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Prospective cohort study of characteristics and sex differences in elderly patients with degenerative valvular disease

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ABSTRACT

Objectives We aimed to describe the characteristics and to compare the sex differences in the clinical features and prognosis of Chinese elderly patients with senile degenerative valvular heart disease (VHD).

Design This study was a nationwide, multicentre, prospective cohort study.

Setting Participants were enrolled consecutively from 69 hospitals nationwide in China from September to December 2016.

Participants A total of 2728 patients aged ≥60 years old with an aetiological diagnosis of moderate to severe degenerative VHD as defined by echocardiography were recruited.

Main outcome measures The baseline data and 1-year follow-up data were collected, and disease distribution, clinical features, treatment and prognosis were compared between different sex groups.

Results Aortic disease was more common in men, and mitral disease was more common in women. Male patients were more likely to have smoking, coronary heart disease, cardiomyopathy, chronic obstructive pulmonary disease and coronary artery bypass grafting histories, while female patients had more hypertension and atrial fibrillation. The average age and left ventricular ejection fraction were significantly lower in men than in women (p<0.001), while the intervention rate (p=0.026) and total hospitalisation cost (p=0.016) of male patients were higher than those of female patients. There were no significant differences in perioperative complications, in-hospital outcomes or short and intermediate prognoses between the two groups.

Conclusions Currently, the intervention rate of elderly patients with VHD is still not ideal, with dominant factor—patient rejection. Heart failure was the critical reason for rehospitalisation. There were some differences between men and women in the distribution, severity, clinical characteristics and interventions in senile degenerative valvular disease.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study was a national, multicentre, prospective cohort study of elderly patients with valvular heart disease.
⇒ We has a strong and dedicated study team and completed a 1-year follow-up of patients.
⇒ This study was conducted in hospitals capable of performing heart surgery, so that there was selection bias.

INTRODUCTION

The burden from different valvular heart diseases (VHDs) has demonstrated diverse changes at the global level over the past three decades. Although rheumatic heart disease burden has obvious means for mitigation, a substantially high incidence of non-rheumatic VHD was observed over this time period, especially in elderly individuals, which could lead to high healthcare costs and signify the potential for even higher costs in the future.[1]

The incidence of senile degenerative VHD (SDVHD) is increasing annually with the prolongation of the human lifespan, seriously affecting the heart health and quality of life in elderly individuals.[2 3] In industrialised countries, the incidence of VHD in people older than 75 years old was as high as 13.2%, while in people younger than 75 years old, it was less than 2%.[4 5] The critical aetiology was senile degeneracy, with clinical manifestations of aortic stenosis (AS) and mitral regurgitation (MR). With the progress of China's social ageing and improvements in quality of life and medical level, the number of patients with SDVHD has gradually increased, and the aetiology has changed significantly—rheumatic heart disease has decreased significantly and gradually evolved into degenerative valvular disease.[6] Similar to the statistical results from the Chinese adult cardiac surgery database,[7] from 1997 to 2013, the proportion of degenerative valvular disease increased annually, from less than 10% to nearly 30%. Since medication therapy is often ineffective for the treatment of advanced VHD, surgery is recommended by the 2014 American College

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of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of patients with VHD.[8] However, there are currently only a few single-centre clinical studies on VHD in China, and the results of large-scale epidemiological investigations remain lacking.

The China-DVD (China Elderly Valve Disease; ClinicalTrials.gov: NCT02865798) study is a nationwide, multicentre, prospective cohort study for elderly inpatients aged ≥60 years old with VHD.[9] The data in this study came from the China-DVD database. The objective of the paper was to describe the demographic characteristics, clinical characteristics, diagnosis and treatment status of patients and to analyse sex differences in SDHVD. We present the following article in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology reporting checklist.

MATERIALS AND METHODS

China-DVD study design

The study was designed to include all consecutive consenting patients who met the inclusion criteria at 69 medical centres throughout mainland China between 1 September 2016 and 30 December 2016.

Inclusion criteria

Age ≥60 years and;

- Moderate or severe native VHD as defined by echocardiography using an integrative approach according to the 2014 AHA/ACC guidelines.[8]
- Diagnosis of suspected or definite endocarditis as assessed by Duke criteria.
- Patients who had undergone any operation on a cardiac valve (percutaneous balloon commissurotomy, valve repair, valve replacement).

Exclusion criteria

- Patients who could not participate in the follow-up for various reasons.
- Patients with serious diseases whose life expectancy was less than 1 year.

The case report form was completed by investigators in each hospital (online supplemental file 1), including details regarding the demographic, clinical and echocardiographic characteristics; aetiology; treatment modalities; in-hospital complications and discharge status of the patient. A follow-up was to be performed either personally or by telephone by the local investigator at 6 months and 1 year, including changes in symptoms, major complications, cardiovascular events, rehospitalisation, treatment modalities, etc.

