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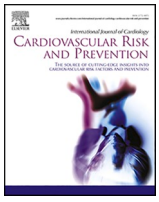

Contemporary spectrum, characteristics, and outcomes of adult patients with rheumatic valvular disease in China: Insights from the China-VHD study

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ABSTRACT

Background: Rheumatic valvular disease (RVD) represents a significant health concern in developing countries, yet a scarcity of detailed data exists. This study conducts a comprehensive examination of RVD patients in China, exploring aspects of the disease's spectrum, characteristics, investigation, management, and outcomes.

Methods: The China Valvular Heart Disease (China-VHD) study, a nationwide, multicenter, prospective observational study, enrolled 13,917 adults with moderate-to-severe valvular heart disease from April to June 2018. Among these, 2402 patients with native RVD (19.7% of native VHD patients) were analyzed.

Results: Among the RVD patients, the median age was 57 years (interquartile range 50–65), with 82.5% falling within the 40–70 age range; females were notably predominant (63.9%). Rheumatic etiology prevailed, particularly in southern regions (48.8%). Multivalvular involvement was observed in 47.4% of RVD cases, and atrial fibrillation emerged as the most common comorbidity (43.2%). Severe RVD affected 64.2% of patients. Valvular interventions were undertaken by 66.9% of RVD patients, predominantly involving surgical valve replacement (90.8%). Adverse events, encompassing all-cause mortality and heart failure hospitalization, occurred in 7.3% of patients during the 2-year follow-up. Multivariable analysis identified factors such as age, geographical region, low body mass index, renal insufficiency, left atrial diameter, and left ventricular ejection fraction <50% (all $P < 0.05$) associated with adverse events, with valvular intervention emerging as a protective factor (HR: 0.201; 95%CI: 0.139 to 0.291; $p < 0.001$).

Conclusions: This study delivers a comprehensive evaluation of RVD patients in China, shedding light on the spectrum, characteristics, investigation, management, and outcomes of this prevalent condition.

1. Introduction

Rheumatic heart disease (RHD) remains a prominent infectious disease in low- and middle-income countries (LMICs), although its incidence has significantly decreased in China due to rapid economic development [1,2]. Despite this decline, RHD continues to impact approximately 40 million individuals globally, claiming nearly 300,000 lives annually, with a substantial proportion of RHD-related deaths occurring in China in 2015 [3]. Recognizing the ongoing significance of RHD, it is imperative to assess its current status in China.

Valvular involvement is a hallmark manifestation of RHD, leading to the development of rheumatic valvular disease (RVD) [4]. In contrast to

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other cardiovascular diseases, the existing literature on valvular heart disease (VHD) in China reveals a notable scarcity of comprehensive registers or trials. This disparity underscores the necessity for a meticulous investigation into the contemporary spectrum, characteristics, and outcomes of adult patients grappling with RVD.

Therefore, the aims of the study were four-fold: (i) to assess the frequency and distribution of RVD, (ii) to describe the characteristics of patients with RVD, (iii) to evaluate the management, and (iv) to evaluate the survival outcomes of patients with RVD within this expansive and contemporary cohort. By addressing these objectives, we aim to contribute valuable insights into the current landscape of RVD in China filling a critical gap in the existing literature.

2. Methods

2.1. Study design

The China Valvular Heart Disease (China-VHD; NCT03484806) study is a nationwide, multicenter, prospective observational study. Adults (≥18 years) with a diagnosis of moderate or severe VHD were consecutively enrolled in outpatient clinics or inpatient wards at 46 medical centers throughout Mainland China, based on clinical and echocardiographic criteria [5] (Supplementary material online, Table S1). Details about data collection and quality control of the China-VHD study were described in Supplementary Methods. Recruitment was performed from April to June 2018. Follow-up was done personally or telephonically every six months for two years. This project was approved by the central and site Institutional Review Board or Ethics Committees. Written informed consent was obtained from all participants before registration.

2.2. Inclusion criteria and diagnostic definitions

In China-VHD study, patients were included if they fulfilled the following criteria: signed informed consent, age ≥18 years, moderate or severe VHD, suspected or definite endocarditis (based on the Duke criteria), or previous valvular intervention.

Detailed criteria for clinically significant native VHD were as follows:

- aortic stenosis (AS) with a valve area of ≤1.5 cm^2 or a maximal jet velocity of ≥3 m/s or a mean pressure gradient of ≥20 mmHg,
- or aortic regurgitation (AR) with a grade of ≥2/4,
- or mitral stenosis (MS) with a valve area of ≤1.5 cm^2,
- or mitral regurgitation (MR) with a grade of ≥2/4,
- pulmonary stenosis (PS), pulmonary regurgitation (PR), tricuspid stenosis (TS), and tricuspid regurgitation (TR) with a moderate or severe grade.

Severe VHD was defined as follows:

- AS with a valve area of ≤1.0 cm^2 or a maximal jet velocity of ≥4 m/s or mean pressure gradient of ≥40 mmHg,
- or AR with a regurgitation grade of ≥3/4, MS with a valve area of ≤1.0 cm^2,
- MR with a regurgitation grade of ≥3/4,
- or pulmonary stenosis with a maximal jet velocity of ≥4 m/s,
- or PR with a severe grade, TS with a valve area of ≤1.0 cm^2 or pressure gradient of ≥5 mmHg, and TR with a severe grade.

