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Cardiovascular Risk Factors in Patients with Valvular Heart Disease: A Nationwide Observational Cohort Study

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Purpose: Conventional cardiovascular risk factors may contribute to the development of valvular heart disease (VHD). The present study sought to investigate the distribution of conventional modifiable cardiovascular risk factors (smoking, hypertension, hyperlipidemia, and diabetes) in various VHDs, the impact of risk factors on outcomes, and the prognostic indicators in patients with distinct burdens of risk factors.

Patients and methods: The study included 11862 patients with moderate or greater VHD. The primary outcome was a composite of all-cause mortality, hospitalization for heart failure, and myocardial infarction within two years.

Results: Of 11862 patients with VHD, the mean age was 61.77 ± 13.51 years, and 44.4% were female. The prevalences of smoking, hypertension, hyperlipidemia, and diabetes were 14.9%, 45.0%, 13.4%, and 14.5% in the total cohort. Patients with zero, one, two, three, or four risk factors accounted for 39.4%, 38.2%, 17.7%, 4.3%, and 0.3%, respectively. The number of conventional risk factors was independently associated with two-year outcome in patients with mitral regurgitation (MR; three/four vs zero: hazard ratio [HR, 95% confidence interval (CI)]: 1.600 [1.106–2.315], P = 0.013; two vs zero: HR [95% CI]: 1.153 [0.867–1.532], P = 0.328; one vs zero: HR [95% CI]: 0.892 [0.687–1.159], P = 0.393). Stratified by the etiology of mitral valve lesions, each one risk factor increase was independently related to a 17.3% higher risk of adverse events in secondary MR. In patients with three or four risk factors, females had a significantly poorer outcome than males (P = 0.002).

Conclusion: More than one of five VHD patients had at least two conventional cardiovascular risk factors. The increasing number of risk factors indicated poor prognosis in patients with significant MR. Optimizing risk factor control may improve secondary prevention as well as long-term outcomes of VHD.

Keywords: valvular heart disease, secondary prevention, mitral regurgitation, risk factor

Introduction

Globally, valvular heart disease (VHD) is an enormous health burden.[1,2] Over the past two decades, a series of novel transcatheter techniques have emerged for treating different types of valvular diseases, providing definitive therapies for eligible patients previously considered surgically inoperable.[3–5] However, a large number of VHD patients still have

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a high risk of worsening heart failure or mortality, even after a successful correction of valvular lesions,[5–7] which may be attributed to the irreversible global cardiac damage and remodeling.[7] Importantly, such cardiac impairments can not only be induced by the long-term VHD-related hemodynamic abnormality[8] but also related to other pathophysiological pathways, such as through concomitant cardiovascular risk factors, which are commonly present in elderly population.[9–11] Better understanding and management of the conventional modifiable cardiovascular risk factors (smoking, hypertension, hyperlipidemia, and diabetes) may provide additional value over the evolving techniques for valvular interventions in improving outcomes of patients with VHD.

The roles of standard modifiable cardiovascular risk factors (SMuRFs) have been well investigated in patients with coronary artery disease.[12,13] In the field of VHD, previous studies suggested that conventional cardiovascular risk factors, including smoking, hypertension, dyslipidemia, and diabetes, contributed to the development of aortic stenosis (AS),[14,15] and could lead to poor prognosis.[16–18] However, available data on other types of VHD are limited and contradictory.[17–21] Recently, we confirmed that diabetes was highly prevalent (19.1%) in a large series of patients with moderate or greater mitral regurgitation (MR) and was an independent predictor of two-year outcome,[16] which implied the potential value of controlling traditional risk factors in patients with significant mitral valve lesions. Nevertheless, evidence on the prevalence of other traditional cardiovascular risk factors, the synergistic burden of risk factors, as well as their prognostic impact in patients with different types of VHD is still limited so far.

Therefore, the present study aimed to investigate the distribution of conventional modifiable cardiovascular risk factors in various VHDs, the individual and synergistic impact of risk factors on clinical outcomes, and the prognostic factor profiles in patients with distinct burdens of risk factors.

Methods

Study Design and Population

This study was conducted using data from the China Valvular Heart Disease (China-VHD; NCT03484806) registry, which was a nationwide, multicenter, observational cohort study for adult patients (≥18 years) with at least moderate VHD (defined by echocardiography). The China-VHD study recruited patients consecutively between April and June 2018 from inpatient wards and outpatient clinics at 46 medical centers in China. Data collection, quality control, and other details of the China-VHD study have been described previously.[22] The study was approved by the Institutional Review Board at Fuwai Hospital, National Center for Cardiovascular Diseases of China (Approval No. 2017–968), and performed in accordance with the Declaration of Helsinki. All eligible participants gave written informed consent before registration.

The eligible criteria for patients of this analysis have been detailed in our previous publication.[16] In brief, among 13917 patients with significant VHD in the China-VHD study, those with ≥ moderate tricuspid stenosis, pulmonary valve disease, infective endocarditis, previous valvular intervention, or patients without any follow-up data were excluded. The study population of the present analysis included 11862 patients with moderate or greater aortic regurgitation (AR), AS, MR, mitral stenosis (MS), tricuspid regurgitation (TR), mixed AS and AR, mixed MS and MR, and multiple VHD (MVHD).[16]

Echocardiography

All participants in China-VHD study underwent comprehensive transthoracic two-dimensional and Doppler echocardiography using standard ultrasound systems. The chambers of heart were quantified in accordance with the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[23] Quality control, echocardiographic measurements, and echocardiographic criteria of significant valvular lesions in the China-VHD study have been described and published previously.[22,24]

Cardiovascular Risk Factors

Hypertension was defined as a previous diagnosis of hypertension (systolic blood pressure ≥140mmHg or diastolic blood pressure ≥90mmHg without using antihypertensive drugs) or taking antihypertensive medications currently.

Hyperlipidemia were defined as a previous diagnosis of hyperlipidemia or fasting serum cholesterol more than 5.72 mmol/L and/or triglyceride over 1.7 mmol/L. Patients with diabetes were those with classic symptoms of hyperglycemia or hyperglycemic crisis and a random plasma glucose ≥200 mg/dL (11.1 mmol/L), or those with blood-fasting sugar >126 mg/dL (7.0 mmol/L), or postprandial blood sugar ≥200 mg/dL (11.1 mmol/L) during oral glucose tolerance test (OGTT), or glycosylated hemoglobin ≥6.5%.[16] Current smoking was defined as smoking within the past month before admission. When analyzing the association of the number of cardiovascular risk factors with outcomes, we divided patients with AS, AR, MR, TR, and MVHD into four groups (zero, one, two, or three/four risk factors) according to the number of risk factors, considering a relatively small sample size of patients with four risk factors. Patients with MS, mixed AS and AR, and mixed MS and MR were divided into three groups (zero, one, or two/three risk factors) because none of them had four risk factors.