The National Coordination Centre was responsible for training investigators, as well as data review, management, preservation and analysis. Site audits for source document verification versus data collected in the central database were randomly performed by the NCC staff at the sample sites.

Study population

The study enrolled 2728 patients with an aetiological diagnosis of degenerative VHD, who came from 8227 consecutive patients with moderate or severe native VHD as defined by echocardiography in the China-DVD study.

Analysis index

This study not only described the demographic and clinical characteristics (including risk factors, comorbidities, symptoms, disease stage, left ventricular ejection fraction (LVEF)), disease distribution, type of intervention and causes, operative mortality and morbidity but also analysed the rehospitalisation rate, cardiovascular event incidence (including acute heart failure, acute myocardial infarction, stroke, thrombosis, etc) and prognosis during the follow-up. Furthermore, we also compared the differences between patients across sex groups.

Patient and public involvement

Patients were not directly involved in protocol development. NCC staff evaluated, edited and approved the protocol and all study materials. Heads of research centres participated in developing procedures that would minimise their time and effort on study.

Statistical analysis

All testing was performed using SAS statistical software, V.9.4. Summary statistics (means, SD and proportions) were calculated to describe patients' baseline demographics and clinical characteristics. Differences between groups were compared using the t-test or analysis of variance for quantitative data and the χ^2 test for qualitative data. Survival curves were plotted using the Kaplan-Meier method, and intergroup comparisons were performed using the log-rank test. Significant differences between groups were defined as a two-sided alpha level of $p<0.05$.

RESULTS

Type and severity of heart valve disease

Among the 2728 patients with degenerative heart valve disease, multiple valve disease was the most common (941, 34.49%). However, among single native valve diseases, MR was the most frequent (625, 22.91%), followed in order by aortic regurgitation (AR) (464, 17.01%), tricuspid regurgitation (TR) (398, 14.59%), AS (265, 9.71%), mitral stenosis (MS) (28, 1.03%), pulmonic regurgitation (6, 0.22%), tricuspid stenosis (1, 0.04%) and pulmonic stenosis (0, 0%).

It was found that aortic disease was more frequent in male patients (male vs female: 488, 49.39% vs 241, 30.16%; $p<0.001$), while mitral disease was more frequent in female patients (male vs female: 305, 30.87% vs 348, 43.55%; $p<0.001$) (figure 1A). Regarding the severity of valve disease, although there were differences between the two groups, the difference was not statistically significant (figure 1B).

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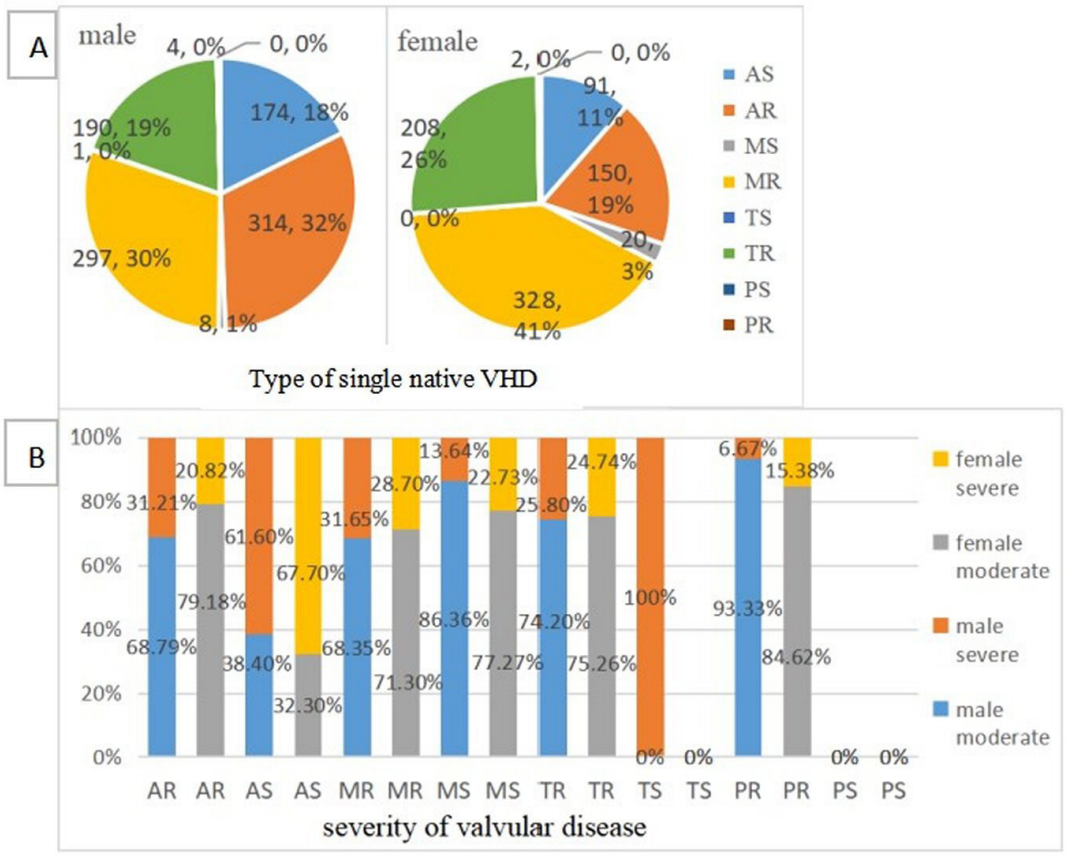