In our study, patients with moderate-to-severe RVD in China-VHD were selected after we excluded patients with suspected or definite endocarditis (n = 9) or previous valvular intervention (n = 744) (Fig. 1). The etiological definition of rheumatic valvular disease refers to the structural damage, fibrosis, adhesion, and shortening of heart valves caused by rheumatism, resulting in stenosis or insufficiency of one or more valves. Typical rheumatic valve changes can be seen by echocardiography.

Isolated RVD was defined as a stenotic or regurgitant lesion on a single valve. Mixed RVD was defined as both significant stenosis and regurgitation on a single valve. Mixed aortic VHD (AS + AR or MaVHD) was defined as both significant stenosis and regurgitation on an aortic valve. Mixed mitral VHD (MS + MR or MmVHD) was defined as both significant stenosis and regurgitation on a mitral valve. Multiple VHD (MVHD) was characterized by the combination of at least moderate stenotic or regurgitant lesions on ≥2 valves. Severe multiple RVD was defined by the presence of severe lesions on at least one valve.

2.3. Study variables

Data variables with standard definitions included patient demographics, comorbidities, medical history, presentation, investigations, interventions, complications, medications, and outcomes.

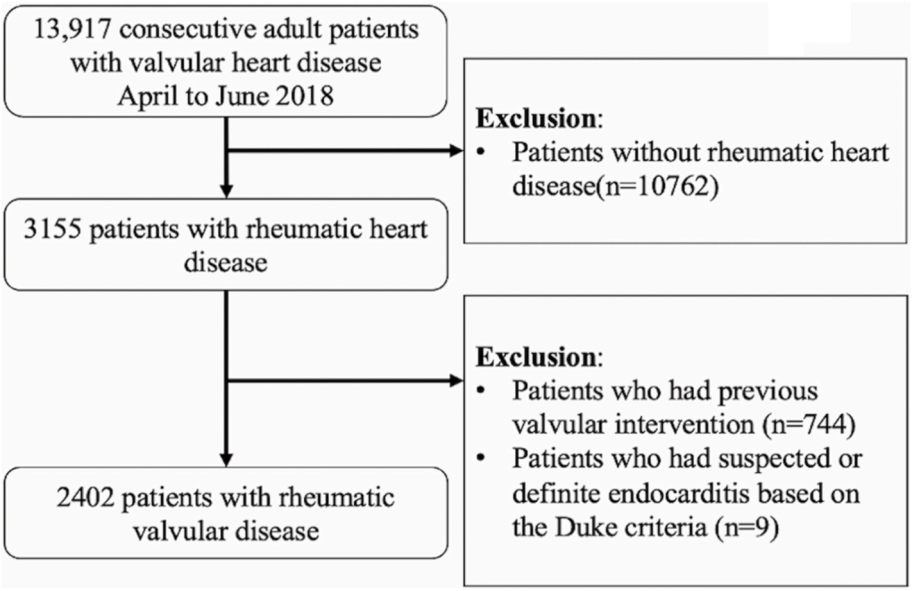

Fig. 1. Flow chart of the study population.

Vital status, rehospitalization, and intervention were collected during follow-up. The etiologies of VHD were classified based on clinical context, echocardiography, computed tomography, and surgical findings (if available).

2.4. Echocardiography

All patients underwent comprehensive 2-dimensional transthoracic echocardiography using standard ultrasound systems. Dimensions of the left ventricle (LV) and left atrium (LA) were measured as recommended by the American Society of Echocardiography and the European Association of Cardiovascular Imaging [6] and indexed to body surface area. LV systolic function was assessed using LV ejection fraction (LVEF) using the biplane modified Simpson method. Before recruitment, images from sampled centers were verified for diagnostic accuracy and measurement consistency at the core laboratory at Fuwai Hospital. Operators were blinded to the results from each center. Detailed quality control of echocardiographic measurements is in Supplementary Methods.

2.5. Clinical outcomes

The primary endpoint was a composite of all-cause death or heart failure (HF) hospitalization in two years. HF hospitalization was defined as the first or recurrent hospitalization with a diagnosis of HF where the patient showed evidence of HF and received initiation or intensification of treatment specifically for HF. Outcome data were collected from patient visits, medical records, and telephone interviews (detailed in Supplementary Methods).

2.6. Statistical analysis

Statistical analyses were performed using SAS, version 9.4 at Medical Research & Biometrics Center, Fuwai Hospital. Continuous variables were described as mean with standard deviations or median with interquartile ranges and compared using a 1-way analysis of variance or the Kruskal-Wallis H test, as appropriate. Categorical variables were expressed as numbers (percentage) and comparisons were performed using the chi-square test. The unpaired *t* test was used to determine group differences for continuous variables. Two-year survival rates were calculated using the Kaplan-Meier method with 95% confidence

Table 1
Characteristics of patients with rheumatic valvular disease.