Follow-Up and Outcomes

Follow-up of the China-VHD study was performed at six months, one year, 18 months, and two years through clinical visits, telephone calls, or medical records. Clinical outcomes, including death, myocardial infarction (MI), and hospitalization for heart failure (HHF), were collected. The primary outcome of interest in the present analysis was the composite of all-cause mortality, HHF, and MI. The secondary outcome of this study was all-cause mortality.

Statistical Analysis

Continuous variables were summarized as mean ± standard deviation (SD) or medians (interquartile range [IQR]) according to the data distribution and compared by Kruskal–Wallis test or Mann–Whitney *U*-test according to the number of groups. Categorical variables were shown as number (percentages) and compared by Chi-square or the Fisher's exact test where appropriate. All reported p values are two-tailed, and statistical significance was set at $p < 0.05$. All statistical analyses were performed using R software (version 4.2.2, R Foundation for Statistical Computing, Vienna, Austria).

Association of Cardiovascular Risk Factors with Outcomes

To assess the prognostic impact of the number of conventional cardiovascular risk factors in patients with VHD, Kaplan–Meier curves were constructed, and the differences among groups were checked by the Log rank test. Multivariable Cox proportional hazards models were also used to analyze the associations of the individual risk factor as well as the number of risk factors with two-year outcomes. Covariates in the minimally adjusted model were age and sex. The statistically significant associations in the minimally adjusted model were further evaluated in the fully adjusted model, which included age, sex, body mass index (BMI), coronary artery disease, cardiomyopathy, atrial fibrillation or flutter, chronic lung disease, chronic kidney disease, New York Heart Association (NYHA) functional class, hemoglobin, creatinine, albumin, left atrial end-diastolic dimension (LA), left ventricular end-diastolic dimension (LVEDD), left ventricular ejection fraction (LVEF), pulmonary hypertension, severity of VHD, and valvular intervention. This analysis was also performed based on the etiology of valvular lesions (primary or secondary). We used Schoenfeld residual plots (for continuous variables) and log-log survival plots (for categorical variables) to examine the proportional hazards assumptions.

Determinants of Outcome According to the Number of Cardiovascular Risk Factors

Determinants of outcome were screened according to the number of risk factors (zero, one, two, and three/four risk factors) through a multivariable Cox regression model, with age, sex, BMI, coronary heart disease, cardiomyopathy, atrial fibrillation or flutter, chronic lung disease, chronic kidney disease, NYHA functional class, hemoglobin, creatinine, albumin, LA, LVEDD, LVEF, pulmonary hypertension, severity of VHD, and valvular intervention entered. Results were summarized as hazard ratios (HRs) with 95% confidence intervals (CIs).

Results

Baseline Characteristics

Of 11862 patients in the present study, the mean age was 61.77 ± 13.51 years, and 44.4% (5264/11862) were female. The prevalence of diabetes has been reported in our previous analysis.[16] The proportions of current smoker, patients with hypertension, and those with hyperlipidemia were 14.9% (1773/11,862), 45.0% (5340/11,862), and 13.4% (1592/11862) in the overall population (Figure 1), 16.9% (96/568), 46.0% (261/568), and 20.4% (116/568) in AS, 19.6% (306/1562), 57.4% (896/1562), and 15.7% (245/1562) in AR, 7.4% (40/544), 20.8% (113/544), and 11.6% (63/544) in MS, 19.4% (572/1562), 49.4% (1454/2943), and 17.1% (503/2943) in MR, 12.1% (236/1956), 42.8% (837/1956), and 11.1% (218/1956) in TR, 14.9% (40/269), 39.0% (105/269), and 16.0% (43/269) in mixed AS and AR, 6.0% (12/200), 21.5% (43/200), and 13.0% (26/200) in mixed MS and MR, and 12.4% (472/3820), 42.7% (1631/3820), and 9.9% (378/3820) in MVHD. In the total study cohort, patients with zero, one, two, three, or four conventional cardiovascular risk factors accounted for 39.4% (4679/11,862), 38.2% (4531/11,862), 17.7% (2100/11,862), 4.3% (513/11,862), and 0.3% (39/11,862), respectively. In 568 patients with AS, 199 (35.0%) patients had no risk factor, 228 (40.1%), 100 (17.6%), 39 (6.9%), and 2 (0.4%) patients had one, two, three, and four risk factors. In 1562 patients with AR, 443 (28.4%), 714 (45.7%), 317 (20.3%), 82 (5.2%), and 6 (0.4%) patients had zero, one, two, three, and four risk factors. In 544 patients with MS, 341 (62.7%), 160 (29.4%), 36 (6.6%), and 7 (1.3%) patients had zero, one, two, and three risk factors. In 2943 patients with MR, 935 (31.8%), 1154 (39.2%), 647 (22.0%), 185 (6.3%), and 22 (0.7%) patients had zero, one, two, three, and four risk factors. In 1956 patients with TR, 847 (43.3%), 710 (36.3%), 333 (17.0%), 64 (3.3%), and 2 (0.1%) patients had zero, one, two, three, and four risk factors. In 269 patients with mixed AS and AR, 121 (45.0%), 102 (37.9%), 37 (13.8%), and 9 (3.3%) patients had zero, one, two, and three risk factors. In 200 patients with mixed MS and

