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Insights in heart valve disease 2022

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Insights in heart valve disease: 2022

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Editorial: New insights in heart valve disease 2022

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Editorial on the Research Topic
Insights in heart valve disease: 2022

Heart valve disease (HVD) represents a significant burden for health systems around the world. The growing advances in imaging and diagnostics need to be correlated with improvements in management. In total, nine articles have been published in this Research Topic, with interesting new findings summarized in **Table 1**. The articles have reached significant visibility, with more than 10,000 views so far. In this editorial, we aim to discuss the articles that highlighted the progress that has been made in the field of heart valve disease in 2022.

The burden of rheumatic and non-rheumatic valvular disease

The widespread use of penicillin-like drugs and improved access to healthcare reduced the burden of rheumatic heart disease (RHD) in the past century. In some developed countries, the false perception of its under-control burden has diminished alerts in the diagnosis of RHD, worsened by reduced compliance with penicillin treatment. Regional disparities contribute to the vast medical and economic burdens of RHD. It remains the leading cause of severe valvular heart disease with the highest significant cost among cardiovascular diseases, particularly in low-income countries. The valvular involvement frequently leads to heart failure, shortening life expectancy, and is responsible for 320,000 deaths annually. The projections of the global burden in the next decade indicate, mainly in low- and middle-income countries, an increasing trend in incidence, affecting more female subpopulations. The regional disparities may be attributable to the restricted access to healthcare, education, and housing Hu et al.

On the other side of the heart valvular disease spectrum, non-rheumatic, calcific aortic valve and mitral valve diseases are significant causes of public health concern, affecting mainly older adults in Western countries. These are highly treatable diseases and efforts to reduce the burden should be directed to modifiable risk factors, affecting the natural history of the disease, and improving interventional lines of management (1).

TABLE 1 Data regarding the articles published in the research topic "New Insights in Heart Valve Disease"; the number below the authors' details corresponds to the number of references.

Author	Date of publication	Title	Main findings
Hu et al.	18/10/2022	The projections of global and regional rheumatic heart disease burden from 2020 to 2030	"The RHD burden will remain severe. There are large variations in the trend of RHD burden by region, sex, and age."
Stöbe et al.	10/01/2023	Left ventricular hypertrophy, diastolic dysfunction and right ventricular load predict the outcome in moderate aortic stenosis	"The presence of two pathophysiological changes is a strong predictor of outcome in moderate AS and may be useful for risk stratification, particularly for scheduling follow-up time intervals and deciding the timing of AVR."
Han et al.	23/02/2023	Diabetes Is Associated With Rapid Progression of Aortic Stenosis: A Single-Center Retrospective Cohort Study	"Diabetes was strongly and independently associated with rapid progression of AS."
Salim et al.	07/11/2022	HIF1A inhibitor PX-478 reduces pathological stretch-induced calcification and collagen turnover in the aortic valve	"HIF1A inhibitor PX-478 may impart its anti-calcific and anti-matrix remodeling effect in a stretch independent manner."
Shechter et al.	02/03/2023	Racial disparities in characteristics and outcomes of patients undergoing mitral transcatheter edge-to-edge repair	"Mitral TEER patients of different racial backgrounds exhibit major differences in baseline characteristics. Among those with functional MR, non-whites and blacks also experience a less favorable 1-year clinical outcome."
Pugliese et al.	24/03/2023	Flow dynamic assessment of native mitral valve, mitral valve repair, and mitral valve replacement using vector flow mapping intracardiac flow dynamic in mitral valve regurgitation	"Intracardiac flow patterns can be clearly defined using VFM." Restoration of a physiological blood flow pattern inside the LV directly depends on the procedure used to address MV disease.
Graziani et al.	29/11/2022	Impact of severe valvular heart disease in adult congenital heart disease patients	"In ACHD patients, the presence of S-VHD is independently associated with the occurrence of cardiovascular mortality and hospitalization. The prognostic value of S-VHD is incremental above other established prognostic markers."
Oettinger et al.	02/05/2023	Treatment of pure aortic regurgitation using surgical or transcatheter aortic valve replacement between 2018 and 2020 in Germany	"TAVR is a viable alternative to SAVR in the treatment of pure aortic regurgitation for selected patients, showing overall low in-hospital mortality and complication rates, especially with regard to self-expanding transfemoral TAVR."
Yasuhara et al.	28/04/2023	Congenital aortic valve stenosis: from pathophysiology to molecular genetics and the need for novel therapeutics	Narrative review of molecular mechanisms and therapeutic options regarding congenital aortic valve stenosis