	Total RVD	Isolated AS	Isolated AR	AS + AR	Isolated MS	Isolated MR	MS + MR	Right-Sided VHD	MultipleVHD	P value
Demographics										
Age, yr [Median (IQR)]	57 (50–65)	60 (54–64)	54 (47–62)	56 (51–65)	55 (49–64)	56 (48–65)	56 (50–63)	64 (55–71)	58 (50–66)	<0.001
Female, no. (%)	1535 (63.9)	26 (39.4)	32 (32.3)	24 (47.1)	370 (70.7)	156 (56.7)	124 (67.4)	58 (87.9)	745 (65.5)	<0.001
BMI, kg/m^2 [Median (IQR)]	22.8 (20.7–25.0)	23.3 (21.9–25.2)	23.7 (21.3–25.5)	22.7 (20.3–25.0)	22.9 (20.8–25.2)	23.4 (21.3–25.5)	22.8 (20.7–25.2)	22.8 (20.8–25.8)	22.5 (20.4–24.6)	0.006
Region, no. (%)										
Total RVD[a]	2402 (19.7[a])	66 (2.7)	99 (4.1)	51 (2.1)	523 (21.8)	275 (11.4)	184 (7.7)	66 (2.7)	1138 (47.4)	<0.001
East	285 (13.5)	5 (6.6)	2 (1.0)	9 (22)	60 (95.2)	33 (6.1)	26 (92.9)	5 (1.5)	145 (17.2)	
South	201 (48.8)	22 (55)	8 (23.5)	7 (63.6)	67 (98.5)	26 (29.2)	11 (100)	4 (7.3)	56 (53.8)	
West	348 (24.9)	7 (14.3)	24 (30.3)	10 (30.3)	83 (98.8)	33 (13.1)	17 (100)	11 (4.0)	163 (32)	
North	1171 (19.9)	25 (7.2)	50 (13.4)	20 (13.4)	238 (94.4)	147 (9.6)	101 (90.2)	35 (3.8)	555 (33.1)	
Central	397 (16.7)	7 (11.3)	15 (13.9)	5 (13.9)	75 (91.5)	36 (6.4)	29 (85.3)	11 (2.4)	219 (25.4)	
P		<0.001	<0.001	0.175	<0.001	0.234	0.085	0.71	<0.001	
Risk factors and comorbidities, no. (%)										
Smoking	522 (21.7)	28 (42.4)	35 (35.4)	13 (25.5)	97 (18.5)	74 (26.9)	31 (16.8)	5 (7.6)	239 (21.0)	<0.001
Hypertension	610 (25.4)	18 (27.3)	43 (43.4)	16 (31.4)	109 (20.8)	94 (34.2)	38 (20.7)	11 (16.7)	281 (24.7)	<0.001
Diabetes	159 (6.6)	4 (6.1)	4 (4.0)	1 (2.0)	33 (6.3)	22 (8.0)	17 (9.2)	5 (7.6)	73 (6.4)	0.582
Dyslipidemia	217 (9.0)	7 (10.6)	6 (6.1)	4 (7.8)	59 (11.3)	30 (10.9)	23 (12.5)	5 (7.6)	83 (7.3)	0.124
Atrial fibrillation	1037 (43.2)	3 (4.5)	13 (13.1)	6 (11.8)	226 (43.2)	88 (32.0)	96 (52.2)	36 (54.5)	569 (50.0)	<0.001
Coronary artery disease	184 (7.7)	11 (16.7)	6 (6.1)	1 (2.0)	37 (7.1)	32 (11.6)	17 (9.2)	6 (9.1)	74 (6.5)	0.02
Prior Myocardial infarction	24 (1.0)	2 (3.0)	0 (0)	0 (0)	7 (1.3)	6 (2.2)	2 (1.1)	0 (0)	7 (0.6)	0.172
Aortic disease	32 (1.3)	1 (1.5)	3 (3.0)	2 (3.9)	7 (1.3)	1 (0.4)	1 (0.5)	2 (3.0)	15 (1.3)	0.408
Peripheral artery disease	37 (1.5)	1 (1.5)	2 (2.0)	0 (0)	7 (1.3)	4 (1.5)	7 (3.8)	1 (1.5)	15 (1.3)	0.57
Renal insufficiency	41 (1.7)	1 (1.5)	0 (0)	1 (2.0)	8 (1.5)	5 (1.8)	3 (1.6)	2 (3.0)	21 (1.8)	0.833
Baseline symptoms, no. (%)										
Chest pain	286 (13.1)	16 (26.7)	10 (12.2)	4 (8.9)	68 (14.7)	33 (13.3)	28 (17.0)	13 (23.2)	114 (10.8)	0.007
Dyspnea	1888 (86.8)	52 (86.7)	75 (91.5)	37 (82.2)	389 (84.2)	221 (89.1)	140 (84.8)	45 (80.4)	929 (87.8)	0.294
Palpitation	1177 (54.1)	18 (30.0)	42 (51.2)	19 (42.2)	242 (52.4)	153 (61.7)	88 (53.3)	25 (44.6)	590 (55.8)	<0.001
Syncope	80 (3.7)	6 (10.0)	3 (3.7)	4 (8.9)	21 (4.5)	7 (2.8)	4 (2.4)	4 (7.1)	31 (2.9)	0.12
Edema	407 (18.7)	4 (6.7)	7 (8.5)	8 (17.8)	88 (19.0)	42 (16.9)	26 (15.8)	19 (33.9)	213 (20.1)	0.002
NYHA functional classification, no. (%)										0.073
III	791 (84.0)	22 (84.6)	16 (88.9)	23 (85.2)	179 (90.9)	76 (84.4)	59 (81.9)	16 (66.7)	400 (82.0)	
IV	151 (16.0)	4 (15.4)	2 (11.1)	4 (14.8)	18 (9.1)	14 (15.6)	13 (18.1)	8 (33.3)	88 (18.0)	

Values are presented as median [interquartile range (IQR)] or number (percent).

[a] The denominator in this calculation is the number of patients corresponding to native valvular disease (excluding patients underwent valvular intervention and diagnosed infective endocarditis) in the region. Abbreviation: RVD, rheumatic valvular disease; VHD, valvular heart disease; MS, mitral stenosis; MR, mitral regurgitation; AS, aortic stenosis; AR, aortic regurgitation; MVHD, multiple valvular heart disease; BMI, body mass index; NYHA, New York Heart Association.

intervals (CIs). The Kaplan-Meier cumulative event curves were drawn for moderate or severe patients and all-cause death and HF hospitalization. A 2-tailed P value < 0.05 was considered statistically significant.

