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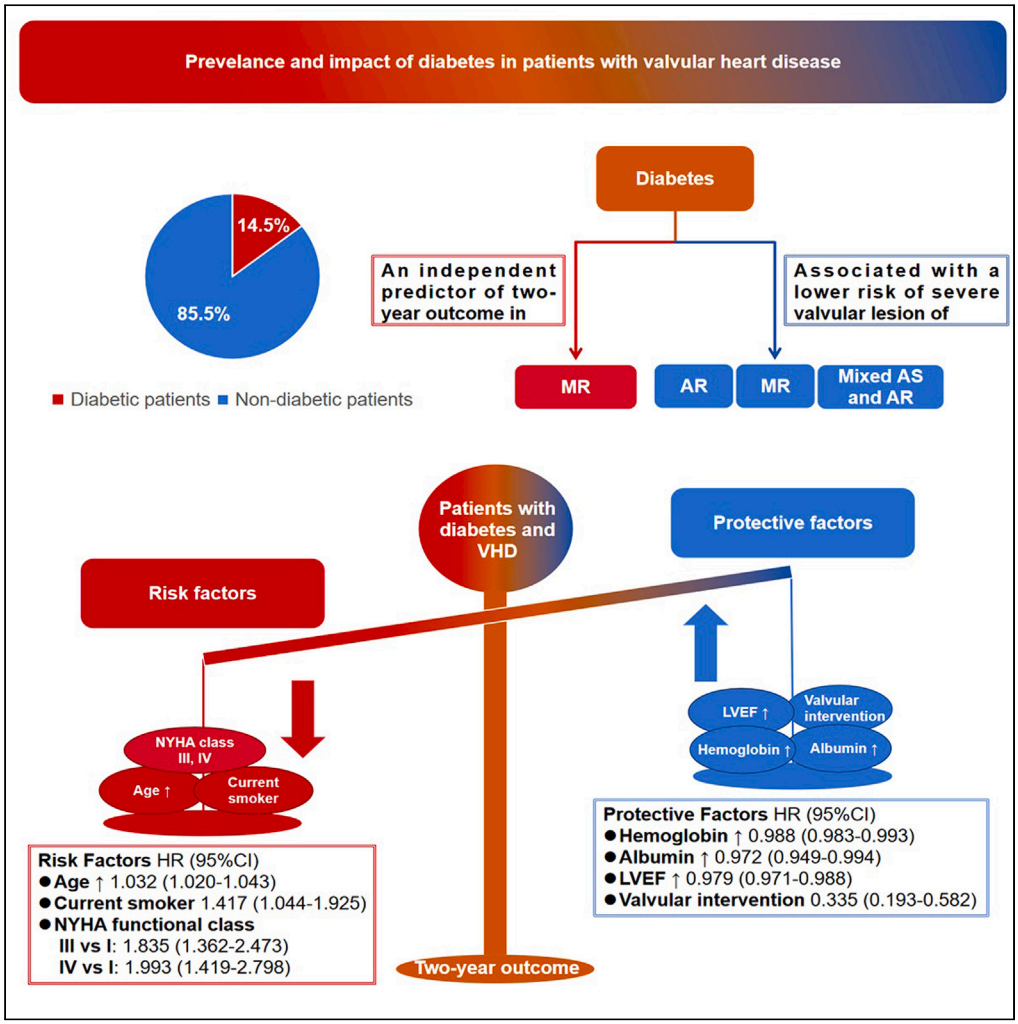

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Highlights

Diabetes is common in patients with valvular heart disease

Diabetes is associated with a lower risk of severe aortic and mitral regurgitation

Diabetes indicated poor prognosis in patients with mitral regurgitation

Better management is needed in patients with both diabetes and valvular heart disease

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Prevalence and impact of diabetes in patients with valvular heart disease

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SUMMARY

This study aimed to investigate the prevalence of diabetes in valvular heart disease (VHD), as well as the relationship of diabetes with severity of valvular lesions and clinical outcome. A total of 11,862 patients with significant (≥moderate) VHD from the China Valvular Heart Disease study were included in the analysis. The primary outcome was the composite of all-cause death, hospitalization for heart failure, and myocardial infarction during two-year follow-up. The prevalence of diabetes was 14.5% (1,721/11,862) in VHD. After adjusting for patients' demographics, diabetes was associated with a significantly lower risk of severe valvular lesion in aortic regurgitation and mitral regurgitation (MR). In multivariable analysis, diabetes was identified as an independent predictor of two-year outcome in patients with MR (hazard ratio: 1.345, 95% confidence interval: 1.069–1.692, p = 0.011). More efforts should be made to enhance our understanding and improve outcomes of concomitant VHD and diabetes.

INTRODUCTION

The prevalence of valvular heart disease (VHD) has increased globally due to the aging of population.[1] The number of patients with VHD will continue to grow in the next five decades, and this cardiac issue is likely to cause severe socioeconomic burden.[2,3] Chronic VHD often accompanies with various comorbidities, such as diabetes, which may exacerbate cardiac remodeling and dysfunction beyond valvular lesions, leading to poor prognosis.[4]

Diabetes has already been proposed as a risk factor of aortic stenosis (AS),[5–8] accelerating the development of valvular lesion through several complicated mechanisms.[9–12] However, the impact of diabetes on the occurrence of different types of VHD seems not to be consistently promoting, given that a recent study including more than 710,000 diabetic patients found that those with type 2 diabetes displayed a significantly lower risk of aortic regurgitation (AR) and mitral regurgitation (MR).[13] Currently, the precise nature and relationship between diabetes and the development of different types of severe valvular diseases still remain unknown. Besides, there are scarce data regarding the association of diabetes with outcomes in various VHD. Narrowing these knowledge gaps may enable better clinical decision making, thereby improving outcomes of patients with both VHD and diabetes eventually.

Hence, using a large, contemporary, nationwide, prospective cohort, the present study sought to investigate the prevalence and impact of diabetes in patients with VHD.