New insights need a new classification

The guidelines suggest treatment for severe valvular disease, identifying echocardiographic parameters of severity that professionals in the medical field can refer to in case of asymptomatic disease. A poor prognosis is associated with severe HVD and its surgical correction is mandatory to reverse cardiac remodeling and restore quality of life.

What emerges from recent literature and most of the articles published in this Research Topic is the necessity to revise surgical timing. The diagnostic assessment needs to include the grading of valve disease, a mirror of the altered morphology, and the dynamic response of the overloaded and/or over-pressured heart chambers. The study of the extra-valve cardiac involvement may allow for defining different stages of the disease, with a notable prognostic impact and crucial role for surgical implications.

Aortic stenosis

Pathophysiological changes of the left and right ventricles are induced by aortic valve stenosis. Stöbe et al. focused their research on cardiac involvement in patients affected by moderate aortic stenosis. They differentiated the population study according to the number of pathophysiological changes: increased left ventricular mass index, diastolic dysfunction, and increased right ventricle (RV) load. The study population was homogenous for comorbidities, excluding patients with severe comorbidities as these were not attributable entirely to aortic stenosis. The group with more extent cardiac damage resulted in a significantly lower survival rate without aortic valve replacement (AVR) or progression of aortic stenosis. The extra-valve cardiac involvement may be crucial for clinical outcomes after AVR, with a staging classification that appears to have important prognostic implications (2).

The natural history of aortic valve stenosis proceeds along pathophysiological changes and triggering factors may influence the clinical outcomes. A rapid progression of aortic stenosis associated with diabetes was demonstrated by Han et al. with an annual increase of peak aortic jet velocity (V_{max}) >0.3 m/s/year. The systemic inflammatory response and impairing endothelial function are recognized as causes of aortic valve degeneration. The adverse effect of diabetes on left ventricle hypertrophic remodeling with increased left ventricle (LV) filling pressures may accelerate the pathophysiological changes, proceeding along with the staging of cardiac damage extent.

The resulting mechanical forces, such as tensile and shear stress, are powerful promoters of aortic valve pathogenesis, with biological responses typical of aortic valve calcification Salim et al. Overall, this emergent staging classification provides an incremental prognostic value in patients with valve disease.

Mitral regurgitation

The novel classification system was demonstrated to be significantly helpful for risk stratification and timing of surgery

for primary mitral regurgitation. Grouping the population study according to the natural history of cardiac involvement in the context of primary mitral regurgitation, for each increase in the group, a 17% higher risk of all-cause mortality was observed (3).

The discussion regarding racial disparities in characteristics and outcomes of patients undergoing mitral transcatheter interventions may lead to full implementation of knowledge of surgical timing Shechter et al. Observations regarding the flow dynamic assessment in the native mitral valve and after surgery may be conducted in a standardized fashion, able to offer valid and crucial results Pugliese et al.

Conclusion

Identifying factors of greater severity in a patient, with the same group of valvular disease, is fundamental for recognizing the differences in early and long-term prognosis. Although our considerations are focused mainly on surgical timing and prognostic implications, the armamentarium of surgical techniques with less invasive access (4) needs to be at the basis of new studies. While surgical procedures improve the quality of a patient's life, thus far, no drug therapy has been developed to treat HVD, and while efforts have been made to improve surgical techniques and management, further innovative research must be focused on developing non-invasive treatments of valvular diseases.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Diabetes Is Associated With Rapid Progression of Aortic Stenosis: A Single-Center Retrospective Cohort Study

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Background: Mounting evidence indicates that rapid progression of aortic stenosis (AS) is significantly associated with poor prognosis. Whether diabetes accelerates the progression of AS remains controversial.