Association between all baseline variables and the occurrence of adverse events was tested in a univariable regression model and those variables found to be significant ($p < 0.1$) or had been reported to be associated with adverse events were selected as inputs into a multivariate Cox regression model using stepwise backward elimination. Results were reported as hazard ratios with associated 95% confidence intervals (CI).

3. Results

A comprehensive total of 13,917 consecutive adult patients with VHD were diligently enrolled in this study. Notably, 19.7% of these VHD patients (2402 individuals) were identified as having native RVD (Fig. 1).

3.1. Baseline characteristics

Baseline characteristics of all RVD patients are shown in Table 1. The median age of the RVD cohort was 57 years, displaying a diverse distribution across age groups: 1.2% between 18 and 29, 5.1% between 30 and 39, 82.5% (1981/2402) between 40 and 70, 9.9% between 70 and 79, and 1.3% aged ≥80 (Fig. 2; Supplementary material online, Table S2). Females constituted the majority, comprising 63.9% of the RVD patients. Within this cohort, 39.2% of individuals were classified as New York Heart Association (NYHA) class III or IV. A detailed presentation of symptoms is provided in Table 1. Atrial fibrillation emerged as the most prevalent complication, documented in 43.2% (1037/2402) of patients with RVD. Geographical regions within China were stratified into eastern, southern, western, northern, and central regions, as shown in Table 1 and Fig. 3. Rheumatic etiology constituted the highest proportion among all causes of VHD in the southern regions (48.8%), followed by the western (24.9%), northern (19.9%), central (16.7%), and eastern regions (13.5%).

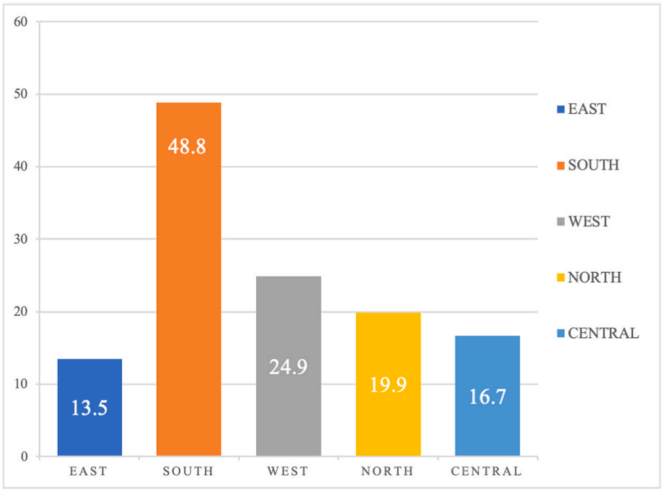

Fig. 3. Geographical regions distribution of RVD in China.

3.2. Spectrum and distribution of RVD

Among the patients with RVD, a considerable 64.2% exhibited severe RVD (Supplementary material online, Table S3). The spectrum of multiple VHD (MVHD) was notably prevalent, encompassing 47.4% of cases, followed by MS in 21.8%, MR in 11.4%, MmVHD in 7.7%, AR in 4.1%, AS in 2.7%, MaVHD in 2.1% and right-sided VHD in 2.7% (Table 1, Fig. 4). Fig. 2 indicates an age-related increase in the proportion of MVHD, while the proportion of isolated MR decreases with age. Additionally, Fig. 5 illustrates the gender-specific pattern of RVD, with isolated MS, MmVHD, right-sided VHD, and MVHD more prevalent in females, whereas aortic disease is more common in males ($P < 0.001$).

3.3. Investigations

Table 2 delineates the investigations conducted, revealing that echocardiography displayed a median left atrial (LA) dimension of 50 mm in RVD patients. Notably, the left ventricular end-diastolic dimension was most prominent in AR ($P < 0.001$). Pulmonary hypertension

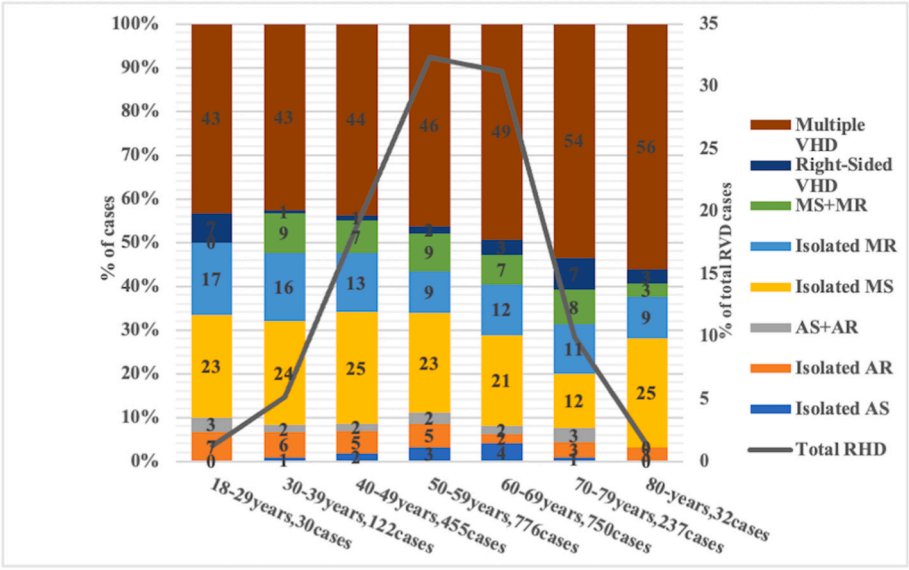

Fig. 2. Distribution of Patients with RVD according to age. The value on the left vertical axis represents the proportion of each valve subtype in total RVD (shown in the histogram of different colors in the figure), and the value on the right vertical axis represents the proportion of RVD in each age group in total RVD (shown in the line chart in the figure). Abbreviation: VHD, valvular heart disease; MS, mitral stenosis; MR, mitral regurgitation; AS, aortic stenosis; AR, aortic regurgitation; RVD, rheumatic valvular disease.

