and

so was long-term outcomes; and (2) NYHA functional class, use of beta-blocker, a history of AF, diabetes, hypertension and CKD were independent predictors of long-term MACEs in patients aged over 65 years. For MACEs, interactions between age-group and MR and between age-group and use of digoxin were statistically significant.

VHD is an important cause of reduced functional capacity, heart failure, arrhythmia, recurrent hospital admission, and early mortality.<sup>[8,9]</sup> There is, therefore, a pressing need to better understand the contemporary clinical characteristics of VHD, particularly in the elderly population. Patients included in the study were recruited from hospitalized patients with VHD examined by echocardiogram, which guaranteed the consistency of their medical condition and reduced selection bias. Echocardiograms were interpreted by experienced doctors and the comorbidities were re-evaluated during the review of the clinical database according to guidelines.<sup>[7,9]</sup> These factors might partly explain the difference in prognosis between the groups.

### 4.2 Impact of age

The prevalence of VHD increases with age and an estimated 13.2% of patients aged 75 years and over have VHD.<sup>[1]</sup> These problems are getting more and more attention with the aggravation of the aging process, which constitutes a growing health burden.<sup>[1]</sup> It is probably due to the

association of older age with various complications as well as the decline in the function of multiple organs and the consequent shorter life expectancy. We excluded 5.9% of the overall enrollment (4.8% of those aged  $\geq 75$  years) from final analysis on account of a previous or new diagnosis of malignant diseases, and 5.1% on the account of undergoing cardiac surgery for VHD during the study (0.7% of those aged  $\geq 75$  years). We reasonably believed that cardiac surgery had a great impact on long-term survival both for the reason of curative effect and the potential confounding complications of surgery. That means that patients aged  $\geq 75$  years have a higher risk of suffering an ischemic stroke, MACEs and all-cause death than the 65–74 years group. The incidence of ischemic stroke in the present study was 13.5% vs. 20.2% ( $P = 0.038$ ). And we drew Kaplan-Meier curves showing the discrepancy between two age group in the cumulative incidence of ischemic stroke (log rank  $P = 0.043$ ).

### 4.3 Comorbidities

Cardiac and non-cardiac co-morbidities in elderly patients who present with a VHD are frequent. They not only aggravate VHD but also influence prognosis. There is a paucity of literature about the effect of advanced age and comorbidities on outcomes of elderly patients with VHD, especially in less developed countries. In our population baseline, the older group was more likely to have COPD (31.6% in the advanced age group). We also found that up to 67.3% of patients had concomitant hypertension, 43.6% had atrial fibrillation, and 29.1% had diabetes. COPD is common in the elderly, particularly those aged over 75 years. Indeed, we found that hypertension, diabetes and COPD were independent predictors of long-term MACEs in patients over 75 years old. In the Cox regression analysis, we found current or previous AF and a history of diabetes as clinical variables associated with MACEs in the 65–74 years old group. It is suggested that concomitant diseases, especially diabetes, were independently associated with adverse clinical events in older individuals. The frequent coexistence of AF, diabetes, hypertension, and COPD in the elderly may complicate the treatment, exacerbate the diseases, and ultimately jeopardize long-term outcomes. In addition, previous studies have shown that chronic renal insufficiency is a predictor of operative mortality and poor long-term survival, especially during cardiac surgery in the elderly.<sup>[10,11]</sup> In our study, CKD coexisted with 12.4% of the total population and show significance in Cox regression analysis.

### 4.4 Etiology and VHD types

In developing countries, a rheumatic etiology of VHD is prevalent,<sup>[12]</sup> whereas, in developed countries, degenerative VHD predominates and is found in 63% of patients.<sup>[2]</sup> Similar low prevalence was observed in infective VHD and congenital VHD in both age group. The prevalence of VHD increases with age, with degenerative valve disease, thought to be the most common VHD in the elderly.<sup>[1,2,13]</sup> Our results have shown MR was the most prevalent valvular disorders in the elderly and was associated with long-term MACEs in the advanced age group. These observations are in accordance with the findings of recent research concluding MR in the developed world is mainly associated with primary degenerative causes or ischemic heart disease.<sup>[14]</sup> Still, the mechanisms underlying these observations remain unclear, and further mechanistic studies are needed.

The relationship between VHD and advanced age varies with valve disease types. We observed distinct VHD profiles for different age group, the ratios of AS and MS are significantly higher in the 65–74 years group. Recent research showed symptomatic, untreated severe AS is associated with a 50% risk of death within 1 or 2 years.<sup>[15–17]</sup> The leading cause of AR in many developing countries is rheumatic fever.<sup>[7]</sup> However, data in industrialized countries demonstrated that in patients  $\geq 65$  years AR etiology was mostly degenerative and the popularity markedly increased with aging.<sup>[1]</sup> In our population, among the four types of VHD diseases in the present study, MR was the most frequent (425 patients, 79.9%). Enriquez-Sarano, *et al.*<sup>[18]</sup> reported that asymptomatic severe MR is associated with a 5-year cardiac mortality rate of nearly 40%.

### 4.5 NYHA

Functional status was frequently misestimated, making it difficult to reflect the severity of disease in elderly patients accurately. This may be attributable to increased age is accompanied by a decline in activity, coupled with changes in lifestyle. In the present investigation, categorization as NYHA class was estimated according to clinical routine. But this difference did not reach statistical significance between the two groups. Cox regression analysis disclosed that NYHA class was linked with long-term MACEs in both groups. This could be partly explained because an assessment of the functional status of elderly patients reflects the general condition to some extent. However, with increasing age, daily activities decrease and lifestyle changes. Consequently, it is difficult for the attending practitioner to accurately assess the functional status of elderly patients with heart disease, especially those with a long-term medical history.<sup>[19,20]</sup>

#### 4.6 Drug therapy

Treatment depends on VHD type and severity but, when severe and symptomatic, usually involves mechanical intervention. In terms of drug treatment, ACEI, beta-blockers and anticoagulant were mostly prescribed to elderly patients. Also, compared with the 65–74 years group, the older patients were less probably being prescribed ACEI, but more diuretics. Although baseline showed no difference in use of beta-blocker or digoxin, interactions between age-group and use of digoxin were statistically significant, and use of beta-blocker, diuretic and digoxin were associated with long-term MACEs in the 65–74 years group. Findings from in a post-hoc analysis by Ahmed *et al.* in elderly heart failure patients suggested that the use of digoxin in low doses was significantly associated with reduced mortality and hospitalization.<sup>[21]</sup> However, data on dose of medications was not available in the present study.

#### 4.7 Limitations

The main limitation of this retrospective, observational study is that the findings are mostly based on a regional single-center database, which makes it difficult to obtain comprehensive information regarding VHD prevalence and so on, due to potential selection bias. In addition, data on the dosage of medications were not available in the current study. Finally, comorbidity was based on broad pathophysiological disease categories to explore potential causal mechanisms. We were therefore mostly unable to fully detect associations between combined diagnoses and prognosis among older patients. Any observed associations should also be viewed as correlations and not taken as proof of causality without further evidence. Future studies to confirm our findings can be enhanced by a more comprehensive assessment.

#### 4.8 Conclusion

In geriatric patients with VHD, there were apparent differences between the 65–74 years old group and the  $\geq 75$ -year old group. Patients aged  $\geq 75$  years had a worse prognosis and reduced survival than the 65–74 years old group. Comorbidities in the elderly are frequent and profoundly affect long-term outcomes.

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