Figure 1 (A) The type of single native VHD in the two groups. (B) The severity of VHD in the two groups. AR, aortic regurgitation; AS, aortic stenosis; MR, mitral regurgitation; MS, mitral stenosis; PR, pulmonic regurgitation; PS, pulmonic stenosis; TR, tricuspid regurgitation; TS, tricuspid stenosis; VHD, valvular heart disease.

Clinical characteristics

The baseline characteristics of all patients and comparisons between different sex groups are summarised in table 1. Among the 2728 patients, the mean age was 72.19±7.75 years, and 1520 (55.72%) were men. Of these patients, 1150 (42.16%) were aged 60–70 years, 1033 (37.86%) were aged 70–80 years and 545 (19.98%) were ≥80 years. In contrast, the mean age of male patients was lower than that of female patients (male vs female: 71.65±7.73 vs 72.84±7.74; p<0.001), and there was also a significant difference between the two groups in age stratification (p=0.003). Male patients in the low age group 60–70 years old were significantly more numerous than female patients. Compared with female patients, male patients had worse cardiac function, lower LVEF and a more advanced stage.

There were only 477 (17.49%) patients who had known heart valve disease before, and more than half of the patients (1491, 54.66%) were hospitalised for cardiovascular diseases other than VHD, 1185 (43.44%) for VHD and 52 (1.91%) for other diseases. Among all of the enrolled patients, 271 (9.99%) were hospitalised repeatedly due to VHD within 3 months, of whom there were significantly more male patients than female patients (male vs female: 168, 11.12% vs 103, 8.57%; p=0.027).

Interventions performed

An intervention was planned in 762 (27.93%) patients during the study period, of whom 43 patients completed the intervention during the 1-year follow-up. Of 719 patients who underwent interventions during registration, either surgical (645, 89.71%) or percutaneous (74, 10.29%), interventions were performed on an elective basis in 607 (84.42%), urgently in 111 (15.44%) (performed during the same hospital stay), and as an emergency in 1 (0.14%) (within 24 hours after admission).

The proportion of intervention in male patients was significantly higher than that in female patients (male vs female: 426, 28.03% vs 293, 24.25%; p=0.026), but there was no significant difference in modalities (p=0.708) (figure 2A) or combined procedures (male vs female: 152, 35.68% vs 94, 32.08%; p=0.318) nor in the type of combination (p=0.253) (figure 2B).

The utilisation rate of bioprostheses was higher (237, 64.95%) than that of mechanical prostheses (128, 35.05%) among prosthetic valve replacements, with no difference in sex (male vs female: 217, 63.27% vs 148, 67.58%; p=0.296) (figure 3A). Moreover, the utilisation rate of bioprostheses increased with increasing age (figure 3B).

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Table 1 The baseline characteristics of the enrolled patients