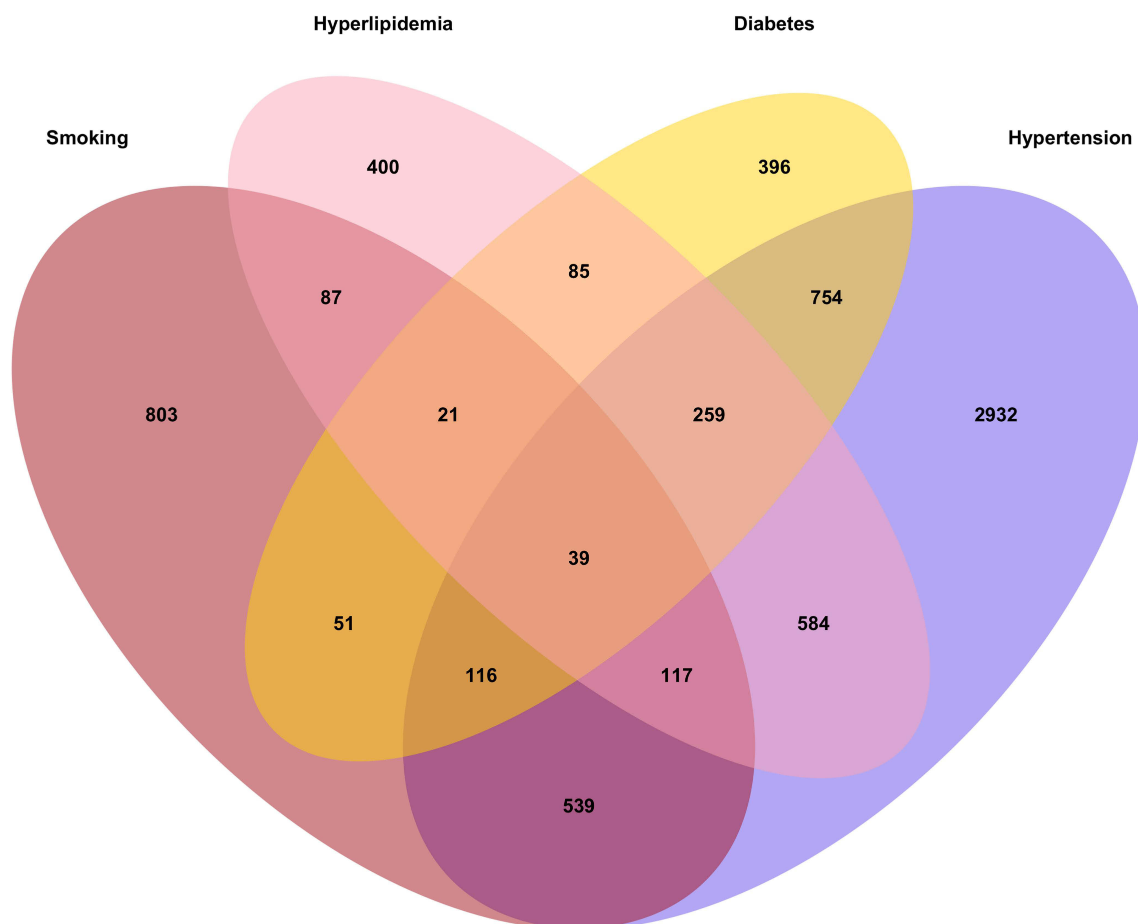

Figure 1 Venn diagram of risk factors in total cohort.

MR, 121 (60.5%), 60 (30.0%), 17 (8.5%), and 2 (1.0%) patients had zero, one, two, and three risk factors. In 3820 patients with MVHD, 1672 (43.8%), 1403 (36.7%), 613 (16.0%), 125 (3.3%), and 7 (0.2%) patients had zero, one, two, three, and four risk factors, respectively.

Baseline characteristics were presented in Tables 1, 2, and 3. Compared with those without any cardiovascular risk factor, patients with more risk factors tended to be older (P < 0.001). They were more likely to be male and had higher

Table 1 Baseline Characteristics of Patients with Isolated VHD

Variables	AS (n=568)	AR (n=1562)	MS (n=544)	MR (n=2943)	TR (n=1956)	P value
Age, yrs	63.01±11.88	59.95±13.75	55.53±10.79	61.33±12.75	62.64±16.19	<0.001
Male	337 (59.3)	1159 (74.2)	159 (29.2)	1780 (60.5)	925 (47.3)	<0.001
BMI, kg/m^2	23.87±3.27	24.11±3.43	23.25±3.21	24.00±3.56	23.25±3.95	<0.001
Cardiovascular risk factors						
Current smoker	96 (16.9)	306 (19.6)	40 (7.4)	571 (19.4)	236 (12.1)	<0.001
Hypertension	261 (46.0)	896 (57.4)	113 (20.8)	1454 (49.4)	837 (42.8)	<0.001
Hyperlipidemia	116 (20.4)	245 (15.7)	63 (11.6)	503 (17.1)	218 (11.1)	<0.001
Diabetes	80 (14.1)	171 (10.9)	37 (6.8)	563 (19.1)	285 (14.6)	<0.001
Coronary artery disease	177 (31.2)	545 (34.9)	69 (12.7)	1339 (45.5)	624 (31.9)	<0.001
Prior MI	25 (4.4)	124 (7.9)	9 (1.7)	533 (18.1)	168 (8.6)	<0.001
Prior PCI	45 (7.9)	220 (14.1)	16 (2.9)	645 (21.9)	239 (12.2)	<0.001
Prior CABG	17 (3.0)	33 (2.1)	10 (1.8)	117 (4.0)	54 (2.8)	0.002
Cardiomyopathy	8 (1.4)	48 (3.1)	0 (0.0)	428 (14.5)	115 (5.9)	<0.001
Atrial fibrillation or flutter	38 (6.7)	132 (8.5)	237 (43.6)	605 (20.6)	714 (36.5)	<0.001
Chronic lung disease	33 (5.8)	78 (5.0)	14 (2.6)	148 (5.0)	201 (10.3)	<0.001
Chronic kidney disease	19 (3.3)	65 (4.2)	9 (1.7)	199 (6.8)	112 (5.7)	<0.001
NYHA functional class						<0.001
I	162 (28.5)	682 (43.7)	156 (28.7)	980 (33.3)	945 (48.3)	
II	201 (35.4)	554 (35.5)	180 (33.1)	783 (26.6)	386 (19.7)	
III	181 (31.9)	260 (16.6)	187 (34.4)	841 (28.6)	441 (22.5)	
IV	24 (4.2)	66 (4.2)	21 (3.9)	339 (11.5)	184 (9.4)	
Hemoglobin, g/L	134.08±18.08	136.19±18.44	135.21±16.82	132.83±20.06	132.36±24.02	<0.001
Creatinine, μmol/L	73 (64–88)	79 (67.81–94.7)	73.76 (63–87)	81 (68–99.84)	77 (64–94.5)	<0.001
Albumin, g/l	41.36±5.03	40.51±4.71	41.71±4.46	39.56±5.07	39.00±5.38	<0.001
LA, mm	38.99±6.52	39.47±6.50	50.77±9.17	46.00±8.27	41.01±8.34	<0.001
LVEDD, mm	49.25±7.17	58.68±10.34	46.81±5.14	58.11±10.09	46.30±8.32	<0.001
LVEF, %	62 (56–66)	59 (53–64)	61 (56–65)	52 (37–62)	60 (53–64)	<0.001
Pulmonary hypertension	60 (10.6)	136 (8.7)	212 (39.0)	831 (28.2)	1158 (59.2)	<0.001
Severe VHD	412 (72.5)	564 (36.1)	292 (53.7)	988 (33.6)	604 (30.9)	<0.001
Valvular intervention	361 (63.6)	671 (43.0)	389 (71.5)	709 (24.1)	179 (9.2)	<0.001
Etiology						<0.001
Primary VHD	568 (100.0)	1080 (72.8)	544 (100.0)	1175 (41.2)	634 (33.4)	
Secondary VHD	0 (0.0)	403 (27.2)	0 (0.0)	1675 (58.8)	1267 (66.6)	
Medications						
Diuretics	415 (73.1)	1020 (65.3)	439 (80.7)	2127 (72.3)	1135 (58.0)	<0.001
β blockers	337 (59.3)	925 (59.2)	241 (44.3)	1924 (65.4)	957 (48.9)	<0.001
ACEI/ARB	165 (29.0)	720 (46.1)	112 (20.6)	1504 (51.1)	739 (37.8)	<0.001
Warfarin	320 (56.3)	700 (44.8)	414 (76.1)	807 (27.4)	428 (21.9)	<0.001
Aspirin	162 (28.5)	564 (36.1)	74 (13.6)	1352 (45.9)	654 (33.4)	<0.001
$P2Y_{12}$ inhibitors	109 (19.2)	375 (24.0)	32 (5.9)	983 (33.4)	488 (24.9)	<0.001