RESULTS

Baseline characteristics

Among 11,862 patients with significant VHD (Figures 1 and 2), the mean age was 61.77 ± 13.51 years, and 55.6% (6,598/11,862) were male. The prevalence of diabetes in the study population was 14.5% (1,721/11,862). Divided by subtypes of VHD, the prevalences of diabetes were 14.1% (80/568) in AS, 10.9% (171/1,562) in AR, 6.8% (37/544) in mitral stenosis (MS), 19.1% (563/2,943) in MR, 14.6% (285/1,956) in tricuspid regurgitation (TR), 5.6% (15/269) in mixed AS and AR, 9.5% (19/200) in mixed MS and MR, and 14.4% (551/3,820) in multiple VHD (MVHD). According to the etiology of VHD, individuals with diabetes accounted for 6.7% (159/2,370), 16.7% (492/2,951), 6.2% (58/940), 28.7% (326/1,135), and 16.5% (607/3,686) in patients with rheumatic VHD, degenerative VHD, congenital VHD, ischemic VHD, and functional VHD, respectively. Notably, there was a monotonic growth in diabetes rate as the age increased (Figures S1 and S2).

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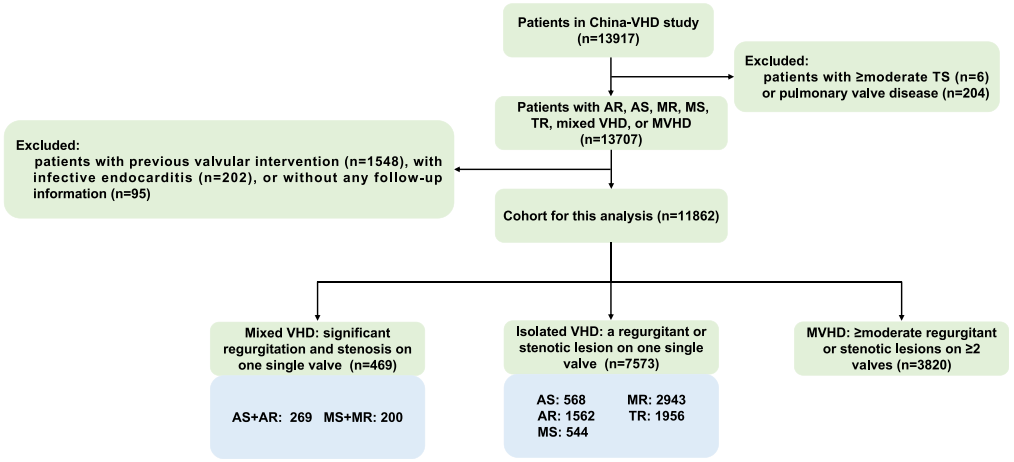

Figure 1. Flowchart illustrating the study participants

China-VHD, China Valvular Heart Disease; TS, tricuspid stenosis; AR, aortic regurgitation; AS, aortic stenosis; MR, mitral regurgitation; MS, mitral stenosis; TR, tricuspid regurgitation; MVHD, multiple valvular heart disease.

Baseline characteristics stratified by diabetes are presented in Table 1. Compared with those without diabetes, patients with diabetes were older (66.74 ± 10.64 vs. 60.92 ± 13.77 years, $p < 0.001$), and more likely to have higher body mass index (BMI, 24.56 ± 3.59 vs. 23.41 ± 3.63, $p < 0.001$). In the diabetic group, there were larger proportions of patients with hypertension (67.9% vs. 41.1%, $p < 0.001$), hyperlipidemia (23.5% vs. 11.7%, $p < 0.001$), coronary heart disease (CAD) (61.8% vs. 29.3%, $p < 0.001$), cardiomyopathy (10.3% vs. 7.7%, $p < 0.001$), and chronic kidney disease (11.7% vs. 4.6%, $p < 0.001$). Diabetes was also related to higher left ventricular end-diastolic dimension (LVEDD, 55.09 ± 9.85 vs. 54.25 ± 10.96, $p < 0.001$) and poorer left ventricular ejection fraction (LVEF, 52% vs. 58%, $p < 0.001$).

Association of diabetes with VHD severity

After adjusting for patients' demographics, diabetes was associated with a significantly lower risk of severe valvular lesion in AR (odds ratio [OR]: 0.579, 95% confidence interval [CI]: 0.390–0.860, p = 0.007), MR (OR: 0.647, 95%CI: 0.523–0.800, p < 0.001), mixed AR and AS (OR: 0.258, 95%CI: 0.087–0.765, p = 0.015), and MVHD (OR: 0.816, 95%CI: 0.678–0.982, p = 0.031). Similar results were observed in patients with primary VHD (AR, OR: 0.593, 95%CI: 0.371–0.946, p = 0.028; MR, OR: 0.680, 95%CI: 0.475–0.973, p = 0.035; mixed AR and AS, OR: 0.258, 95%CI: 0.087–0.765, p = 0.015), as well as in those with isolated secondary MR (OR: 0.713, 95%CI: 0.538–0.944, p = 0.018) (Figure S3).

After further adjusting for potential risk factors of VHD, diabetes was also associated with a lower risk of severe valvular lesion in AR (OR: 0.596, 95%CI: 0.399–0.891, p = 0.012), MR (OR: 0.683, 95%CI: 0.550–0.849, p = 0.001), and mixed AS and AR (OR: 0.299, 95%CI: 0.096–0.933, p = 0.038). In patients with primary VHD, diabetes remained to be a significant predictor of valvular lesion severity in AR (OR: 0.580, 95%CI: 0.359–0.938, p = 0.026) and mixed AR and AS (OR: 0.299, 95%CI: 0.096–0.933, p = 0.038). A similar finding was also obtained in patients with secondary MR (OR: 0.749, 95%CI: 0.562–0.999, p = 0.05) (Figure S4).