Items	Total N=2728	Male n=1520	Female n=1208	P value
Age (year)	72.19±7.75	71.65±7.73	72.87±7.74	<0.001
Age stratification (year)				0.003
60–69	1150 (42.16%)	674 (44.34%)	476 (39.40%)	
70–79	1033 (37.86%)	574 (37.76%)	459 (38.00%)	
≥80	545 (19.98%)	272 (17.89%)	273 (22.60%)	
BMI (kg/m^2)	23.47±3.50	23.60±3.23	23.30±3.80	<0.001
Current smoke	852 (31.23%)	795 (52.44%)	57 (4.73%)	<0.001
hypertension	1581 (57.95%)	842 (55.43%)	739 (61.23%)	0.002
CAD	913 (33.47%)	534 (35.13%)	379 (31.37%)	0.039
Diabetes	511 (18.73%)	275 (18.12%)	236 (19.59%)	0.329
Hyperlipidaemia	227 (8.32%)	128 (8.52%)	99 (8.28%)	0.397
AF	832 (30.57%)	413 (27.26%)	419 (34.71%)	<0.001
Cardiomyopathy	119 (4.36%)	81 (5.34%)	38 (3.17%)	0.006
Stroke	322 (11. 80%)	186 (12.24%)	136 (11.27%)	0.436
Aortic disease	202 (7.44%)	120 (7.93%)	82 (6.83%)	0.281
Renal insufficiency	205 (7.52%)	125 (8.22%)	80 (6.64%)	0.132
COPD	173 (6.35%)	127 (8.36%)	46 (3.81%)	<0.001
Previous intervention	664 (24.34%)	382 (25.13%)	282 (23.34%)	0.279
PCI	291 (10.67%)	177 (11.64%)	114 (9.44%)	0.063
CABG	55 (2.02%)	41 (2.70%)	14 (1.16%)	0.004
Pacemaker	162 (5.94%)	85 (5.59%)	77 (6.37%)	0.390
Catheter ablation	54 (1.98%)	29 (1.91%)	25 (2.07%)	0.763
Peripheral vascular stent implantation	27 (0.99%)	17 (1.12%)	10 (0.83%)	0.446
Others	190 (6.96%)	105 (6.91%)	85 (7.04%)	0.895
Repeated hospitalisation due to HVD within 3 months	271 (9.99%)	168 (11.12%)	103 (8.57%)	0.027
Symptom				
Angina pectoris	781 (33.08%)	455 (34.55%)	326 (31.23%)	0.088
Palpitation	817 (34.49%)	412 (31.31%)	405 (38.46%)	<0.001
Syncope	116 (4.99%)	60 (4.64%)	56 (5.42%)	0.392
Cardiac insufficiency	1841 (76.87%)	1045 (77.93%)	796 (75.52%)	0.381
Systolic pressure (mm Hg)	132.42±21.00	131.66±21.21	133.41±20.65	0.031
Diastolic pressure (mm Hg)	74.20±13.65	73.66±13.94	74.85±13.24	0.023
HR (beats/min)	78.39±17.77	77.39±16.34	79.64±19.34	0.001
NYHA Class				0.505
Class I	65 (3.51%)	42 (4.03%)	23 (2.85%)	
Class II	564 (30.49%)	323 (30.97%)	241 (29.86%)	
Class III	898 (48.54%)	499 (47.84%)	399 (49.44%)	
Class IV	323 (17.46%)	179 (17.16%)	144 (17.84%)	
Disease stage				0.042
Stage A	13 (0.48%)	5 (0.33%)	8 (0.68%)	
Stage B	1091 (40.68%)	574 (38.34%)	517 (43.63%)	
Stage C1	318 (11.86%)	185 (12.36%)	133 (11.22%)	
Stage C2	16 (0.60%)	8 (0.53%)	8 (0.68%)	
Stage D	1243 (46.35%)	725 (48.43%)	518 (43.71%)	
LVDD (mm)	54.12±20.61	56.42±18.96	51.20±22.20	<0.001
LVEF (%)	55.16±12.56	53.86±13.00	56.82±11.78	<0.001

Continued

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Table 1 Continued

Items	Total N=2728	Male n=1520	Female n=1208	P value
PAH	1046 (38.34%)	553 (36.38%)	493 (40.81%)	0.018
NT-pro-BNP (pg/mL)	3983.68±6309.31	4041.95±6307.03	3912.56±6316.93	0.717

AF, atrial fibrillation/ atrial flutter; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary heart disease; COPD, chronic obstructive pulmonary disease; HR, heart rate; LVDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PCI, percutaneous coronary intervention.

Of 2009 patients without intervention, 991 had no indications for intervention after evaluation currently. In addition, the reasons for not performing an intervention in patients with indications while in New York Heart Association (NYHA) class III or IV, were high risk for intervention (202, 27.01%), high cost (13, 1.74%) and a principal reason—patient rejection (255, 34.09%) (figure 3C).

The average length of stay of 2728 patients was 12.15±9.89 days, including 1.67±3.76 days in the intensive care unit (ICU). Sixty-four patients (8.90%) had complications during the perioperative period among the 719 patients who underwent interventions. The postoperative complication with the highest incidence was massive haemorrhage (18, 20.45%), followed by renal insufficiency (7, 7.95%), severe nosocomial infection (5, 5.68%), stroke (2, 2.27%), atrial fibrillation (2, 2.27%) and high-grade atrioventricular block (2, 2.27%). There were no acute myocardial infarctions or thromboembolic events. Furthermore, it was found that there was no significant differences in perioperative complications, hospital stay or ICU stay between patients of different sexes. However, the hospitalisation cost of male patients was significantly higher than that of female patients (male vs female: 61334.61±93 934.56 vs 53 669.08±65 609.98; p=0.016).

One-year follow-up

A total of 2103 (77.09%) of the patients completed a 1-year follow-up, with a median follow-up time of 373 days, including 30 deaths during study registration. The overall 1-year survival patients was 1884 (89.59%), with no sex difference (male vs female: 1032, 89.12% vs 852, 90.16%; p=0.438) (figure 4).