Notes: Data are presented as mean ± standard deviation, median (IQR), or number (%) without imputation.

Abbreviations: VHD, valvular heart disease; AS, aortic stenosis; AR, aortic regurgitation; MS, mitral stenosis; MR, mitral regurgitation; TR, tricuspid regurgitation; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; NYHA, New York Heart Association; LA, left atrial end-diastolic dimension; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 2 Baseline Characteristics of Patients with Mixed or MVHD

Variables	AS+AR (n=269)	MS+MR (n=200)	MVHD (n=3820)	P value
Age, yrs	61.04±12.45	56.35±10.24	63.44±12.83	<0.001
Male	169 (62.8)	69 (34.5)	2000 (52.4)	<0.001
BMI, kg/m^2	23.62±3.54	23.19±3.95	23.22±3.68	0.098
Cardiovascular risk factors				
Current smoker	40 (14.9)	12 (6.0)	472 (12.4)	0.011
Hypertension	105 (39.0)	43 (21.5)	1631 (42.7)	<0.001
Hyperlipidemia	43 (16.0)	26 (13.0)	378 (9.9)	0.003
Diabetes	15 (5.6)	19 (9.5)	551 (14.4)	<0.001
Coronary artery disease	52 (19.3)	29 (14.5)	1195 (31.3)	<0.001
Prior MI	9 (3.3)	4 (2.0)	313 (8.2)	<0.001
Prior PCI	16 (5.9)	6 (3.0)	392 (10.3)	<0.001
Prior CABG	4 (1.5)	0 (0.0)	72 (1.9)	0.100
Cardiomyopathy	3 (1.1)	0 (0.0)	358 (9.4)	<0.001
Atrial fibrillation or flutter	21 (7.8)	100 (50.0)	1582 (41.4)	<0.001
Chronic lung disease	12 (4.5)	3 (1.5)	252 (6.6)	0.007
Chronic kidney disease	4 (1.5)	3 (1.5)	255 (6.7)	<0.001
NYHA functional class				<0.001
I	81 (30.1)	48 (24.0)	900 (23.6)	
II	96 (35.7)	74 (37.0)	1020 (26.7)	
III	78 (29.0)	64 (32.0)	1349 (35.3)	
IV	14 (5.2)	14 (7.0)	551 (14.4)	
Hemoglobin, g/L	134.02±17.27	134.51±16.91	129.93±19.98	<0.001
Creatinine, μmol/L	78.17 (65.63–87.61)	75.05 (63–88)	81 (67–100)	<0.001
Albumin, g/l	40.53±4.24	41.04±4.17	38.90±5.10	<0.001
LA, mm	41.27±6.59	54.02±10.57	50.27±10.24	<0.001
LVEDD, mm	56.99±8.66	48.63±6.58	55.83±10.89	<0.001
LVEF, %	60 (50.5–65)	60 (55–65)	55 (41–62)	<0.001
Pulmonary hypertension	45 (16.7)	85 (42.5)	2377 (62.2)	<0.001
Severe VHD	190 (70.6)	101 (50.5)	2389 (62.5)	<0.001
Valvular intervention	190 (70.6)	134 (67.0)	1271 (33.3)	<0.001
Etiology				<0.001
Primary VHD	269 (100.0)	200 (100.0)	2267 (60.6)	
Secondary VHD	0 (0.0)	0 (0.0)	1476 (39.4)	
Medications				
Diuretics	223 (82.9)	168 (84.0)	3131 (82.0)	0.720
β blockers	132 (49.1)	100 (50.0)	2232 (58.4)	0.001
ACEI/ARB	84 (31.2)	48 (24.0)	1712 (44.8)	<0.001
Warfarin	186 (69.1)	151 (75.5)	1689 (44.2)	<0.001
Aspirin	63 (23.4)	33 (16.5)	1070 (28.0)	<0.001
$P2Y_{12}$ inhibitors	31 (11.5)	15 (7.5)	725 (19.0)	<0.001

Notes: Data are presented as mean ± standard deviation, median (IQR), or number (%) without imputation.
Abbreviations: MVHD, multiple valvular heart disease; AS, aortic stenosis; AR, aortic regurgitation; MS, mitral stenosis; MR, mitral regurgitation; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; NYHA, New York Heart Association; LA, left atrial end-diastolic dimension; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; VHD, valvular heart disease; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

BMI (both P < 0.001). Patients without any risk factor had a lower prevalence of coronary heart disease, as well as chronic kidney disease (both P < 0.001). The increase in the number of risk factors was related to larger left ventricular end-diastolic dimension and worse ejection fraction (both P < 0.001).