Objectives: The purpose of the present study was to investigate whether diabetes was associated with rapid progression of AS.

Methods: We retrospectively analyzed 276 AS patients who underwent transthoracic echocardiography at least twice with a maximum interval ≥ 180 days from January 2016 to June 2021. AS severity was defined by specific threshold values for peak aortic jet velocity (V_{max}) and/or mean pressure gradient. An increase of V_{max} ≥ 0.3 m/s/year was defined as rapid progression. The binary Logistic regression models were used to determine the association between diabetes and rapid progression of AS.

Results: At a median echocardiographic follow-up interval of 614 days, the annual increase of V_{max} was 0.16 (0.00–0.41) m/s. Compared with those without rapid progression, patients with rapid progression were older and more likely to have diabetes ($P = 0.040$ and $P = 0.010$, respectively). In the univariate binary Logistic regression analysis, diabetes was associated with rapid progression of AS (OR = 2.02, $P = 0.011$). This association remained significant in the multivariate analysis based on model 2 and model 3 (OR = 1.93, $P = 0.018$; OR = 1.93, $P = 0.022$). After propensity score-matching according to V_{max}, diabetes was also associated rapid progression of AS (OR = 2.57, $P = 0.045$).

Conclusions: Diabetes was strongly and independently associated with rapid progression of AS.

Keywords: diabetes, aortic stenosis, rapid progression, transthoracic echocardiography, valvular disease

BACKGROUND

Aortic stenosis (AS) is one of the most common valvular heart diseases affecting up to nearly 10% of the senior population (1–3). AS is a progressive disease and its rapid progression has been shown to be associated with poor prognosis (4–8). Patients with rapid progression of AS may not be easily identified at the initial diagnosis; however, these patients should be considered intervention early rather than at the onset of symptoms (8). Indeed, one study showed that early intervention in asymptomatic severe AS patients with rapid progression of AS was associated with a significant reduction in mortality (9). Many studies defined rapid progression of AS as an increase of aortic jet velocity (V_{max}) $\geq$ 0.3 m/s/year (7, 10). Both ACC/AHA and ESC guidelines consider an increase of $V_{max} \geq$ 0.3 m/s/year as one of the indications for AS intervention (classes of recommendations: IIa, level of evidence: B-C) (11, 12). Although the pathogenesis of AS is similar to that of coronary artery disease (CAD), the determinants of its rapid progression remain unclear (13). Although many promising pharmacotherapeutic studies have shown the potential benefits in detaining the progression of AS, currently, there is no effective drug treatment for AS, and valve replacement represents the only treatment for end-stage AS (14). Identification of risk factors for rapid progression of AS may allow for its secondary prevention.

Two studies have shown that diabetes can accelerate the progression of AS (15, 16). However, one of the studies only included mild AS patients above the age of 60 and defined AS progression by the yearly increase of peak transvalvular gradient (15). The other study comprised more than 99% of male patients and defined AS progression according to the annual decrease of aortic valve area (16). Whether diabetes can significantly accelerate AS progression as shown by V_{max} is unknown. Since the rapid increase in V_{max} is currently an indication for AS intervention, therefore, the present study was to investigate the association of diabetes with the progression of AS according to V_{max}.