The events at the 1-year follow-up and the comparisons between different sex groups are shown in table 2: rehospitalisation (823, 39.7%) and mortality (189, 9.12%). The dominant cause for rehospitalisation was heart failure, and for death, it was cardiogenic. There was no significant difference between sexes in rehospitalisation (p=0.134) or mortality (p=0.838) over the 1-year follow-up.

DISCUSSION

SDVHD is the most common heart valve disease in elderly individuals, with the incidence being second only to hypertension and coronary heart disease (CHD).[10] According to the results of the Euro Heart Survey on VHD,[2 11] degenerative aetiologies accounted for approximately 81.9% of all AS, AR for 50.3%, MS for 12.5% and MR for 61.3%. Age is a major risk factor for SDVHD, with an older age

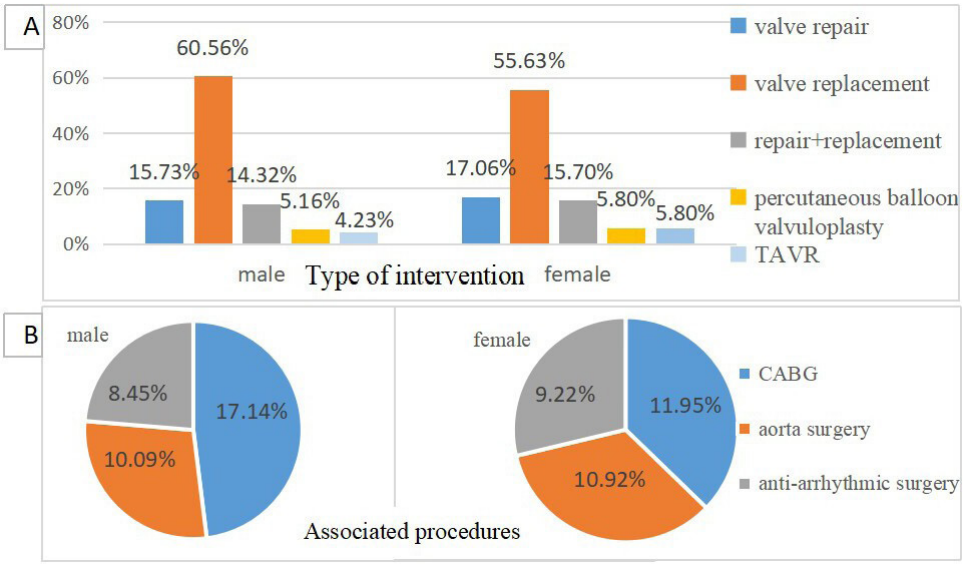

Figure 2 Interventions and prognoses of patients with VHD. (A) Distribution of intervention types in patients of different sexes. (B) Associated procedures for patients of different sexes. CABG, coronary artery bypass grafting; TAVR, transcatheter aortic valve replacement; VHD, valvular heart disease.

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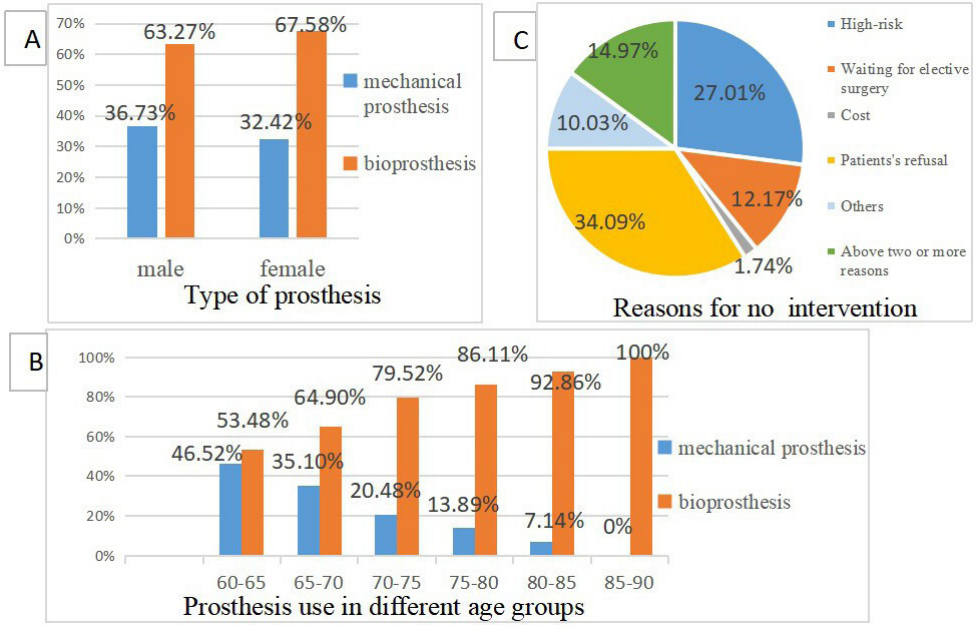