Table 3 Baseline Characteristics According to the Number of Risk Factors

Variables	0 (n=4679)	1 (n=4531)	2 (n=2100)	3–4 (n=552)	P Value
Age, yrs	57.58±14.22	63.87±12.78	65.78±11.31	64.69±11.34	<0.001
Male	2120 (45.3)	2692 (59.4)	1374 (65.4)	412 (74.6)	<0.001
BMI, kg/m^2	22.72±3.46	23.80±3.58	24.54±3.69	25.34±3.75	<0.001
Cardiovascular risk factors					
Current smoker	0 (0.0)	803 (17.7)	677 (32.2)	293 (53.1)	<0.001
Hypertension	0 (0.0)	2932 (64.7)	1877 (89.4)	531 (96.2)	<0.001
Hyperlipidemia	0 (0.0)	400 (8.8)	756 (36.0)	436 (79.0)	<0.001
Diabetes	0 (0.0)	396 (8.7)	890 (42.4)	435 (78.8)	<0.001
Coronary artery disease	801 (17.1)	1661 (36.7)	1181 (56.2)	387 (70.1)	<0.001
Prior MI	192 (4.1)	461 (10.2)	380 (18.1)	152 (27.5)	<0.001
Prior PCI	262 (5.6)	630 (13.9)	495 (23.6)	192 (34.8)	<0.001
Prior CABG	48 (1.0)	119 (2.6)	97 (4.6)	43 (7.8)	<0.001
Cardiomyopathy	395 (8.4)	353 (7.8)	162 (7.7)	50 (9.1)	0.490
Atrial fibrillation or flutter	1464 (31.3)	1303 (28.8)	544 (25.9)	118 (21.4)	<0.001
Chronic lung disease	257 (5.5)	296 (6.5)	145 (6.9)	43 (7.8)	0.030
Chronic kidney disease	115 (2.5)	285 (6.3)	189 (9.0)	77 (13.9)	<0.001
NYHA functional class					<0.001
I	1454 (31.1)	1525 (33.7)	756 (36.0)	219 (39.7)	
II	1308 (28.0)	1347 (29.7)	525 (25.0)	114 (20.7)	
III	1437 (30.7)	1222 (27.0)	581 (27.7)	161 (29.2)	
IV	480 (10.3)	437 (9.6)	238 (11.3)	58 (10.5)	
Hemoglobin, g/L	132.43±19.76	132.89±20.23	131.44±21.44	132.92±21.17	0.175
Creatinine, μmol/L	75 (63–90)	80 (67.2–97)	84.75 (71–104)	91 (73–116)	<0.001
Albumin, g/l	39.88±5.02	39.56±5.04	39.12±5.29	39.52±5.32	<0.001
LA, mm	46.24±10.98	45.42±9.55	44.86±8.03	44.62±7.90	<0.001
LVEDD, mm	53.34±11.67	54.71±10.32	55.46±10.01	56.24±9.31	<0.001
LVEF, %	58 (47–64)	58 (45–63)	56 (42–62)	54 (39–62)	<0.001
Pulmonary hypertension	2070 (44.2)	1807 (39.9)	828 (39.4)	199 (36.1)	<0.001
Severe VHD	2519 (53.8)	2039 (45.0)	785 (37.4)	197 (35.7)	<0.001
Valvular intervention	1937 (41.4)	1433 (31.6)	443 (21.1)	91 (16.5)	<0.001
Etiology					<0.001
Primary VHD	3001 (65.7)	2540 (57.8)	949 (46.3)	247 (45.2)	
Secondary VHD	1565 (34.3)	1856 (42.2)	1101 (53.7)	299 (54.8)	
Medications					
Diuretics	3623 (77.4)	3253 (71.8)	1413 (67.3)	369 (66.8)	<0.001
β blockers	2327 (49.7)	2751 (60.7)	1371 (65.3)	399 (72.3)	<0.001
ACEI/ARB	1409 (30.1)	2247 (49.6)	1122 (53.4)	306 (55.4)	<0.001
Warfarin	2261 (48.3)	1761 (38.9)	558 (26.6)	115 (20.8)	<0.001
Aspirin	962 (20.6)	1566 (34.6)	1099 (52.3)	345 (62.5)	<0.001
$P2Y_{12}$ inhibitors	599 (12.8)	1085 (23.9)	792 (37.7)	282 (51.1)	<0.001

Notes: Data are presented as mean ± standard deviation, median (IQR), or number (%) without imputation.
Abbreviations: BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; NYHA, New York Heart Association; LA, left atrial end-diastolic dimension; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; VHD, valvular heart disease; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Association of the Number of Risk Factors with Outcome

During a median follow-up of 732 days, a total of 1696 adverse events, including 978 all-cause deaths, 63 MIs, and 655 HHFs, occurred in 1531 (12.9%) patients. The relationships of conventional cardiovascular risk factors with two-year outcome in various types of VHD were shown in Supplementary Tables 1–4, Supplementary Figure 1, and Supplementary Figure 2. The increase in the number of risk factors indicated poor prognosis in patients with MR, TR,

and MVHD (Supplementary Figure 1). After adjustment for age and sex, MR patients with three or four risk factors had significantly worse outcomes compared with those with no risk factor (Supplementary Table 2; three/four vs zero: adjusted HR [95% CI]: 1.667 [1.168–2.378], P = 0.005; two vs zero: adjusted HR [95% CI]: 1.255 [0.957–1.646], P = 0.101; one vs zero: adjusted HR [95% CI]: 0.884 [0.685–1.142], P = 0.346). In the fully adjusted model, the number of risk factors, as both categorical and continuous variables, was also independently associated with two-year outcome in patients with MR (Supplementary Table 3; three/four vs zero: HR [95% CI]: 1.600 [1.106–2.315], P = 0.013; two vs zero: HR [95% CI]: 1.153 [0.867–1.532], P=0.328; one vs zero: HR [95% CI]: 0.892 [0.687–1.159], P = 0.393; number of risk factors [per one risk factor increase]: HR [95% CI]: 1.159 [1.036–1.298], P = 0.010). As a continuous variable, the number of risk factors was identified as an independent predictor of all-cause mortality in MR (Supplementary Table 4; adjusted HR [95% CI]: 1.168 [1.007–1.355], P = 0.04). Results of the analysis according to the etiology of mitral valve lesions were shown in Supplementary Tables 3 and 4. Per one risk factor increase, the relative risks of two-year adverse events and mortality increased by 17.3% and 20.5%, respectively, in patients with secondary MR (the composite outcome: adjusted HR [95% CI]: 1.173 [1.028–1.338], P = 0.017; all-cause mortality: adjusted HR [95% CI]: 1.205 [1.010–1.438], P = 0.039).

Combined Prognostic Role of Risk Factors in MR

Compared with non-diabetic patients, patients with both diabetes and at least one other risk factor had a significantly higher risk of all-cause mortality and the composite endpoint, whereas there was no statistical difference on two-year outcomes between those without diabetes and diabetic patients without any other risk factor (Table 4; composite endpoint: diabetes with at least one other risk factor vs no diabetes: adjusted HR [95% CI], 1.498 [1.176–1.909], P = 0.001; diabetes without any other risk factor vs no diabetes: adjusted HR [95% CI], 0.958 [0.610–1.506], P = 0.854; all-cause mortality: diabetes with at least one other risk factor vs no diabetes: adjusted HR [95% CI], 1.411 [1.024–1.945], P = 0.036; diabetes without any other risk factor vs no diabetes: adjusted HR [95% CI], 1.335 [0.776–2.295], P = 0.296). Similarly, compared with no risk factor, concomitant diabetes and at least one other risk factor were independently associated with poorer outcomes, while no difference was observed among those with no risk factor, no diabetes, and diabetic patients without any other risk factor (Table 4 and Figure 2).