Association of diabetes with outcome

The median follow-up of the study population was 732 days. At two-year follow-up, 1,531 (12.9%) patients experienced 1,696 adverse events, which included 978 deaths, 655 hospitalizations for heart failure (HHF**s**), and 63 myocardial infarctions (MIs). Diabetes indicated poor prognosis in total cohort, MR, TR, and MVHD (Figure 3; all $P_{log\text{-}rank}<0.001$; Figure S5). In the multivariable model adjusted for clinical characteristics and echocardiographic findings, diabetes was an independent predictor of two-year outcome in patients with significant MR (Table 2; hazard ratio [HR]: 1.345, 95%CI: 1.069–1.692, p = 0.011). There was no significant interaction observed between sex and diabetes on two-year outcome ($P_{interaction}$ = 0.323). In the multivariable analysis, there was no statistical significance of the association between diabetes and two-year all-cause mortality in patients with VHD (Table S1).

Determinants of outcome in patients with VHD and diabetes

The median follow-up of patients with diabetes was 732 days. At two-year follow-up, 344 (20.0%) patients experienced 390 adverse events, which included 216 deaths, 156 HHFs, and 18 MIs. In multivariable analysis, age (HR: 1.032, 95%CI: 1.020–1.043, p < 0.001), current smoker (HR: 1.417, 95%CI: 1.044–1.925, p = 0.026), New York Heart Association (NYHA) functional class (III vs. I: HR, 1.835, 95%CI: 1.362–2.473, p < 0.001; IV vs. I: HR, 1.993, 95%CI, 1.419–2.798, p < 0.001), hemoglobin (HR: 0.988, 95%CI: 0.983–0.993, p < 0.001), albumin (HR: 0.972, 95%CI: 0.949–0.994, p = 0.015), LVEF (HR: 0.979, 95%CI: 0.971–0.988, p < 0.001), and valvular intervention (HR: 0.335, 95%CI: 0.193–0.582, p < 0.001) were independent predictors of outcome (Tables 3 and S2). There was no significant difference between males and females with both VHD and diabetes on two-year outcome (Table S2; male vs. female: HR, 0.841, 95%CI: 0.655–1.079, p = 0.174). A nomogram model

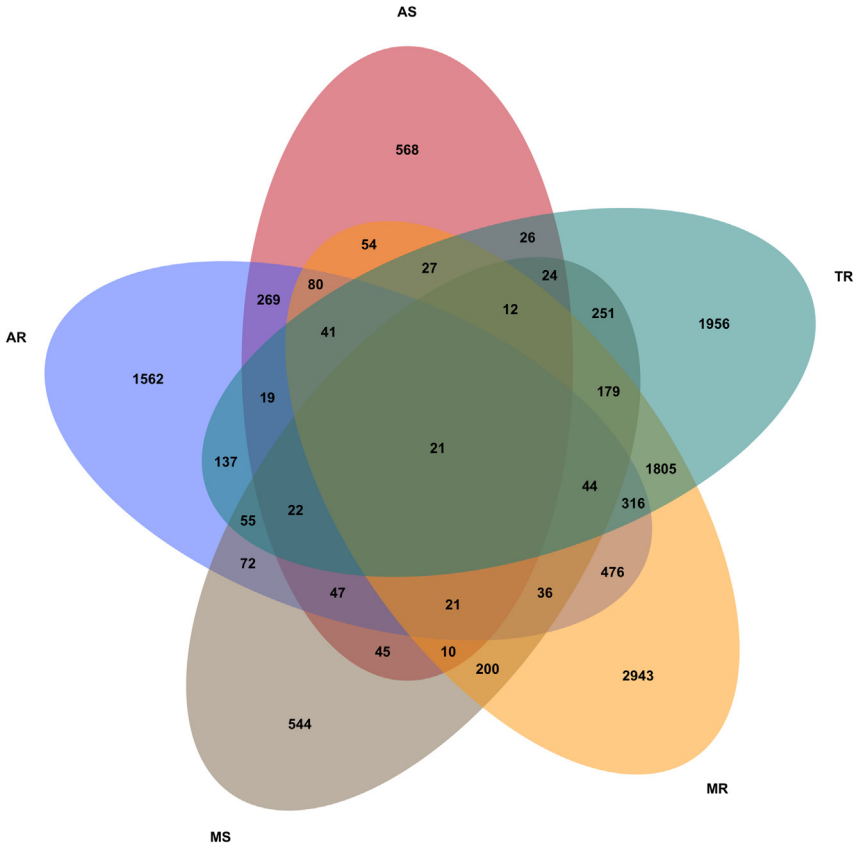

Figure 2. Venn diagrams of distributions of VHD

VHD, valvular heart disease. AS, aortic stenosis; AR, aortic regurgitation; MS, mitral stenosis; MR, mitral regurgitation; TR, tricuspid regurgitation.

incorporating seven independent predictors was established to assess two-year prognosis in patients with VHD and diabetes (Figure 4), with good discrimination (C index [95%CI]: 0.722 [0.697–0.747]) and calibration properties (Figure S6).

DISCUSSION

In this multicenter cohort study of 11,862 individuals with significant VHD, we found that diabetes was present in more than one of seven patients. The prevalences of diabetes were 14.1% in AS, 10.9% in AR, 6.8% in MS, 19.1% in MR, 14.6% in TR, 5.6% in mixed AS and AR, 9.5% in mixed MS and MR, and 14.4% in MVHD. Divided by the etiology of VHD, individuals with diabetes accounted for 6.7%, 16.7%, 6.2%, 28.7%, and 16.5% in patients with rheumatic VHD, degenerative VHD, congenital VHD, ischemic VHD, and functional VHD, respectively. The present study showed that diabetes was associated with a significantly lower risk of severe valvular lesions in AR, MR, and mixed AR with AS, but was an independent predictor of two-year adverse events in patients with MR. In patients with concomitant VHD and diabetes, age, smoking status, NYHA functional class, hemoglobin, albumin, LVEF, and valvular intervention were independently related to two-year event-free survival, and were used to develop a nomogram model for prognostic evaluation.