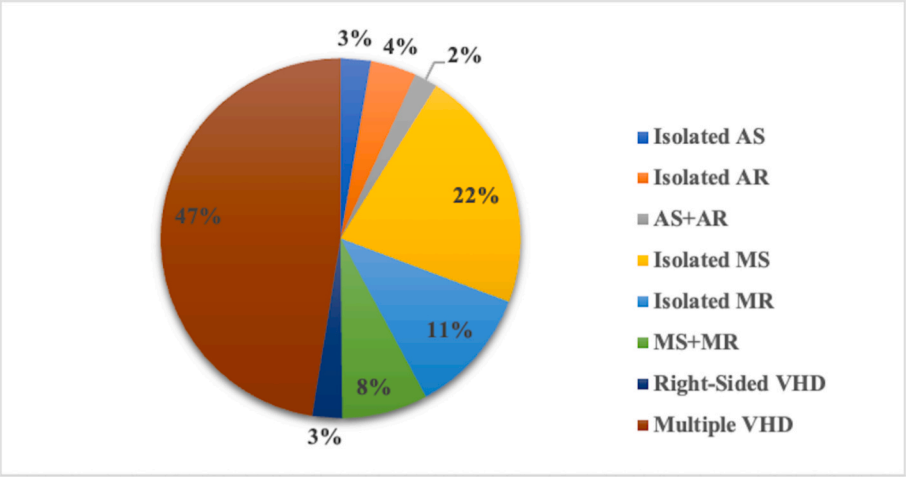

Fig. 4. Distribution of Patients with RVD Abbreviation: AS, aortic stenosis; AR, aortic regurgitation; MS, mitral stenosis; MR, mitral regurgitation; VHD, valvular heart disease.

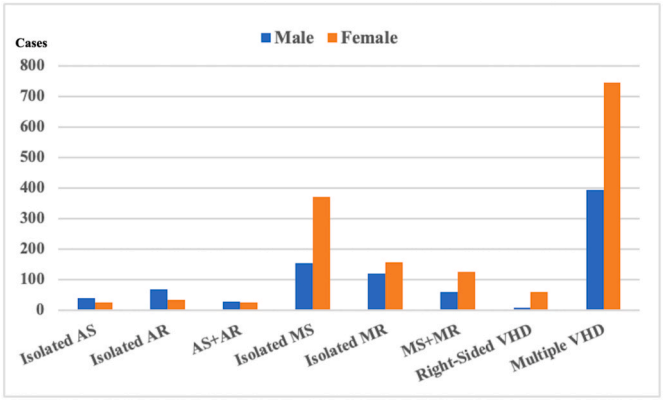

Fig. 5. Gender Distribution of Patients with RVD Abbreviation: AS, aortic stenosis; AR, aortic regurgitation; MS, mitral stenosis; MR, mitral regurgitation; VHD, valvular heart disease.

was evident in 38.2% of patients, and 11.6% exhibited a LVEF less than 50%. Transesophageal echocardiography was performed in 25.3% of patients, coronary angiography in 29.7%, and stress tests in 0.4%.

3.4. Medications and interventions

Table 3 outlines medications prescribed for RVD patients, including diuretics, warfarin, beta-blockers, digitalis, and ACEI/ARB, administered in 85.1%, 75.1%, 49%, 43.1%, and 29.3% of cases, respectively. During hospitalization, 66.9% of patients underwent valvular interventions, with surgical valve replacement accounting for 60.7%. Surgical valve repair was performed in 40.2% of cases, and antiarrhythmic surgery, coronary artery bypass grafting, and aortic surgery were observed in 16.8%, 6.3%, and 2.6% of patients, respectively.

3.5. Two-year outcomes

Within the first admission, 0.7% of patients (17 patients) died. Among the 2384 patients discharged alive, a detailed 2-year follow-up was available for 90.0% (2145 patients). During this follow-up, 3.2% (67 patients) were hospitalized due to HF, and 4.5% (97 patients) died (Supplementary material online, Table S4). Two-year adverse event rates varied among different valvular pathologies, with an overall rate of 7.3%. Specifically, rates were 5.4% for AS, 4.2% for MaVHD, 5.4% for MS, 5.7% for MR, 10.9% for MmVHD, 12.5% for right-sided VHD, and 8.7% for MVHD (Supplementary material online, Table S5). Two-Year Kaplan-Meier Cumulative Event Curves for Patients with RVD were detailed in Supplementary Figs. S1 and S2.

Table 4 presents the adverse events of the survival analysis for patients with RVD. In the Cox univariable analysis, factors associated with the primary endpoint included age, region, BMI, renal insufficiency, LA, and LVEF<50%. Notably, valvular intervention emerged as a protective factor (all $P < 0.1$) (Supplementary material online, Table S6).