Determinants of Outcome According to the Number of Risk Factors

Age, NYHA functional class, LVEF, and pulmonary hypertension were common independent prognostic factors in patients with different numbers of cardiovascular risk factors (zero, one, two, and three/four; Supplementary Tables 5 and 6). In patients without any risk factor, BMI (HR [95% CI]: 0.939 [0.913–0.965], P < 0.001), coronary heart disease (HR [95% CI]: 1.268 [1.030–1.560], P = 0.025), cardiomyopathy (HR [95% CI]: 1.353 [1.040–1.760], P = 0.024),

Table 4 Combined Prognostic Role of Cardiovascular Risk Factors in MR

	Composite Endpoint		All-Cause Mortality	
	Adjusted HR (95% CI)*	**P Value**	**Adjusted HR (95% CI)***	**P Value**
Cardiovascular risk factor				
No diabetes	Reference	Reference	Reference	Reference
Diabetes without any other risk factors	0.958 (0.610–1.506)	0.854	1.335 (0.776–2.295)	0.296
Diabetes with at least 1 other risk factor	1.498 (1.176–1.909)	0.001	1.411 (1.024–1.945)	0.036
Cardiovascular risk factor				
No risk factor	Reference	Reference	Reference	Reference
No diabetes	0.925 (0.719–1.191)	0.546	0.985 (0.701–1.386)	0.933
Diabetes without any other risk factors	0.912 (0.564–1.472)	0.705	1.322 (0.738–2.371)	0.348
Diabetes with at least 1 other risk factor	1.421 (1.057–1.911)	0.020	1.397 (0.938–2.080)	0.100

Notes: *Adjusted for age, sex, BMI, coronary artery disease, cardiomyopathy, atrial fibrillation or flutter, chronic lung disease, chronic kidney disease, NYHA functional class, hemoglobin, creatinine, albumin, LA, LVEDD, LVEF, pulmonary hypertension, severity of VHD, and valvular intervention.
Abbreviations: MR, mitral regurgitation; BMI, body mass index; NYHA, New York Heart Association; LA, left atrial end-diastolic dimension; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; VHD, valvular heart disease; HR, hazard ratio; CI, confidence interval.

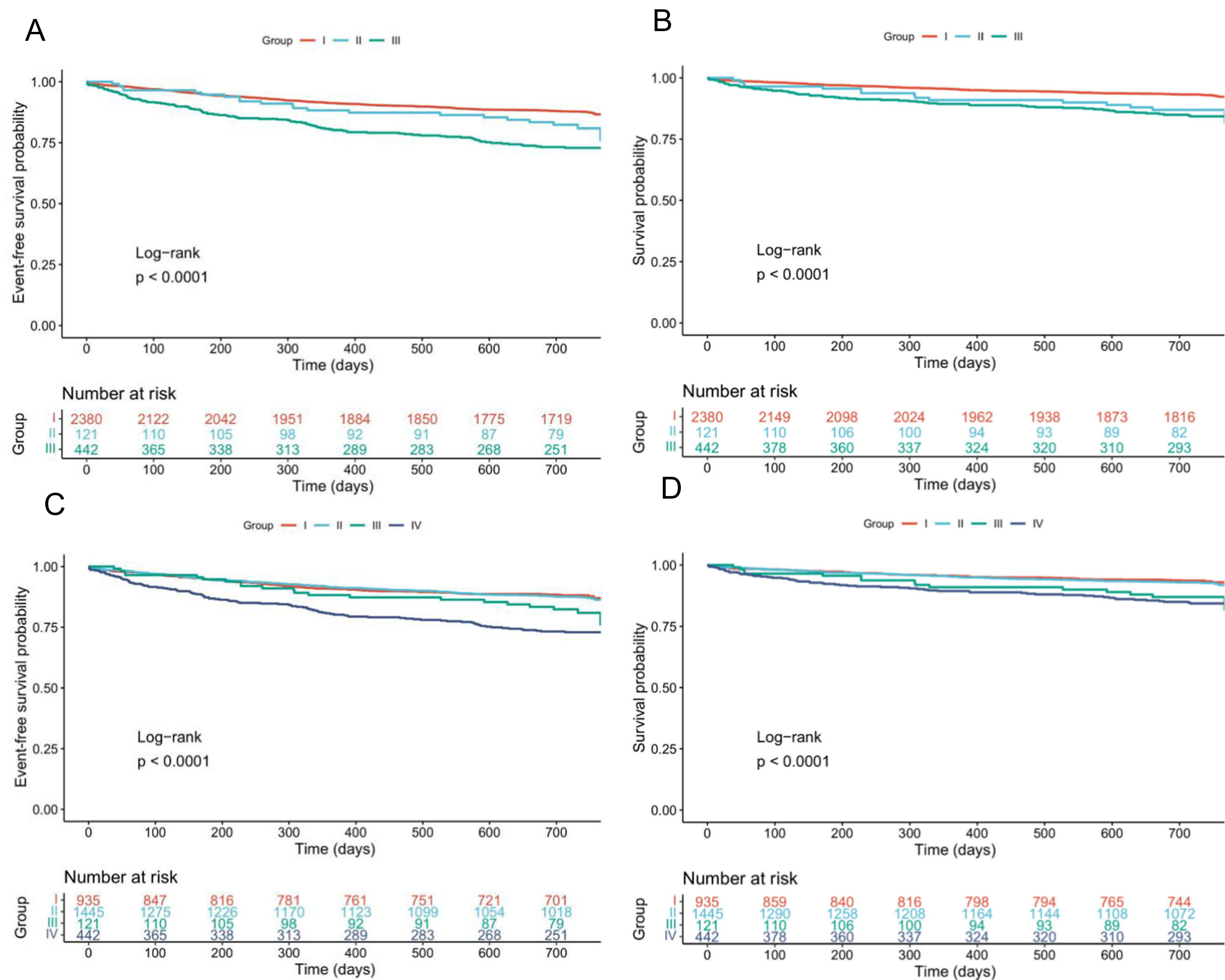

Figure 2 Combined prognostic effects of multiple risk factors in MR. (**A**) Kaplan–Meier curves of two-year composite outcome. Group I, patients without diabetes; Group II, diabetic patients without any other risk factors; Group III, patients with both diabetes and at least one risk factor. (**B**) Kaplan–Meier curves of mortality. Group I, patients without diabetes; Group II, diabetic patients without any other risk factors; Group III, patients with both diabetes and at least one risk factor. (**C**) Kaplan–Meier curves of two-year composite outcome. Group I, patients without any risk factors; Group II, patients without diabetes; Group III, diabetic patients without any other risk factors; Group IV, patients with both diabetes and at least one risk factor. (**D**) Kaplan–Meier curves of mortality. Group I, patients without any risk factors; Group II, patients without diabetes; Group III, diabetic patients without any other risk factors; Group IV, patients with both diabetes and at least one risk factor.
Abbreviation: MR, mitral regurgitation.