Figure 3 Prosthetic valve usage in patients with VHD. (A) Use of prostheses in patients of different sexes. (B) Reasons why patients with indications for intervention did not undergo intervention. (C) Distribution of bioprostheses with age. VHD, valvular heart disease.

related to a higher prevalence of SDVHD. A single-centre community-based survey in southern China showed that 36.9% of people older than 65 years old were diagnosed with degenerative valvular disease, and degeneration was the most common aetiology of VHD.[12 13] It also demonstrated that the prevalence of SDVHD increased with advancing age to up to 53.0% among those ≥75 years of age, and it differed by region of residence, educational level and occupation. The distribution of SDVHD differs in different populations: AS is more common in European populations, while valve regurgitation is more common in Chinese populations.

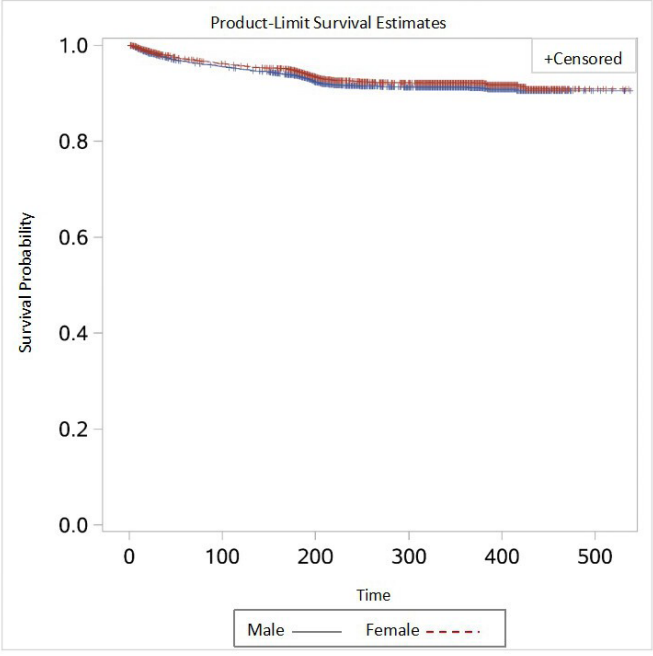

Figure 4 One-year survival of all patients of different sexes.

Currently, there are no definite conclusions on sex differences in degenerative valvular disease. Previous studies have demonstrated that mitral annular calcification is more frequent in women and aortic valve calcification in men. Furthermore, aortic valve calcification in men was twice as common as in women, as shown by Stewartd *et al* in their research on aortic valve calcification in elderly individuals.[14] It has also been reported that the severity of AS in female patients was higher than that in men[15]; however, the gender difference reported in domestic reports is not as obvious as that in foreign countries. In this study, there were more male patients in total than female patients, but the male patients were younger. Similar to previous reports regarding single native valvular disease, aortic valve lesions, including stenosis and regurgitation, were more common in male patients than in female patients, while mitral valve lesions were more common in female patients. This finding might be related to the increased number of male patients with atherosclerosis. The data in this study also suggested that there were significantly more male patients with CHD and a history of coronary artery bypass grafting (CABG) than female patients. In addition, it was found that the proportions of women with severe AS, severe MS and severe PR were larger, but the differences were not statistically significant.

In this study, male patients were more complicated by CHD, cardiomyopathy and chronic obstructive pulmonary disease, which could be associated with more than half of male patients having a smoking history and a higher body mass index. Moreover, compared with men, female patients were more prone to having palpitations, as well as with a higher blood pressure and heart rates. This difference might

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Table 2 Events at the 1-year follow-up for patients of different sexes

	Total N=2073	Male N=1137	Female N=936	P value
Rehospitalisation	823 (39.70%)	468 (41.16%)	355 (37.93%)	0.134
Reasons				0.425
Stroke	22 (2.67%)	10 (2.14%)	12 (3.38%)	0.273
New AF	15 (1.82%)	6 (1.28%)	9 (2.54%)	0.183
Heart failure	322 (39.13%)	173 (36.97%)	149 (41.97%)	0.145
AMI	16 (1.94%)	9 (1.92%)	7 (1.97%)	0.960
Haemorrhage	2 (0.24%)	1 (0.21%)	1 (0.28%)	1.000
Thromboembolism	3 (0.36%)	1 (0.21%)	2 (0.56%)	0.810
Renal failure	5 (0.61%)	3 (0.64%)	2 (0.56%)	1.000
Pacemaker	5 (0.61%)	2 (0.43%)	3 (0.85%)	0.756
Prosthesis dysfunction	8 (0.97%)	3 (0.64%)	5 (1.41%)	0.452
Others	272 (33.05%)	164 (35.04%)	108 (30.42%)	0.163
Missing data	153 (18.59%)	96 (20.51%)	57 (16.06%)	0.104
Mortality	189 (9.12%)	105 (9.23%)	84 (8.97%)	0.838
Reasons				0.378
Cardiac death	119 (62.96%)	71 (67.62%)	48 (57.14%)	0.138
Non-cardiac death	13 (6.88%)	7 (6.67%)	6 (7.14%)	0.898
Unknown	18 (9.52%)	10 (9.52%)	8 (9.52%)	1.000
Missing data	39 (20.63%)	17 (16.19%)	22 (26.19%)	0.091