METHODS

Patient Population

Patients diagnosed with AS were retrospectively identified by the electronic medical system of Beijing Anzhen Hospital, Capital Medical University from January 2016 to June 2021. AS was diagnosed by transthoracic echocardiography according to V_{max} and/or mean pressure gradient (MPG). All patients underwent comprehensive echocardiography by experienced sonographers and the following diagnostic criteria were used: (1) mild AS (V_{max} 2.00–2.99 m/s and/or MPG 10.0–19.9 mmHg); (2) moderate AS (V_{max} 3.00–3.99 m/s and/or MPG 20.0–39.9 mmHg); (3) severe AS ($V_{max} \geq$ 4.00 m/s and/or MPG $\geq$ 40.0 mmHg). Then, a total of 3,780 adult patients who underwent transthoracic echocardiography at least twice were selected. If the patient had more than one echocardiography after the first echocardiography, the one with the highest V_{max} was selected as the last echocardiography. The exclusion criteria were: (1) congenital heart disease other than bicuspid aortic valve (BAV); (2) history of aortic valve surgery or transcatheter aortic valve implantation; (3) lack of clinical history, echocardiographic or laboratory data; (4) maximal interval from the first echocardiography to the last echocardiography $<$ 180 days; (5) left ventricular ejection fraction (LVEF) at the first or last echocardiography $<$ 40% (**Figure 1**). Patients with a history of atrial fibrillation (AF) or concomitant significant valvular diseases were not excluded. For patients with AF, echocardiography was performed over at least five cardiac cycles, and the V_{max} was averaged. The first (baseline) and the last echocardiography were used for analysis. Information about age, sex, smoking, drinking, hypertension, diabetes, dyslipidemia, CAD, heart failure, chronic kidney disease (CKD), BAV, and medications (such as statins, ACEI/ARBs, and β-blockers) during the observation period were obtained from the electronic medical system or telephone interviews. Rapid progression of AS was defined as the rate of V_{max} progression $\geq$ 0.3 m/s/year.

Statistical Analysis

Continuous variables with normal distribution were expressed as mean ± standard deviation, otherwise median and quartile. For continuous variables, the unpaired *t*-test and Mann-Whitney *U*-test were used as appropriate. Categorical variables were expressed as numbers and percentages, where the χ^2 test or Fisher exact test was used accordingly. Three different Logistic regression models were used to determine the association of diabetes with rapid progression: (1) unadjusted; (2) adjusted for sex and age; (3) adjusted for sex, age, hypertension, CKD, dyslipidemia, and smoking. Paired patient data depending on the diagnosis of diabetes was acquired by propensity score-matching based on the baseline V_{max}. All statistical analyses were performed by SPSS 26.0 (SPSS, Inc, Chicago, Illinois) and a 2-sided *P*-value $<$ 0.05 was considered statistically significant.

RESULTS

A total of 276 AS patients constituted the study population, including 69 (25.0%) mild, 129 (46.7%) moderate, and 78 (28.3%) severe AS. The baseline characteristics of the population were summarized in **Table 1**. Among the study population, the mean age was 65 ± 11 years, 131 (47.5%) were female, 76 (27.5%) had diabetes, and 82 (29.7%) had BAV. Patients with rapid progression were older ($P = 0.040$) and more likely to have diabetes ($P = 0.010$). Compared with those without diabetes, patients with diabetes had lower baseline V_{max} and MPG, but had higher rates of hypertension, dyslipidemia, CAD, and use of medications (**Table 2**). The progression of AS in diabetic patients was more pronounced than in non-diabetic patients (**Table 2**).

The median time interval from the first echocardiography to the last echocardiography was 614 days (interquartile range: 350–932 days). During the period, the V_{max} and MPG were increasing. The V_{max} increased from 3.52 ± 0.78 m/s to 3.88 ± 0.87 m/s, with an annual increase of 0.16 (0.00–0.41) m/s. The MPG was increased from 30 ± 15 mmHg to 36 ± 18 mmHg, with an annual increase of 2.78 (0.00–6.86) mmHg. Compared with those without diabetes, patients