hemoglobin (HR [95% CI]: 0.995 [0.990–1.000], P = 0.041), creatinine (HR [95% CI]: 1.003 [1.001–1.004], P < 0.001), albumin (HR [95% CI]: 0.976 [0.957–0.996], P = 0.019), and valvular intervention (HR [95% CI]: 0.341 [0.261–0.445], P < 0.001) were also independent predictors of two-year outcome. Additional prognostic factors in patients with one risk factor included chronic kidney disease (HR [95% CI]: 1.446 [1.115–1.876], P = 0.005), hemoglobin (HR [95% CI]: 0.988 [0.984–0.993], P < 0.001), LA (HR [95% CI]: 1.011 [1.001–1.021], P = 0.026), severe VHD (HR [95% CI]: 1.195 [1.004–1.423], P = 0.045), and valvular intervention (HR [95% CI]: 0.329 [0.238–0.454], P < 0.001). Chronic kidney disease (HR [95% CI]: 1.421 [1.021–1.978], P = 0.037), albumin (HR [95% CI]: 0.956 [0.935–0.979], P<0.001), and valvular intervention (HR [95% CI]: 0.298 [0.178–0.501], P < 0.001) were additional prognostic factors in patients with two risk factors. In patients with three or four risk factors, sex (male vs female, HR [95% CI]: 0.442 [0.261–0.748], P = 0.002) was a unique determinant of two-year outcome, while BMI (HR [95% CI]: 0.919 [0.862–0.980], P = 0.010), creatinine (HR [95% CI]: 1.002 [1.001–1.004], P = 0.010), and albumin (HR [95% CI]: 0.941 [0.895–0.990], P = 0.018) were also identified as independent prognostic factors.

Discussion

The present observational cohort study, including more than 11,000 patients with moderate or greater VHD, found that over one of the five patients had at least two conventional modifiable cardiovascular risk factors. The prevalences of smoking, hypertension, hyperlipidemia, and diabetes were 14.9%, 45.0%, 13.4%, and 14.5%, respectively, in the overall population. The increasing number of risk factors indicated poor two-year outcomes in patients with significant MR, and the coexistence of diabetes and at least one other risk factor was independently associated with a higher risk of adverse events. In VHD patients with different numbers of risk factors, age, NYHA functional class, LVEF, and pulmonary hypertension were common prognostic indicators, whereas sex was a significant outcome determinant only in those with three/four risk factors.

SMuRF is a well-known medical concept and plays a pivotal role throughout the natural history of coronary artery disease. Importantly, the risks related to SMuRFs are largely preventable by lifestyle interventions or appropriate medications, and these targeted strategies against modifiable risk factors have significantly improved both prevention and treatment of coronary artery disease.[25,26] In the realm of VHD, a growing number of studies have suggested the substantial contributions of traditional cardiovascular risk factors to the development of valvular lesions.[14] Nevertheless, there are only a few publications comprehensively reporting the distribution of risk factors in the VHD population.[27,28] In the present large contemporary cohort study, we observed that the prevalences of hyperlipidemia, diabetes, smoking, and hypertension ranged from 13.4% to 45.0% in adults with significant VHD, and a majority (60.6%) of patients had at least one of the four modifiable cardiovascular risk factors. It is worth noting that the data obtained in this analysis are not entirely consistent with some previous investigations. For instance, the results of the China Elderly Valve Disease (China-DVD) study, which was conducted by us in 2016, showed that smoking, hypertension, dyslipidemia, and diabetes accounted for 29.4%, 52.2%, 7.4%, and 19.3% of 8929 elderly patients (≥60 years) with moderate or severe VHD.[27] In both the total cohort and specific subtype of VHD, participants of the China-DVD study had generally larger burdens of cardiovascular risk factors compared with those in the China-VHD registry. The distinct inclusion criteria on age are most likely to explain such differences between two studies, as the China-VHD registry focused on all adult patients, rather than the elderly population alone. In addition, the China-DVD study only enrolled inpatients, while the participants of China-VHD registry were recruited from both inpatient wards and outpatient clinics.[22,27] Altogether, the China-VHD cohort was a more representative hospital-based cohort, and the present analysis provided more generalizable and contemporary information on cardiovascular risk factor burden in patients with significant VHD. There also existed some differences in the prevalence of risk factors between Chinese patients and VHD population in western countries. As shown in the EURObservational Research Programme Valvular Heart Disease II survey, the prevalences of hypertension, hyperlipidemia, and diabetes were 67.0%, 46.9%, and 21.5%, separately, higher than those in our study.[28] Racial differences and distinct socioeconomic backgrounds between Asia and Europe may be the main explanations of these findings.[29] Going beyond previous investigations, the present study further evaluated the coexistence of multiple risk factors in individuals with VHD, and found that more than one in five patients had two or more risk factors. The highly prevalent coexistence of multiple risk factors in VHD may significantly challenge the decision-making of individualized therapeutic strategies, as well as increasing the total expenditure of medical care.

In 2943 patients with significant MR, the current study found that the presence of three or four conventional cardiovascular risk factors was independently related to a 60.0% higher risk of two-year adverse events, which included death, HHF, and MI, compared with no cardiovascular risk factor. Previous research predominantly investigated the prognostic impact of individual cardiovascular risk factor in patients with mitral valve dysfunction,[16–20,30–32] and only a few of them did reveal statistically significant associations of risk factors with outcomes in different follow-up durations.[16,18] For example, a sub-analysis of the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (COAPT) trial reported a higher two-year rate of death in MR patients with diabetes (40.8%) compared with those without diabetes (32.3%).[18] Another analysis using the COAPT trial database sought to establish a simple risk score for the prediction of outcome in patient with severe MR (n = 614), with the cardiovascular risk factor burden ≥3 as a candidate of model predictor, which referred to three or more risk factors in diabetes, hypertension, hypercholesterolemia, and obesity.[33] However, cardiovascular risk factor burden ≥3 was not associated with the two-year rate of death or heart failure hospitalization in multivariable Cox regression model, with