AF, atrial fibrillation; AMI, acute myocardial infarction.

be because anxiety and hypertension were more frequent in women than in men. We found that there was no significant difference in NYHA, disease stage or N-terminal pro-B-type natriuretic peptide in the different sexes; nevertheless, the male patients in stage D were more numerous than the women, and LVEF measured by echocardiography was lower than that of female patients. We also found that the rehospitalisation rate of men due to VHD was higher than that of women. Therefore, it is suggested that male patients have worse cardiac function and more serious conditions, which could account for the higher rate of intervention in male patients.

Although there was no significant difference between the two groups in terms of serious perioperative complications, hospitalisation days, or ICU days, the total cost of hospitalisation for male patients was significantly higher than that for women. Presumably, this outcome occurred because men were sicker, had worse cardiac function and had a higher rate of interventions, especially surgery. Furthermore, the follow-up data indicated that heart failure was the foremost factor affecting the rehospitalisation and quality of life of patients with VHD. Accordingly, strengthening the monitoring and management of cardiac function of patients posthospitalisation is of great significance to improve patients' quality of life.

It has been reported in past research that sex is an important indicator affecting the prognosis of cardiac surgery.[16] Compared with men, female patients had a higher short-term mortality rate after CABG[17 18] and a worse long-term prognosis after CABG combined with valve surgery.[19 20] Chandrasekhar *et al* suggested that male patients with AS treated with transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR) had the same effect,[15] while female patients treated with transfemoral TAVR had a significantly higher survival rate than those treated with SAVR. For mitral disease, different from European and American guidelines, female patients are more likely to undergo valve replacement rather than repair,[21] and they have poorer long-term outcomes.[22] A European registration study of MitraClip (ACCESS-EU) recently confirmed that there were no significant gender differences in safety, effectiveness and survival rate after MitraClip during the 30-day and 1-year follow-ups, but the proportion of female patients going to nursing homes rather than going home after discharge was significantly higher than that of male patients, suggesting that female patients must better optimise their physical state perioperatively.[23] To date, the reason for the poor prognosis of women is not clear. During the 1-year follow-up, no significant differences were found between the male and female groups in terms of rehospitalisation rate, reasons for rehospitalisation, and mortality. This study, which enrolled elderly individuals older than 60 years old, had the limitations of selection bias and a short follow-up time. In the future, it is necessary to expand the sample size and prolong the follow-up time for further analysis.

In conclusion, many studies at home and abroad have suggested that there are ethnic and sex differences in the distribution, clinical characteristics and prognosis of

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SDVHD. It is of great clinical and social significance to strengthen the understanding of risk factors and clinical characteristics of SDVHD and recommend individualised treatment schemes for different patients.

Limitations

First, this study was conducted in hospitals capable of performing heart surgery, so that there was selection bias. Second, there was also a selection bias because only inpatients were included. Finally, We collected 1-year follow-up data, which could not reflect the long-term prognosis of patients with SDVHD.

Conclusions

Currently, the intervention rate of elderly individuals with VHD is still not ideal, with a dominant factor—patient rejection. Heart failure was the critical reason for rehospitalisation. Male patients had worse cardiac function and more serious conditions, which might account for the higher rate of intervention in men. There were some differences between men and women in the distribution, severity, clinical characteristics and interventions in senile degenerative valvular disease.