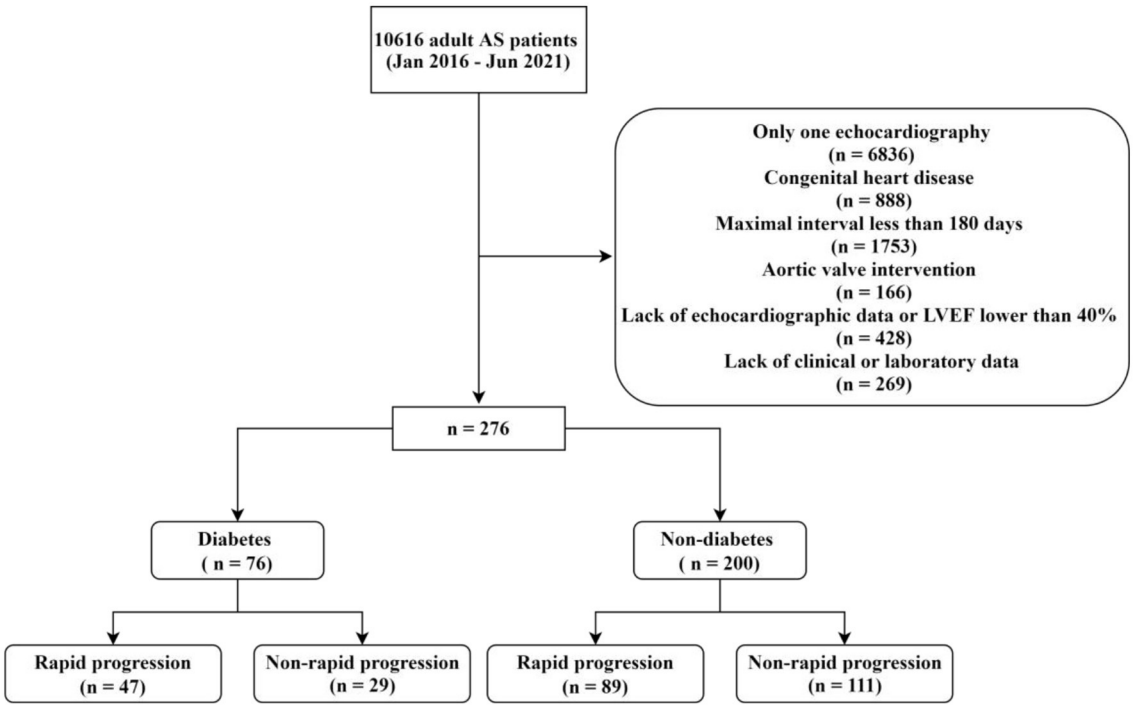

FIGURE 1 | Flow chart of the study.

TABLE 1 | Baseline characteristics of the study population according to V_{max} progression.

Variables	All patients (*n* = 276)	Non-rapid progression (*n* = 140)	Rapid progression (*n* = 136)	*P*-value
Age (years)	65 ± 11	64 ± 12	66 ± 9	0.040
Female, *n* (%)	131 (47.5)	69 (49.3)	62 (45.6)	0.539
Smoking, *n* (%)	68 (24.6)	33 (23.6)	35 (25.7)	0.677
Hypertension, *n* (%)	198 (71.7)	101 (72.1)	97 (71.3)	0.880
Diabetes, *n* (%)	76 (27.5)	29 (20.7)	47 (34.6)	0.010
FPG (mmol/L)	6.58 ± 2.25	6.31 ± 2.05	6.85 ± 2.41	0.051
Dyslipidemia, *n* (%)	163 (59.1)	78 (55.7)	85 (62.5)	0.252
TG (mmol/L)	1.43 ± 0.99	1.45 ± 1.04	1.40 ± 0.93	0.648
TC (mmol/L)	4.42 ± 1.31	4.48 ± 1.39	4.36 ± 1.23	0.448
LDL-C (mmol/L)	2.63 ± 1.12	2.65 ± 1.21	2.60 ± 1.02	0.666
HDL-C (mmol/L)	1.25 ± 0.36	1.28 ± 0.37	1.22 ± 0.35	0.184
CAD, *n* (%)	123 (44.6)	59 (42.1)	64 (47.1)	0.411
CKD, *n* (%)	27 (9.8)	15 (10.7)	12 (8.8)	0.597
Heart failure, *n* (%)	20 (7.2)	11 (7.9)	9 (6.6)	0.691
Statins, *n* (%)	140 (50.7)	67 (47.9)	73 (53.7)	0.334
ACEI/ARBs, *n* (%)	91 (33.0)	41 (29.3)	50 (36.8)	0.186
β-blockers, *n* (%)	122 (44.2)	61 (43.6)	61 (44.9)	0.830
Baseline LVEF (%)	65 (60–68)	65 (60–68)	65 (59–68)	0.826
Baseline V_{max} (m/s)	3.52 ± 0.78	3.58 ± 0.84	3.45 ± 0.71	0.185
Baseline MPG (mmHg)	29.82 ± 15.40	30.68 ± 16.66	28.94 ± 13.18	0.338
BAV, *n* (%)	82 (29.7)	47 (33.6)	35 (25.7)	0.154