The current study included a large sample size of Chinese patients with VHD, and diabetes was present in 14.5%. Several previous studies reported inconsistent results regarding the prevalence of diabetes in patients with VHD.[14,15] In the EURObservational Research Programme Valvular Heart Disease II Survey, the prevalence of diabetes was relatively higher than that in the present analysis, which was 21.6% (1,567/7,274).[14] A possible reason is that the distributions of left-sided regurgitant VHD is different between two cohorts (VHD II Survey: 1,393 [19.2%] vs. China-VHD: 4,505 [38.0%]). However, our study not only revealed the prevalence of diabetes in VHD, but reported its distribution according to subtype and etiology of VHD. Divided by subtype of VHD, the prevalences of diabetes ranged from 5.6% in mixed AS and AR to 19.1% in MR. Furthermore, according to etiology of VHD, the highest proportion of diabetes was 28.7% in ischemic VHD, while the lowest was 6.2% in congenital VHD. Diabetes is related to a series of pathophysiological pathways, including oxidative stress, inflammation, and accumulation of superoxide anions,[16,17] and all these hyperglycemia consequences can lead to dysfunction and apoptosis of endothelial cells, which determines a high prevalence of CAD.[18] CAD further leads to the myocardial ischemia, including the papillary muscles ischemia, which is related to the high occurrence of ischemic VHD.

A previous study conducted in Sweden found that patients with type 2 diabetes had a significantly lower risk for the occurrence of AR and MR, compared with general population.[13] In the present analysis, we found that diabetes was associated with a lower risk of severe left-sided

Table 1. Baseline characteristics stratified by diabetes

Variables	No diabetes (n = 10141)	Diabetes (n = 1721)	p value
Age, yrs	60.92 ± 13.77	66.74 ± 10.64	<0.001
Male	5617 (55.4)	981 (57.0)	0.213
BMI, kg/m^2	23.41 ± 3.63	24.56 ± 3.59	<0.001
Current smoker	1546 (15.2)	227 (13.2)	0.027
Hypertension	4172 (41.1)	1168 (67.9)	<0.001
Hyperlipidemia	1188 (11.7)	404 (23.5)	<0.001
Coronary artery disease	2967 (29.3)	1063 (61.8)	<0.001
Prior MI	812 (8.0)	373 (21.7)	<0.001
Prior PCI	1097 (10.8)	482 (28.0)	<0.001
Prior CABG	204 (2.0)	103 (6.0)	<0.001
Cardiomyopathy	782 (7.7)	178 (10.3)	<0.001
Atrial fibrillation or flutter	2957 (29.2)	472 (27.4)	0.143
Chronic lung disease	622 (6.1)	119 (6.9)	0.216
Chronic kidney disease	464 (4.6)	202 (11.7)	<0.001
NYHA functional class			<0.001
I	3397 (33.5)	557 (32.4)	
II	2948 (29.1)	346 (20.1)	
III	2827 (27.9)	574 (33.4)	
IV	969 (9.6)	244 (14.2)	
Hemoglobin, g/L	133.36 ± 19.96	127.36 ± 21.58	<0.001
Creatinine, μmol/L	78.14 (65.7–94.7)	86 (70–109.08)	<0.001
Albumin, g/L	39.75 ± 5.04	38.78 ± 5.35	<0.001
LA, mm	45.61 ± 10.09	45.59 ± 8.27	0.172
LVEDD, mm	54.25 ± 10.96	55.09 ± 9.85	<0.001
LVEF, %	58 (47–63.7)	52 (38–61.58)	<0.001
Pulmonary hypertension	4093 (40.4)	811 (47.1)	<0.001
Severe VHD	4893 (48.2)	647 (37.6)	<0.001
Severe isolated AS	356 (3.5)	56 (3.3)	0.591
Severe isolated AR	528 (5.2)	36 (2.1)	<0.001
Severe isolated MS	280 (2.8)	12 (0.7)	<0.001
Severe isolated MR	849 (8.4)	139 (8.1)	0.682
Severe isolated TR	525 (5.2)	79 (4.6)	0.306
Severe mixed AS and AR	184 (1.8)	6 (0.3)	<0.001
Severe mixed MS and MR	93 (0.9)	8 (0.5)	0.059
Severe MVHD	2078 (20.5)	311 (18.1)	0.021
Valvular intervention	3643 (35.9)	261 (15.2)	<0.001
Etiology			<0.001
Primary	5992 (60.6)	745 (44.4)	
Rheumatic	2211 (36.9)	159 (21.3)	
Degenerative	2459 (41.0)	492 (66.0)	
Congenital	882 (14.7)	58 (7.8)	
Others	440 (7.3)	36 (4.8)	
Secondary	3888 (39.4)	933 (55.6)	
Ischemic	809 (20.8)	326 (34.9)	
Functional	3079 (79.2)	607 (65.1)	

(*Continued on next page*)

Table 1. *Continued*

Variables	No diabetes (n = 10141)	Diabetes (n = 1721)	p value
Medications			
Diuretics	7434 (73.3)	1224 (71.1)	0.059
β blockers	5657 (55.8)	1191 (69.2)	<0.001
ACEI/ARB	4181 (41.2)	903 (52.5)	<0.001
Warfarin	4313 (42.5)	382 (22.2)	<0.001
Aspirin	3035 (29.9)	937 (54.4)	<0.001
$P2Y_{12}$ inhibitors	2028 (20.0)	730 (42.4)	<0.001

Data are presented as mean ± standard deviation, median (IQR), or number (%). Characteristics are summarized before imputation of missing data. VHD, valvular heart disease; AS, aortic stenosis; AR, aortic regurgitation; MS, mitral stenosis; MR, mitral regurgitation; MVHD, multiple valvular heart disease; 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.

regurgitant valvular diseases, which also supported the notion that the presence of diabetes impeded the development of valvular regurgitation to some extent. One possible mechanism for the lower risk of severe MR in diabetic patients is mitral annular calcification (MAC). Diabetes is a well-established risk factor of MAC,[19] and MAC can limit the dilation and the motion of mitral valve, which may lead to a low risk of severe MR.[13] Similarly, diabetes may also induce molecules calcification in aortic valve,[20] and inflammatory phenotype of valvular endothelial cells, which are associated with calcific aortic valve disease (CAVD).[21] CAVD may limit the dilation of the aortic root, which leads to the low risk of severe AR.