an adjusted p value of 0.46, and therefore was not included in the final COAPT score.[33] To the best of our knowledge, our study for the first time confirmed the prognostic role of the number of conventional modifiable cardiovascular risk factors, as both categorical and continuous variables, in patients with significant MR. In addition, stratified by the etiology of mitral valve dysfunction, we found that the increase in the number of risk factors indicated significantly higher risks of both two-year adverse events and all-cause mortality in those with secondary MR. From the standpoint of secondary prevention, the number of risk factors should be taken into account in prospective risk assessment of MR, especially in those with secondary mitral valve dysfunction, and MR patients presenting with multiple risk factors should be considered as a particularly high-risk group requiring intensive care, including optimal medical therapy, close follow-up, and careful evaluation for the eligibility and potential benefits of valvular intervention. Interestingly, our study also found that the presence of diabetes alongside at least one other cardiovascular risk factor was linked to poor two-year prognosis, whereas there was no difference on event-free survival between patients with diabetes alone and those without any risk factor (or compared with non-diabetic individuals). These results greatly extended the earlier findings in our prior analysis, which suggested that diabetes itself (vs no diabetes) indicated poor prognosis in patients with moderate or greater MR.[16] Although the present clinical research was insufficient to unravel the intrinsic mechanisms behind the phenomenon, it was reasonable to speculate that diabetes acted synergistically with conventional risk factors in MR, which substantially magnified the risks associated with diabetes individually. Our findings could also in part explain why a series of previous studies with distinct follow-up durations did not identify any conventional risk factors as independent outcome determinants in patients with MR.[30–32] After all, the traditional regression-based analyses cannot provide additional information beyond pre-specified input parameters. The rapidly emerging machine learning techniques, which possess the merit of capturing interactions among different variables,[34] may make it easier to account for the accumulative prognostic effects of features, as well as providing accurate prognostication.

A recent study suggested that the number of SMuRFs could affect prognostic factor profiles in patients with coronary artery disease,[35] and thereby provided a novel idea for promoting individualized prognostic assessment with the consideration of SMuRFs. In the current analysis, we for the first time evaluated outcome determinants according to the burden of conventional modifiable risk factors in patients with significant VHD, and found that age, NYHA functional class, LVEF, and pulmonary hypertension were constant predictors of two-year outcomes regardless of the number of risk factors, reinforcing the results of previous studies which showed the prognostic importance of these clinical parameters in VHD.[36–38] However, not all variables held consistent prognostic value across different numbers of risk factors. In particular, our study showed that male had a significantly lower risk of two-year adverse events compared with female, which was only observed in those with three or four conventional risk factors. The pathophysiological mechanism of such sex difference in outcomes is unclear and of urgent need to be clarified. One can hypothesize that the heart of women with significant VHD may be more vulnerable to concomitant cardiovascular risk factors than that of men. In addition, previous studies focusing on coronary artery disease indicated that women had a relatively lower risk factor control rate compared with men.[38,39] If future studies further find a similar phenomenon in VHD patients with multiple risk factors, this may be an important and clinically relevant explanation of currently observed poor prognosis in women. We also found that valvular intervention reduced the two-year risk of adverse events in all patients except those with three or four risk factors, which could be explained by a higher baseline risk of patients with more risk factors, and highlighted the necessity of appropriate patient selection for valvular intervention to achieve optimal outcomes.

Clinical Implications

Showing the burden and prognostic impact of traditional modifiable cardiovascular risk factors in patients with significant VHD, the present study filled several knowledge gaps, and provided practical information for clinical decision-making. Previously, the correction of valvular lesions was the main focus of treating VHD in clinical settings, of which the techniques had updated dramatically in recent years. However, the clinical outcomes of patients have not improved as anticipated.[5–7] Our study indicated a high prevalence of the coexistence of conventional risk factors in patients with various types of VHD and unraveled the relationship of the number of conventional modifiable cardiovascular risk factors with two-year outcomes in those with significant MR, as well as its impact on prognostic factor profiles. These findings may facilitate the early identification of high-risk patients, and more importantly, help find out the causes

that contribute to the poor prognosis in MR, which is of particular importance, inasmuch as the treatment of mitral valve dysfunction includes not only valvular intervention but the modification of risk factors. Indeed, the observed association underscores the crucial role of comprehensive management in routine clinical practice, with one focus on optimizing therapies to achieve better control of smoking, hypertension, hyperlipidemia, and diabetes. In addition, a previous study found that modified Haller index, as calculated by dividing the maximum latero-lateral external thoracic diameter by the minimum anteroposterior internal thoracic diameter, was a significant prognostic indicator in patients with mitral valve prolapse and moderate MR.[40] The combination of cardiovascular risk factor evaluation with the noninvasive chest wall shape assessment may further promote risk stratification of MR.

Limitations

Several limitations existed in the present study. First, data for this analysis were from an observational cohort study. Although we have adopted multivariable regression models to adjust for a series of covariates, there might exist residual confounding factors which could affect our results. Second, the status of cardiovascular risk factors during follow-up was not collected in the China-VHD registry, and therefore we could not analyze the impact of risk factor control on long-term outcomes in patients with different types of VHD. Third, the two-year follow-up duration in the current analysis seemed to be insufficient to reveal the prognostic significance of individual risk factor in some types of VHD, and prospective studies with a longer follow-up period are highly desired. Lastly, the present study sought to assess the burden and impact of conventional modifiable risk factors in patients with VHD. The roles of some newly developed risk factors of VHD, such as lipoprotein (a),[41] were not evaluated. Future studies are still needed to investigate the systemic burden of atypical cardiovascular risk factors in VHD, as well as the potential therapeutic strategies and corresponding benefits of modifying those risk factors.

Conclusions

More than one of the five patients with VHD had at least two conventional modifiable cardiovascular risk factors. The increasing number of risk factors was associated with poor prognosis in significant MR, especially in those with secondary mitral valve dysfunction, and the presence of both diabetes and at least one other risk factor identified individuals with a significantly higher risk of two-year adverse events. Better understanding of cardiovascular risk factors can enhance clinical risk stratification in patients with significant VHD, and optimizing the management of risk factors may serve as a potential way to improve long-term outcomes of these patients.

Abbreviations

VHD, valvular heart disease; SMuRF, standard modifiable cardiovascular risk factor; AS, aortic stenosis; AR, aortic regurgitation; MS, mitral stenosis; MR, mitral regurgitation; TR, tricuspid regurgitation; MVHD, multiple VHD; MI, myocardial infarction; HHF, hospitalization for heart failure; BMI, body mass index; NYHA, New York Heart Association; LA, left atrial end-diastolic dimension; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction.

Data Sharing Statement

The data used during the current study are available from the corresponding authors on reasonable request.

Ethics Approval and Informed Consent

The study was approved by the Institutional Review Board at Fuwai Hospital, National Center for Cardiovascular Diseases of China (Approval No. 2017-968), and performed in accordance with the Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest.

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