FPG, fasting plasma glucose; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; CAD, coronary artery disease; CKD, chronic kidney disease; ACEI/ARBs, angiotensin converting enzyme inhibitor/angiotensin receptor blockers; LVEF, left ventricular ejection fraction; MPG, mean pressure gradient; BAV, bicuspid aortic valve.

TABLE 2 | Baseline characteristics of the study population according to the with and without diabetes.

Variables	All patients ($n = 276$)	Without diabetes ($n = 200$)	With diabetes ($n = 76$)	*P*-value
Age (years)	65 ± 11	64 ± 11	66 ± 9	0.156
Female, *n* (%)	131 (47.5)	99 (49.5)	32 (42.1)	0.272
Smoking, *n* (%)	68 (24.6)	48 (24.0)	20 (26.3)	0.690
Hypertension, *n* (%)	198 (71.7)	134 (67.0)	64 (84.2)	0.005
Dyslipidemia, *n* (%)	163 (59.1)	105 (52.5)	58 (76.3)	<0.001
TG (mmol/L)	1.43 ± 0.99	1.37 ± 0.88	1.58 ± 1.22	0.125
TC (mmol/L)	4.42 ± 1.31	4.48 ± 1.38	4.29 ± 1.14	0.282
LDL-C (mmol/L)	2.63 ± 1.12	2.69 ± 1.18	2.47 ± 0.95	0.167
HDL-C (mmol/L)	1.25 ± 0.36	1.26 ± 0.35	1.23 ± 0.38	0.401
CAD, *n* (%)	123 (44.6)	78 (39.0)	45 (59.2)	0.003
CKD, *n* (%)	27 (9.8)	21 (10.5)	6 (7.9)	0.515
Heart failure, *n* (%)	20 (7.2)	12 (6.0)	8 (10.5)	0.195
Statins, *n* (%)	140 (50.7)	88 (44.0)	52 (68.4)	<0.001
ACEI/ARBs, *n* (%)	91 (33.0)	54 (27.0)	37 (48.7)	0.001
β-blockers, *n* (%)	122 (44.2)	78 (39.0)	44 (57.9)	0.005
Baseline LVEF (%)	65 (60–68)	65 (59–68)	65 (60–68)	0.471
Baseline V_{max} (m/s)	3.52 ± 0.78	3.58 ± 0.80	3.34 ± 0.72	0.023
Baseline MPG (mmHg)	29.82 ± 15.40	31.10 ± 15.73	26.71 ± 13.05	0.033
BAV, *n* (%)	82 (29.7)	64 (32.0)	18 (23.7)	0.177
Rapid progression, *n* (%)	136 (49.3)	89 (44.5)	47 (61.8)	0.010

Abbreviations as in ***Table 1****.*

with diabetes had a more significant V_{max} progression [0.21 (0.09–0.41) m/s/year vs. 0.13 (−0.02 to 0.42) m/s/year, $P = 0.024$].

At follow-up, the proportion of patients with severe AS increased by 16.3%, while the proportions of patients with mild and moderate AS decreased by 8.7% and 7.6%, respectively. In the 76 diabetic patients, the proportion of moderate-to-severe AS increased by 17.1%, and particularly, severe AS increased by 19.8%. In the patients without diabetes, the proportion of moderate-to-severe AS increased by 3.5%, and severe AS increased by 15.0% (**Figure 2**).