Another important finding of this study was that diabetes indicated higher incidences of all-cause death, HHF, and MI during two-year follow-up in total cohort, MR, TR, and MVHD. After adjusting for clinical characteristics and echocardiographic findings, diabetes was an independent predictor of two-year outcome in patients with significant MR. Several previous studies investigated the impact of diabetes in patients with mitral valve dysfunction, yet not yielded consistent results.[22–25] For instance, in an analysis of the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with functional Mitral Regurgitation (COAPT) trial, individuals with diabetes (229/614) suffered a significantly higher mortality rate than non-diabetic patients, and had a numerically higher rate of heart failure hospitalization.[22] However, three other studies including 1,118, 340, and 58 patients, respectively, found that diabetes was not related to poorer outcome in those receiving transcatheter edge-to-edge mitral valve repair.[23–25] Extending to these studies, the present analysis included a total of 2,943 patients with isolated significant MR regardless of therapeutic strategy, and demonstrated that diabetes was independently associated with a 35% higher risk of two-year adverse events, and thus deserved particular attention in clinical practice. Given that diabetes was a well-established risk factor of perioperative mortality in patients undergoing valvular surgery and accumulating evidence confirmed the safety and efficacy of transcatheter mitral valve intervention in patients with diabetes,[25–28] the latter option may be more appropriate in carefully selected diabetic patients with clinically significant MR to improve long-term survival as well as the quality of life. As for other types of VHD, our study did not show an independent association between diabetes and two-year outcome. This phenomenon can be explained by the relatively small cohort of patients with several subtypes of VHD, or the two-year follow-up duration, which may be insufficient to yield statistically significant results in some subsets.

In the present study, we found that age, smoking, NYHA functional class, hemoglobin, albumin, LVEF, and valvular intervention were independent prognostic factors in patients with both diabetes and VHD, and accordingly developed a predictive model to assess two-year event-free survival. A series of studies have established the prognostic role of age, NYHA functional class, and LVEF in patients with VHD.[29,30] However, there was scarce evidence on the prognostic impact of smoking in this setting. Our results suggested a potential synergistic effect of smoking, diabetes, and valvular dysfunction on myocardium, resulting in a significantly poor outcome within just two years, which underscored the necessity of optimizing the management of traditional cardiovascular risk factors in valvular disease. The current analysis also revealed the associations of hemoglobin and albumin with two-year prognosis. Both hemoglobin and albumin are important factors for the evaluation of frailty, which has been found to be prognostically meaningful in older adults undergoing aortic valve replacement.[31] The two parameters may also be useful indicator of malnutrition or frailty in patients with concomitant diabetes and VHD. Besides, albumin is also a marker of liver synthetic function, which is often vulnerable and prognostically relevant in patients with significant VHD.[32] Noteworthy, all aforementioned mentioned variables are readily accessible, and thus our prognostic instrument, visualized as a nomogram, can be friendly-to-use in routine clinical practice. After further validation in future studies, this model may improve risk stratification of patients with both diabetes and VHD patients, and thereby guide therapeutic decision making.

The present study had some notable strengths. To begin with, this study possessed a large sample size of nearly 12,000 patients, which enabled comprehensive analyses on the prevalence and impact of diabetes in different subtypes and etiologies of VHD. Next, participants in the China-VHD registry were consecutively enrolled from 46 medical centers regardless of the therapeutic option of valvular lesions, which meant that the current study population was less selective and better reflecting the daily clinical setting. This was particularly important,