Independent risk determinants of primary endpoint were identified through multivariable analysis, revealing the following hazard ratios (HR) with associated confidence intervals (CI) and p-values: age (HR:1.566; 95% CI: 1.335 to 1.837; $p < 0.001$), southern region (HR: 2.924; 95% CI: 1.683 to 5.080; $p < 0.001$), western region (HR: 1.921; 95% CI: 1.113 to 3.316; $p = 0.019$), low BMI (HR: 1.933; 95% CI: 1.285 to 2.909; $p = 0.0016$), renal insufficiency (HR: 2.550; 95% CI: 1.443 to 4.508; $p = 0.0013$), LA (HR: 1.026; 95% CI:1.014 to 1.038; $p < 0.001$) and LVEF<50% (HR:1.754; 95% CI:1.197 to 2.569; $p = 0.0039$). Valvular intervention was a significant protective factor, markedly reducing the risk of adverse events (HR:0.201; 95%CI: 0.139 to 0.291; $p < 0.001$).

4. Discussion

Despite China ranking second globally in the number of cases and deaths attributed to RVD [7], there is a scarcity of detailed studies characterizing its features, treatment modalities, and prognosis within the country. This study serves as a pioneering effort, offering a comprehensive overview of the contemporary spectrum, characteristics, management, and outcomes of RVD in China.

4.1. Key findings

The present study highlights multiple findings. First, the majority of RVD patients fell within the age range of 40–70 years (82.5%) and were predominantly female (63.9%). Second, MVHD emerged as the most prevalent type, followed by mitral stenosis and mitral regurgitation. Third, a notable 43.2% of RVD patients presented with atrial fibrillation. Fourth, valvular interventions were administered to 66.9% of patients, with surgical valve replacement dominating the procedures (90.8%). Fifth, valvular intervention significantly reduced adverse events during the 2-year follow-up.

Table 2
Investigations of patients with RVD.

Variable	Total RVD	Isolated AS	Isolated AR	AS + AR	Isolated MS	Isolated MR	MS + MR	Right-Sided VHD	Multiple VHD	P valvue
Echocardiography										
LA, mm [Median (IQR)]	50.0 (44.0–57.0)	37.5 (35.0–42.0)	40.0 (34.0–45.0)	42.0 (36.0–47.0)	50.0 (45.0–55.0)	48.0 (42.0–55.0)	52.0 (47.0–58.5)	48.0 (42.0–54.0)	52.0 (47.0–61.0)	<0.001
LVEDD, mm [Median (IQR)]	49.0 (45.0–55.0)	52.0 (47.0–56.0)	58.0 (53.0–65.0)	57.0 (50.0–63.0)	46.0 (44.0–50.0)	54.0 (49.0–60.0)	48.0 (44.0–52.0)	45.0 (41.0–48.0)	50.0 (45.0–56.0)	<0.001
LVEF, % [Median (IQR)]	60.0 (55.0–65.0)	60.0 (56.0–67.0)	60.0 (54.0–64.0)	62.7 (51.0–67.4)	61.0 (56.0–65.0)	60.0 (56.0–66.0)	60.0 (55.0–65.0)	60.5 (57.0–66.0)	60.0 (54.0–64.0)	0.025
Pulmonary hypertension, no. (%)	918 (38.2)	10 (15.2)	7 (7)	10 (19.6)	162 (31)	58 (21.1)	65 (35.3)	27 (40.9)	579 (50.9)	<0.001
Ascending aortic diameter, mm [Median (IQR)]	32.0 (28.5–35.0)	38.0 (35.0–43.0)	36.5 (33.0–40.0)	39.0 (34.4–43.5)	30.0 (27.0–33.0)	31.0 (28.6–34.5)	30.0 (27.0–33.0)	31.0 (28.0–35.0)	32.0 (29.0–36.0)	<0.001
TOE, no. (%)	608 (25.3)	8 (12.1)	20 (20.2)	7 (13.7)	113 (21.6)	91 (33.1)	44 (23.9)	8 (12.1)	317 (27.9)	<0.001
Stress test, no. (%)	11 (0.4)	0 (0)	0 (0)	0 (0)	4 (0.8)	1 (0.4)	0 (0)	1 (1.5)	5 (0.4)	0.85
CAG, no. (%)	713 (29.7)	28 (42.4)	27 (27.3)	13 (25.5)	171 (32.7)	68 (24.7)	61 (33.2)	15 (22.7)	330 (29.0)	0.081
Right cardiac catheterization, no. (%)	27 (1.1)	1 (1.5)	0 (0)	0 (0)	11 (2.1)	2 (0.7)	1 (0.5)	6 (9.1)	6 (0.5)	<0.001
Left cardiac catheterization, no. (%)	50 (2.1)	1 (1.5)	1 (1.0)	0 (0)	22 (4.2)	2 (0.7)	6 (3.3)	1 (1.5)	17 (1.5)	0.018

Values are presented ad median (IQR) or number (percent).
Abbreviation: LA, left atrium; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; TOE, transesophageal echocardiography; CAG, Coronary angiography.

Table 3
Medication and interventions of patients with RVD.