In the univariate binary Logistic regression analysis (model 1), diabetes was associated with rapid progression of AS (unadjusted OR = 2.02, 95% CI: 1.18–3.47, $P = 0.011$). After adjustment for potential confounders in model 2 and model 3, this association remained significant (**Table 3**). After propensity score-matching, multivariate Logistic regression analysis (adjusted by sex, age, hypertension, CKD, dyslipidemia, and smoking) showed diabetes was associated with rapid progression of AS (OR = 2.57, 95% CI: 1.02–6.47, $P = 0.045$).

DISCUSSION

In this study, we demonstrated that diabetes was significantly and independently associated with the rapid progression of AS. Previous study of Deutscher et al. showed that diabetes was associated with the development of AS (17). Likewise, diabetes was significantly associated with an increased incidence of AS, according to a recent retrospective cohort study involving 78,805 patients with diabetes and 78,805 patients without diabetes (18). Another retrospective cohort study comprised 71,813 subjects showed that diabetes was associated with a 34% increased risk of AS (19). Diabetes leads to elevated valvular and plasma accumulation of glycation end products in AS patients. Additionally, there was a positive correlation between the amount of glycation end products and the severity of AS in diabetic patients (20).

Diabetes can lead to aortic valve calcification, which is a major cause of AS, especially in the elderly. The study of Katz et al. revealed that diabetes was associated with an increased risk of aortic valve calcification detected by computed tomography (21). Furthermore, diabetes has been shown to be associated with stenotic and non-stenotic aortic valve calcification (22). Tucureanu et al. found increased expression of cell adhesion molecules, extracellular matrix remodeling, and osteogenic markers in hyperlipidemia $ApoE^{-/-}$ diabetic mice (23). High glucose can induce osteogenic molecules and increase calcium deposits by increasing the expression of cytokines, cell adhesion molecules, and matrix metalloproteinases in valvular endothelial cells and interstitial cells (24). In the animal model, diabetes can lead to early aortic valve mineralization and calcific AS (25).

Diabetes can also cause inflammation and degeneration that can lead to AS. AS is associated with macrophages, mast cells, T cells and other immune cells infiltrations, emphasizing the role of local inflammation in AS (26–28). In severe AS patients before aortic valve replacement, diabetic individuals had higher levels of C-reactive protein in plasma and aortic valve (29). Diabetes can decrease the number and induce dysfunction of endothelial