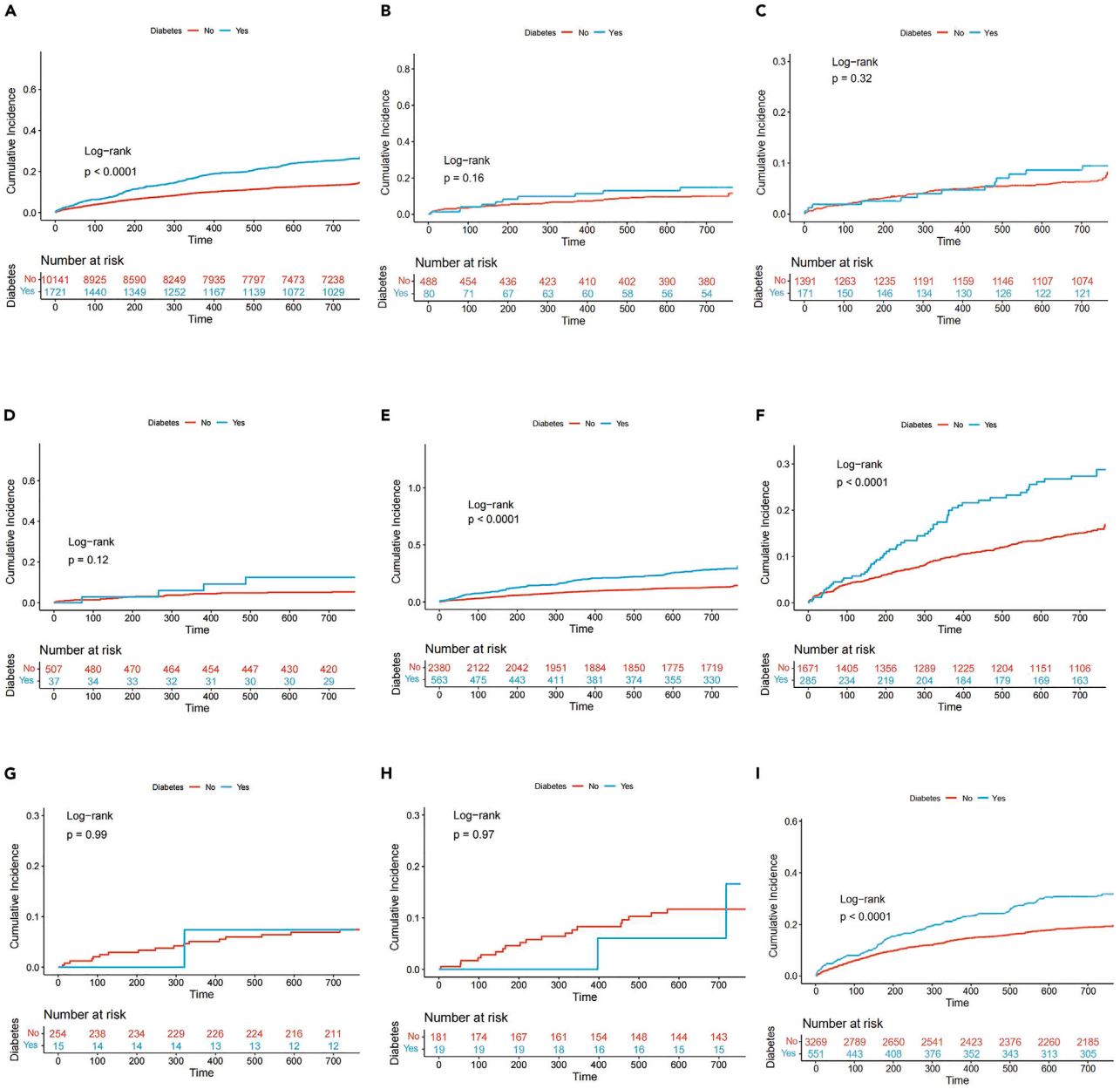

Figure 3. Kaplan-Meier curves of two-year outcome in VHD patients with or without diabetes

(A) Kaplan-Meier curves of total cohort.

(B) Kaplan-Meier curves of AS.

(C) Kaplan-Meier curves of AR.

(D) Kaplan-Meier curves of MS.

(E) Kaplan-Meier curves of MR.

(F) Kaplan-Meier curves of TR.

(G) Kaplan-Meier curves of AS + AR.

(H) Kaplan-Meier curves of MS + MR.

(I) Kaplan-Meier curves of MVHD. VHD, valvular heart disease; AS, aortic stenosis; AR, aortic regurgitation; MS, mitral stenosis; MR, mitral regurgitation; TR, tricuspid regurgitation; MVHD, multiple valvular heart disease.

Table 2. Association of diabetes with outcome in patients with VHD

	Univariable analysis		Multivariable analysis[a]	
	HR (95%CI)	p value	HR (95%CI)	p value
Total cohort (n = 11862)				
Diabetes (vs. no)	1.865 (1.654–2.103)	<0.001	1.080 (0.949–1.228)	0.243
AS (n = 568)				
Diabetes (vs. no)	1.592 (0.823–3.078)	0.167	1.729 (0.833–3.589)	0.142
AR (n = 1562)				
Diabetes (vs. no)	1.341 (0.747–2.407)	0.325	0.682 (0.354–1.316)	0.254
MS (n = 544)[b]				
Diabetes (vs. no)	2.264 (0.788–6.505)	0.129	1.434 (0.392–5.248)	0.586
MR (n = 2943)				
Diabetes (vs. no)	2.126 (1.721–2.627)	<0.001	1.345 (1.069–1.692)	0.011
TR (n = 1956)				
Diabetes (vs. no)	1.764 (1.322–2.355)	<0.001	1.110 (0.807–1.526)	0.523
AS + AR (n = 269)[c]				
Diabetes (vs. no)	0.988 (0.132–7.427)	0.991	0.204 (0.008–5.348)	0.340
MS + MR (n = 200)[d]				
Diabetes (vs. no)	0.974 (0.227–4.182)	0.971	0.583 (0.095–3.574)	0.560
MVHD (n = 3820)				
Diabetes (vs. no)	1.637 (1.349–1.987)	<0.001	0.970 (0.789–1.193)	0.773

[a]Adjusted for age, sex, BMI, smoking status, hypertension, hyperlipidemia, 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.
[b]In patients with MS, cardiomyopathy was not adjusted because no patient had cardiomyopathy.
[c]In patients with mixed AS and AR, cardiomyopathy was not adjusted because no event occurred in patients with cardiomyopathy.
[d]In patients with mixed MS and MR, cardiomyopathy was not adjusted because no patient had cardiomyopathy. VHD, valvular heart disease; AS, aortic stenosis; AR, aortic regurgitation; MS, mitral stenosis; MR, mitral regurgitation; TR, tricuspid regurgitation; MVHD, multiple valvular heart disease; 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; HR, hazard ratio; CI, confidence interval.

because the majority of previous studies only reported the prevalence of diabetes in highly selected cohort of patients with VHD, such as those undergoing trascathether valvular interventions.[25,33] In addition, this study developed a risk prediction model for informing management decisions of patients with both VHD and diabetes.

Table 3. Determinants of outcome in patients with diabetes and VHD (n = 1721)

Variables	Adjusted HR (95%CI)	p value
Age (per 1 year increase)	1.032 (1.020–1.043)	<0.001
Current smoker (vs. no)	1.417 (1.044–1.925)	0.026
NYHA functional class (vs. I)		
II	1.080 (0.735–1.585)	0.696
III	1.835 (1.362–2.473)	<0.001
IV	1.993 (1.419–2.798)	<0.001
Hemoglobin (per 1 g/L increase)	0.988 (0.983–0.993)	<0.001
Albumin (per 1 g/L increase)	0.972 (0.949–0.994)	0.015
LVEF (per 1% increase)	0.979 (0.971–0.988)	<0.001
Valvular intervention (vs. no)	0.335 (0.193–0.582)	<0.001

VHD, valvular heart disease; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; HR, hazard ratio; CI, confidence interval.