Variable	Total	Isolated AS	Isolated AR	AS + AR	Isolated MS	Isolated MR	MS + MR	Right-Sided VHD	Multiple VHD	P value
Medication										
Beta–blocker	1176 (49.0)	27 (40.9)	50 (50.5)	23 (45.1)	228 (43.6)	151 (54.9)	90 (48.9)	29 (43.9)	578 (50.8)	0.075
ACEI/ARB	704 (29.3)	13 (19.7)	36 (36.4)	15 (29.4)	101 (19.3)	114 (41.5)	43 (23.4)	17 (25.8)	365 (32.1)	<0.001
ARNI	6 (0.2)	0 (0)	0 (0)	0 (0)	1 (0.2)	0 (0)	0 (0)	0 (0)	5 (0.4)	0.745
Diuretics	2043 (85.1)	52 (78.8)	80 (80.8)	43 (84.3)	424 (81.1)	231 (84.0)	157 (85.3)	43 (65.2)	1013 (89.0)	<0.001
Digitalis	1035 (43.1)	30 (45.5)	42 (42.4)	23 (45.1)	250 (47.8)	100 (36.4)	79 (42.9)	22 (33.3)	489 (43.0)	0.121
Warfarin	1803 (75.1)	44 (66.7)	67 (67.7)	37 (72.5)	402 (76.9)	179 (65.1)	142 (77.2)	42 (63.6)	890 (78.2)	<0.001
NOAC	38 (1.6)	0 (0)	1 (1.0)	0 (0)	9 (1.7)	6 (2.2)	4 (2.2)	2 (3.0)	16 (1.4)	0.657
Antiplatelet agents	376 (15.7)	17 (25.8)	8 (8.1)	6 (11.8)	95 (18.2)	48 (17.5)	39 (21.2)	15 (22.7)	148 (13.0)	
Valvular Interventions	1606	46	62	39	376	172	124	21	776	
Surgical valve repair	965 (40.2)	8 (12.1)	7 (7.1)	7 (13.7)	205 (39.2)	104 (37.8)	70 (38.0)	15 (22.7)	549 (48.2)	<0.001
Surgical valve replacement	1458 (60.7)	45 (68.2)	60 (60.6)	38 (74.5)	335 (64.1)	127 (46.2)	117 (63.6)	16 (24.2)	720 (63.3)	<0.001
Percutaneous balloon valvuloplasty	95 (4.0)	0 (0)	0 (0)	0 (0)	40 (7.6)	0 (0)	6 (3.3)	1 (1.5)	48 (4.2)	<0.001
TAVI	7 (0.3)	1 (1.5)	1 (1.0)	1 (2.0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (0.4)	0.625
Mitral clip	6 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.7)	0 (0)	0 (0)	4 (0.4)	0.827
Prosthesis type										0.006
Bioprosthesis	377 (25.9)	21 (46.7)	14 (23.3)	9 (23.7)	79 (23.6)	40 (31.5)	20 (17.1)	8 (50.0)	186 (25.8)	
Mechanical valve	1081 (74.1)	24 (53.3)	46 (76.7)	29 (76.3)	256 (76.4)	87 (68.5)	97 (82.9)	8 (50.0)	534 (74.2)	
Concomitant cardiac aortic surgery										
CABG	101 (6.3)	5 (10.9)	3 (4.8)	3 (7.7)	20 (5.3)	10 (5.8)	8 (6.5)	1 (4.8)	51 (6.7)	0.952
Aortic surgery	41 (2.6)	5 (10.9)	8 (12.9)	7 (17.9)	3 (0.8)	1 (0.6)	2 (1.6)	0 (0)	15 (2.0)	<0.001
Antiarrhythmic surgery	270 (16.8)	0 (0)	3 (4.8)	3 (7.7)	63 (16.8)	29 (16.9)	20 (16.1)	4 (19.0)	148 (19.3)	<0.001
Other cardiac surgery	220 (13.7)	7 (15.2)	1 (1.6)	4 (10.3)	57 (15.2)	17 (9.9)	16 (12.9)	6 (28.6)	112 (14.6)	0.015

Values are presented as n (%).
Abbreviation: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; NOAC, Non-vitamin K antagonist oral anticoagulant; TAVI, Transcatheter aortic valve implantation; CABG, coronary artery bypass grafting.

Table 4
Multivariate Cox regression analysis results of the primary endpoint of RVD patients followed up for 2 years.

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Age[a]	1.503 (1.266, 1.784)	<0.0001	1.566 (1.335, 1.837)	<0.0001
Region[b]				
East	0.58 (0.30,1.15)	0.1185	0.696 (0.352, 1.375)	0.297
South	1.91 (1.10,3.29)	0.0205	2.924 (1.683, 5.080)	0.0001
West	1.19 (0.70,2.02)	0.5317	1.921 (1.113, 3.316)	0.019
North	0.81(0.52,1.26)	0.3591	1.297 (0.824, 2.040)	0.261
BMI[c]				
<18.5	2.83 (1.90,4.20)	<0.0001	1.933 (1.285, 2.909)	0.0016
24–27.9	0.57 (0.37,0.88)	0.0115	0.658 (0.425, 1.018)	0.0599
28-	0.58 (0.28,1.20)	0.1447	0.652 (0.314, 1.355)	0.2516
Renal insufficiency	0.13 (0.09,0.18)	<0.0001	2.550 (1.443, 4.508)	0.0013
LA	2.83 (1.90,4.20)	<0.0001	1.026 (1.014, 1.038)	<0.0001
LVEF<50%	6.54 (3.78, 11.33)	<0.0001	1.754 (1.197, 2.569)	0.0039
Valvular intervention	0.13 (0.09,0.18)	<0.0001	0.201 (0.139, 0.291)	<0.0001

Abbreviation: HR, hazard ratio; CI, confidence intervals; BMI, body mass index; LA, left atrium; LVEF, left ventricular ejection fraction.
[a] Age: Per-10-year increase.
[b] Base: central.
[c] Base: 18.5–23.9 kg/m^2.