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Supplemental Table 1 Participating centers in the study

Province	Participated	Local PI
Beijing	Fuwai Hospital	Yongjian Wu
Guangdong	Guangdong Provincial Hospital	Jianfang Luo
Beijing	Beijing Anzhen Hospital	Wei Liu, Haibo Zhang
Chongqing	Xinqiao Hospital	Shiyong Yu
Sichuan	West China Hospital	Mao Chen, Yingqiang Guo
Shanghai	Zhongshan Hospital affiliated to Fudan University	Daxin Zhou
Hubei	Asia Heart Disease Hospital	Xi Su
Hunan	The Second Xiangya Hospital of Central South University	Xinqun Hu
Henan	The First Hospital affiliated to Zhengzhou University	Chunguang Qiu
Fujian	Union Hospital affiliated to Fujian Medical University	Lianglong Chen
Shanxi	Xijing Hospital	Lin Tao, Jian Yang
Shanghai	Shanghai Changhai Hospital	Xianxian Zhao
Henan	Henan Provincial Hospital	Chuanyu Gao
Liaoning	Northern Hospital	Quanmin Jing
Anhui	Anhui Provincial Hospital	Likun Ma
Hunan	Xiangya Hospital Central South University	Zaixin Yu
Guizhou	Guizhou Provincial Hospital	Qiang Wu
Jiangsu	Nanjin First Hospital	Shaoliang Chen
Jiangxi	The First Hospital affiliated to Nanchang University	Zheqi Zheng
Jiangsu	Nanjing Gulou Hospital	Biao Xu
Zhejiang	The Second Hospital affiliated to Zhejiang University	Xiambao Liu
Jiangxi	The Second Hospital affiliated to Nanchang University	Yanqing Wu
Heilongjiang	The Second Hospital affiliated to Haerbin Medical University	Bo Yu
Xinjiang	The First Hospital affiliated to Xinjiang Medical University	Xiang Ma
Tianjin	Taida International Cardiovascular Hospital	Zhigang Liu
Tianjin	Tianjin Chest Hospital	Hongliang Cong
Shanghai	Ruijin Hospital affiliated to Shanghai Jiaotong University	Ruiyan Zhang
Shandong	Linyi People's Hospital	Yanjin We
Shandong	Hospital affiliated to Jinin Medical School	Qingxian Li
Shandong	Qingdao Fuwai Hospital	Xianyan Jiang
Sichuan	Sichuan Provincial Hospital	Jianhong Tao

Zhejiang	Shaoyifu Hospital affiliated to Zhejiang University	Guosheng Fu
Beijing	Army General Hospital	Changfu Liu
Shanxi	The First Hospital affiliated to Xian Jiaotong University	Zuyi Yuan
Gansu	The First Hospital affiliated to Lanzhou University	Zheng Zhang
Jilin	The Second Hospital affiliated to Jilin University	Bin Liu
Yunnan	The First Hospital affiliated to Kunming Medical School	Tao Guo
Jiangsu	Xuzhou Central Hospital	Bin Han
Chongqing	Southwest Hospital	Zhihui Zhang
Jiangxi	Jiangxi Provincial Hospital	Lang Hong
Guangdong	Shenzhen Sunyixian Cardiovascular Hospital	Qiang Liu
Heilongjiang	The First Hospital affiliated to Haerbin Medical University	Yue Liu
Henan	Zhengzhou Seventh People's Hospital	Yiqiang Yuan
Ningxia	General Hospital affiliated to Ningxia Medical University	Saobin Jia
Liaoning	Zhongshan Hospital affiliated to Dalian Medical University	Xiaoming Bian
Sichuan	Nanchong Central Hospital	Haoyu Wang
Guangdong	Meizhou People's Hospital	Wei Zhong
Fujian	First Hospital affiliated to Xiamen University	Weihua Ke
Anhui	Yijishan Hospital affiliated to Wannan Medical School	Yongshen Ke
Guangdong	Sunyixian Hospital affiliated to Zhongshan University	Jingfeng Wang
Fujian	Quanzhou First Hospital	Rong Lin
Shanghai	Shanghai Changzheng Hospital	Chun Liang
Shandong	Tantai Yuhuangding Hospital	Chuanhuan Zhang
Anhui	Hospital affiliated to Bengbu Medical School	Hongju Wang
Shanxi	Shanxi Cardiovascular Hospital	Jian An
Inner Mongolia	Hospital affiliated to Inner Mongolia Medical University	Yuexi Wang
Guangdong	Southern Hospital affiliated to Southern Medical University	Yuqing Hou
Qinghai	Hospital affiliated to Qinghai University	Weijun Liu
Ganshu	Gansu Provincial Hospital	Ping Xie
Tianjin	Tianjin First Central Hospital	Chengzhi Lu
Guangxi	The First Hospital affiliated to Guangxi Medical University	Weifeng Wu
Zhejiang	The First Hospital affiliated to Zhejiang University	Li Zhang
Sahnxi	Tangdu Hospital affiliated to Forth Army Medical University	Haichang Wang

Hubei	Wuhan Union Hospital	Xiang Cheng
Sichuan	Hospital affiliated to Southwestern Medical University	Zhongcai Fan
Guangdong	Shenzhen People's Hospital	Shaohong Dong
Shanxi	Shanxi Provincial Hospital	Hong Zhang
Shanghai	Shanghai Chest Hospital	Xinkai Qu
Inner Mongolia	The First Hospital affiliated to Baotou Medical School	Hanjun Pei