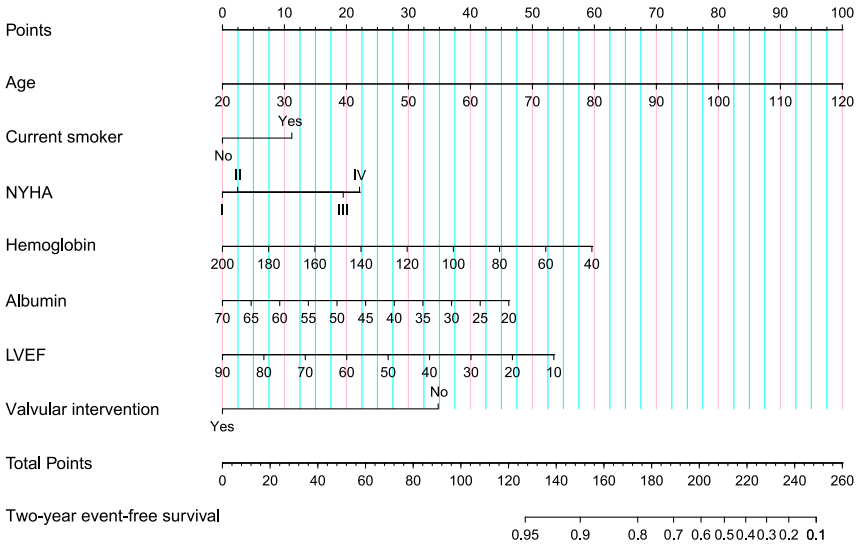

Figure 4. Nomogram to predict two-year event-free survival of patients with concomitant VHD and diabetes

The value of each prognostic component corresponds to a point through drawing a vertical line to the scale of "points". The sum of the points of all prognostic components corresponds to a total point on the scale of "total points", which corresponds to two-year event-free survival probability at the bottom scale. VHD, valvular heart disease; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction.

In conclusion, diabetes was highly prevalent in patients with significant VHD. It was associated with a lower risk of severe left-sided regurgitant valvular diseases, but had a detrimental effect on two-year prognosis in patients with MR. Greater efforts should be made to enhance our understanding and improve outcomes of concomitant VHD and diabetes.

Limitations of the study

This study had several limitations which merited discussion. First, as an observational study, despite using the multivariable statistical methods, it may be influenced by potential confounders. Second, participants in the China-VHD study were consecutively enrolled in large academic hospitals, instead of from random sampling investigation. Hence, the estimation of the prevalence of diabetes might be subject to biases. However, our real-world cohort was strongly representative of the VHD population in routine practice of high-level hospitals in China, and the main focus of the present study was to provide practical information for clinicians, rather than highlighting the potential economic burden associated with concomitant VHD and diabetes to inform the health policy. Third, the analyses of the relationship between diabetes and severity of VHD in the present study were cross-sectional, and thus should be considered as hypothesis generating. Longitudinal studies are needed to further confirm our findings. Finally, some variables, including some recently established risk factors of VHD, were not collected in the China-VHD study. For example, we did not have data on lipoprotein (a) level, which was found to be associated with a higher risk of AS.[34] Also, the current study could not analyze the impact of different types (type I or type II) of diabetes in patients with VHD, due to lack of relevant information.

STAR★METHODS

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2024.109084.

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AUTHOR CONTRIBUTIONS

Y.W., H.X., and R.G. conceived this study; Q.Lu and J.L. wrote the initial manuscript; Q.Lu, J.L., Y.Y., Z.L., W.W., B.Z., Q.Z., Z.Z., H.Z., Q.Liu, B.W., Z.Y., S.G., Z.D., Y.Z., R.G., H.X., and Y.W. contributed to the analysis and interpretation of data, as well as the revisions of the manuscript; J.L., Y.Y., Z.L., W.W., B.Z., Q.Z., Z.Z., H.Z., Q.Liu, B.W., Z.Y., S.G., Z.D., Y.Z., and H.X. contributed to the acquisition of data; all authors approved the final version of the manuscript and its submission.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
R Programming Language version 4.2.2	Foundation for Statistical Computing, Vienna, Austria	https://www.r-project.org
GraphPad Software	Boston, Massachusetts, USA	https://www.graphpad.com

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Yongjian Wu (wuyongjian@fuwaihospital.org).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- The complete original data reported in this study cannot be deposited in a public repository because these data are confidential medical records. To request access, contact Prof. Yongjian Wu (wuyongjian@fuwaihospital.org).
- This paper does not report original code.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Study design and participants

Data in the present analysis were from the China Valvular Heart Disease (China-VHD; ClinicalTrials.gov identifier: NCT03484806) study, which was a nationwide, multicenter, prospective, observational study for adults (≥18 years) with at least moderate VHD. Patients with at least moderate VHD, as identified by echocardiography, were enrolled between April and June 2018 consecutively from inpatient wards and outpatient clinics at 46 medical centers in mainland China. All participants in the China-VHD study were Chinese patients, with a mean age of 60.87 ± 13.68 years (median age: 62 [52–70] years) and 7621 (54.8%) males. Data collection, validation, as well as submission of the China-VHD study were carried out through a web-based electronic data capture system.[30] The study group took a series of measures to ensure the completeness and accuracy of data. The online system performed the internal checks initially. Data were further checked by local monitors at participating centers. Regularly, the data management team provided quality checks, and if there were any illogical, invalid, or missing data, the team sent queries to participating centers for reviewing and correcting. On-site audits were carried out by trained auditors randomly. They ensured that patient enrollment and data collection complied with the study protocol.[30] The study protocol was approved by the Institutional Review Board at Fuwai Hospital, National Center for Cardiovascular Diseases of China (Approval No. 2017-968), and complied with the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all eligible patients before registration.

The China-VHD study included a total of 13,917 patients with various VHD. We excluded the following patients: moderate or greater tricuspid stenosis (n = 6), infective endocarditis (n = 202), pulmonary valve diseases (n = 204), previous valvular intervention (n = 1548), and those without any follow-up information (n = 95). Finally, 11862 Chinese patients [mean age: 61.77 ± 13.51 years; male: 6598 (55.6%)] with AS, AR, MS, MR, TR, AS mixed with AR, MS mixed with MR, and MVHD were included in this study.