4.2. Contemporary spectrum and baseline characteristics

In our study, RVD accounted for 19.7% of VHD. A study from Guangzhou, China, showed that the proportion of rheumatic etiology in valve disease decreased from 43% to 33% in the five years from 2009 to 2013 [8]. In the China-DVD study [9], RVD accounted for 15.0% of VHD in older patients (≥60 years). These data indicate that with the economic development of China and the aging of the population, the proportion of RVD in VHD decreased gradually. In addition, research data from Europe indicate that the proportion of rheumatic etiology in VHD is relatively low, and degenerative etiology is the main cause.

In our study, patients were largely female and RVD often involved the mitral valve and multiple valves, which are consistent with recent findings of large-scale and well-designed RHD studies including the HP-RHD, SOWETO, and REMEDY studies [10–12]. On the other hand, the median age of the patients in our study (57 years) is significantly older than the median or mean age of the patients in those 3 studies. Consistent with the results of the REMEDY study, the proportion of MVHD gradually increased with age, while the proportion of isolated MR gradually decreased with age [12].

4.3. Investigations

Compared with the HP-RHD, SOWETO, and REMEDY study, the proportion of patients with atrial fibrillation, pulmonary hypertension, and NYHA III-IV was respectively higher than that of our study [10–12]. Because patients in our study were significantly older than those in these studies and were selected by a definition of more severe valve disease, patients in this study turned out to have more comorbidities and worse cardiac function.

4.4. Therapy

In our study, surgical treatment was performed in 67% of the patients, and 91% of these procedures were surgical valve replacements. For patients with rheumatic mitral disease, whether valve repair or replacement is superior is a controversial issue. Some recent studies [13, 14] have analyzed the prognosis of patients with RVD after surgical treatment. The research of Fu et al. [13] showed that RVD patients treated with rheumatic mitral valve repair had better prognosis than those treated with mitral valve replacement, and the risk of death and valve-related complications was reduced. The rate of reoperation was not higher among patients who underwent mitral-valve repair than among those who underwent mitral-valve replacement. However, the research of Chen et al. [14] suggested that mitral valve repair did not bring better long-term benefits compared with mitral valve replacement in patients with RVD. Overall, the selection of surgical procedures for rheumatic mitral valve should be based on the individual characteristics of patients, the complexity of lesions, and the experience of the surgeon.

4.5. Two-year outcomes

In this study, low BMI, renal insufficiency, enlarged LA, and LVEF <50% were associated with adverse events. Evidence suggests a link between low BMI and mitral valve prolapse, potentially attributed to malnutrition accelerating valvular calcification [15]. This finding emphasizes the intricate interplay between dietary factors and valvular pathophysiology, urging a comprehensive approach to address nutritional deficiencies in the management of RVD. The finding of the adverse effect of renal insufficiency on patients with RVD is consistent with another study's finding that chronic kidney disease was identified as a significant contributor to both short-term and long-term mortality following valve surgery related to RVD (long-term mortality OR: 1.9, 95 % CI 1.2–2.9) [16]. Moreover, renal failure was the main contributor (19%) to the deaths of patients with RHD in Australia between 2007 and 2009 [17]. The implications of renal failure in the mortality of RHD patients further highlight the need for heightened attention to renal function in the preoperative and postoperative care of individuals with RVD. Mitral stenosis or regurgitation can cause left atrial remodeling and enlargement which increases the risk of atrial fibrillation [18]. Therefore, early detection and treatment to slow the progression of valve lesions are crucial to the prognosis. The heightened risk of adverse events in patients with LVEF <50% reinforces the significance of ventricular function in predicting outcomes. This aligns with the latest guidelines from Europe and the United States, where symptoms and LVEF are paramount considerations when deciding on interventions for left-sided valvular heart disease [19,20]. Monitoring and addressing impaired ventricular function become pivotal in the comprehensive management of RVD. Valvular interventions reduced the risk of adverse events by five times compared to medication or follow-up observation, which reinforced the pivotal role of surgical and interventional approaches in altering the natural history of RVD. The identified risk factors further accentuate the urgency of removing barriers to surgery.

4.6. Limitations

This study is not a comprehensive population-based epidemiological study. Representativeness is therefore suboptimal, and selection bias cannot be excluded. Nevertheless, the inclusion of 46 medical centers throughout Mainland China in this survey provide in-depth insight into the contemporary presentation and prognosis of clinically significant RVD in China. The 2-year follow-up analysis may be impacted by survival bias and the absence of follow-up data for 10% of patients.

5. Conclusions

This survey contributes invaluable contemporary data on RVD in

China, shedding light on its characteristics, management, and outcomes. The findings emphasize the need for tailored interventions, considering patient demographics and the evolving landscape of VHD in the country.

Ethical statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

CRediT authorship contribution statement

Zhenya Duan: Writing – review & editing, Writing – original draft, Resources, Methodology, Formal analysis, Data curation. **Yunqing Ye:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Zhe Li:** Investigation, Data curation. **Bin Zhang:** Investigation, Data curation. **Qingrong Liu:** Investigation, Data curation. **Zhenyan Zhao:** Investigation, Data curation. **Weiwei Wang:** Investigation, Data curation. **Zikai Yu:** Investigation, Data curation. **Haitong Zhang:** Investigation, Data curation. **Qinghao Zhao:** Investigation, Data curation. **Bincheng Wang:** Investigation, Data curation. **Junxing Lv:** Investigation, Data curation. **Shuai Guo:** Investigation, Data curation. **Haocheng Ren:** Software, Formal analysis, Data curation. **Runlin Gao:** Visualization, Supervision, Conceptualization. **Haiyan Xu:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Yongjian Wu:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

All authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

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