METHOD DETAILS

Echocardiography

All patients underwent comprehensive transthoracic two-dimensional and Doppler echocardiography with a standard ultrasound system. Cardiac chamber quantification was performed according to the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[35] We used the biplane modified Simpson method to calculate LVEF. Detailed echocardiographic criteria for significant VHD in the China-VHD study were the following: AS with a valve area ≤1.5cm^2, or a maximal jet velocity ≥3 m/s, or a mean pressure gradient ≥20mmHg, AR with an effective regurgitation orifice ≥0.10cm^2, or regurgitant fraction ≥30%, or regurgitant volume ≥30mL/beat, or jet width ≥25% of LV outflow tract, or vena contracta ≥0.3cm, MS with a valve area ≤1.5cm^2, MR with an effective regurgitation orifice ≥0.20cm^2, or vena contracta ≥0.3cm, or regurgitant volume ≥30mL/beat, or central jet MR>20% left atrium, and TR with

at least moderate grade regurgitation, or a central jet area >5 cm^2.[30,32] The echocardiographic criteria of severe VHD were the following: AS with a valve area ≤1.0cm^2, or a maximal jet velocity ≥4 m/s, or a mean pressure gradient ≥40mmHg, AR with an effective regurgitation orifice ≥0.30cm^2, or regurgitant fraction ≥50%, or regurgitant volume ≥60mL/beat, or jet width ≥65% of LV outflow tract, or vena contracta ≥0.6cm, or regurgitant jet reaching the level of left ventricular chordae tendineae or apex, or holodiastolic flow reversal in descending aorta, MS with a valve area ≤1.0cm^2, MR with an effective regurgitation orifice ≥0.40cm^2 (primary MR) or ≥0.20cm^2 (secondary MR), or vena contracta ≥0.7cm, or regurgitant volume ≥60mL/beat (primary MR) or ≥30mL/beat (secondary MR), or central jet MR>40% left atrium, or regurgitant jet reaching the posterior wall or the top of the left atrium, and TR with an effective regurgitant orifice area ≥40 mm^2, or regurgitant volume ≥45 ml/beat, or vena contracta width >0.7 cm, or central jet area >10 cm^2, or central jet TR > 2/3 right atrium, or flow reversal to the top of right atrium or in the inferior vena cava. Mixed VHD was defined as both at least moderate regurgitant and stenotic lesions on a single valve, and severe mixed VHD was the mixed VHD with at least one severe valvular lesion. MVHD was defined as the combination of at least moderate regurgitant or stenotic lesions on at least two valves, and severe MVHD was the MVHD with at least one severe valvular lesion.[30,32]

Follow-up and endpoints

In the China-VHD study, follow-up information was collected through medical records, telephone calls, or clinical visits at six months, one year, 18 months, and two years. The primary outcome of the present study was the composite of all-cause death, HHF, and MI during two-year follow-up. The secondary outcome was all-cause death.

Definitions

Diabetes was defined as follows: glycosylated hemoglobin ≥6.5% or 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 in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, and with a random plasma glucose ≥200 mg/dL (11.1 mmol/L).[36] Hypertension was defined based on previous diagnosis of hypertension (systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90mmHg without using antihypertensive drugs) or currently on antihypertensive medication.[37] Hyperlipidemia was defined according to previous diagnosis, or fasting serum cholesterol over 5.72 mmol/L in adults and/or triglyceride over 1.7mmol/L.[38] The definitions of risk factors used in the China-VHD study were based on the guidelines before the design of the China-VHD project,[36–38] with consideration of routine clinical practice in hospitals of China.

QUANTIFICATION AND STATISTICAL ANALYSIS

Data were presented as mean ± standard deviation (SD) or medians (interquartile range [IQR]) for continuous variables, and as counts (percentages) for categorical variables. Differences among groups were compared using Kruskal–Wallis test or Mann–Whitney U-test according to number of groups for continuous variables, and using Chi-square or the Fisher's exact test for categorical variables as appropriate. A two-tailed $p < 0.05$ was considered to be statistically significant. Analyses in the present study were conducted using R Programming Language version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism version 9.5.0 (GraphPad Software, Boston, Massachusetts, USA).

Multivariable logistic regression models were constructed to analyze the association of diabetes with VHD severity, and OR with 95% CI were reported. In the minimally adjusted model, only age and sex were adjusted. In the model further adjusting for traditional cardiovascular risk factors, following covariates were included: age, sex, BMI, smoking status, hypertension, hyperlipidemia and chronic kidney disease. Notably, some of abovementioned variables were well-established risk factors of VHD.[5,39]

Multivariable Cox regression models were constructed to analyze the association of diabetes with two-year outcome. The following variables were adjusted: age, sex, BMI, smoking status, hypertension, hyperlipidemia, coronary artery disease, cardiomyopathy, atrial fibrillation or flutter, chronic lung disease, chronic kidney disease, NYHA functional class, hemoglobin, creatinine, albumin, left atrial end-diastolic dimension (LA), LVEDD, LVEF, pulmonary hypertension, severity of VHD, and valvular intervention. The proportional hazards assumptions were checked using log-log survival and Schoenfeld residual plots.

To explore the determinants of outcome in patients with both VHD and diabetes and establish a prognostic instrument, we screened predictors according to multivariable Cox regression model, which incorporated variables mentioned before. After finding out independent predictors of outcome (those with a $p < 0.05$), a prognostic nomogram was created using the "rms" package of R software. The discrimination and calibration properties of the nomogram assessed by Harrell's C index and the calibration curve, respectively.

ADDITIONAL RESOURCES

Clinical trial registry number

NCT03484806.

Protocol download website

https://clinicaltrials.gov/study/NCT03484806?cond=NCT03484806&rank=1.