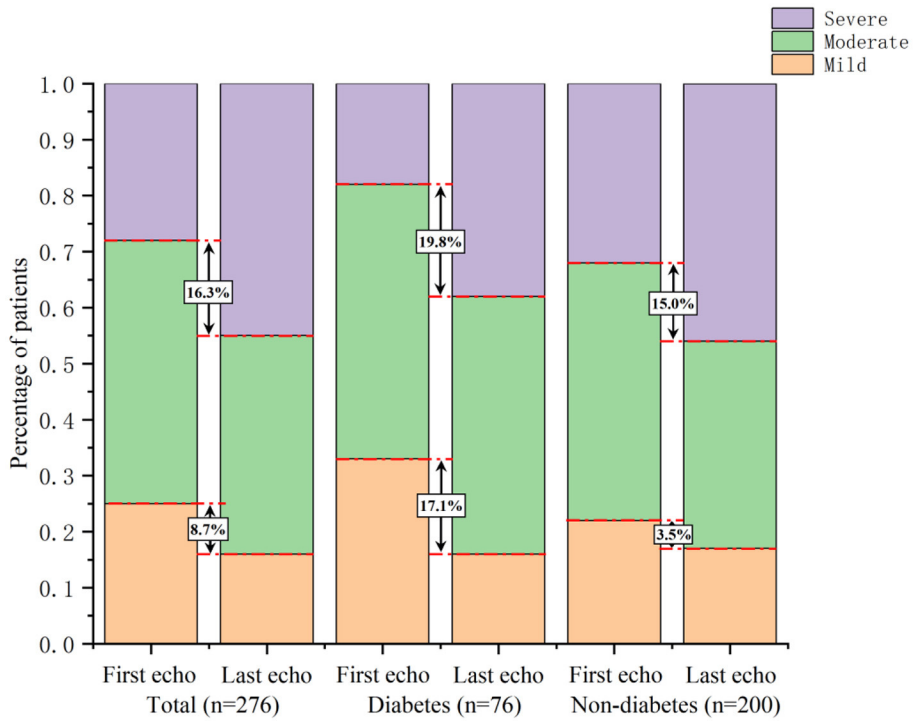

FIGURE 2 | Comparison of AS severity changes between patients with and without diabetes. In diabetic patients, the proportion of moderate-to-severe AS increased by 17.1%, and severe AS increased by 19.8%. In non-diabetic patients, the proportion of moderate-to-severe AS increased by 3.5%, and severe AS increased by 15.0%.

TABLE 3 | Odds ratios and 95% confidence intervals for rapid progression according to with and without diabetes.

	With vs. without diabetes	
Logistic models	**OR (95% CI)**	***P*-value**
Model 1	2.02 (1.18–3.47)	0.011
Model 2	1.93 (1.12–3.33)	0.018
Model 3	1.93 (1.10–3.39)	0.022

Model 1: Unadjusted.
Model 2: Adjusted for sex, age.
Model 3: Adjusted for sex, age, hypertension, CKD, dyslipidemia, smoking.

progenitor cells, impairing valve endothelial repair (30). Indeed, diabetes has been shown to be associated with aortic valve and bioprosthetic aortic valve degeneration (31, 32). At the molecular level, diabetes can lead to the upregulation of biglycan, which may contribute to aortic valve degeneration (33).

In AS patients, diabetes was associated with a worse prognosis. It has been reported that diabetes can impair coronary microvascular function in patients with asymptomatic AS (34). Some studies have shown that diabetes has an adverse effect on hypertrophic remodeling and is associated with reduced systolic function (35, 36). Moreover, diabetes was demonstrated to be associated with systemic inflammatory response syndrome after aortic valve replacement (37). A previous study by Lancellotti et al. showed that diabetes was associated with higher mortality in severe AS patients (38).

In this study, we found diabetes could accelerate the progression of AS, and particularly, lead to a rapid progression ($V_{max} \geq 0.3$ m/s/year). Several studies have demonstrated the association between diabetes and AS progression. The study of Aronow et al. first showed that diabetes was associated with the progression of AS. However, this study only included mild AS patients aged more than 60 years and defined AS progression according to annual decrease of peak transvalvular gradient (15). The study of Kamalesh et al. showed that diabetes significantly accelerated the progression of AS in patients with moderate AS. However, this study included more than 99% of male patients and defined AS progression according to annual decrease of aortic valve area (16). Diabetes was found to be a strong risk factor for the development of severe AS in a prospective cohort study which included 1.12 million individuals without valvular disease history (39). Moreover, diabetes has been shown to accelerate the progression of AS by enhancing the inflammatory response measured by C-reactive protein, where an increase in the inflammatory response was observed within the aortic valve of AS patients (29). Additionally, the density of immune cell infiltration within aortic valve was demonstrated to be correlated with the progression of AS (40). Of note, an increased inflammatory response has also been shown to be associated with the development and progression of diabetes, underlying

a potential link between diabetes and the progression of AS (41).

LIMITATION

Several limitations must be considered when interpreting the results of our study. First, this study was a single-center retrospective study, so the influence of unmeasured and residual confounding variables could not be excluded. Second, the data of this study were limited to the Chinese population, so the ethnic difference cannot be eradicated. Third, this study did not perform the external validation, which may hamper the general applicability of the current findings. Fourth, aortic valve area was not included in this study since it was not measured routinely by sonographers in our cardiovascular center. Fifth, to better reflect the impact of diabetes on the progression of AS in the real world, similar to many previous studies, we did not exclude patients with AF and concomitant significant valve diseases. Excluding patients with those conditions may determine the association between diabetes and AS progression more directly and accurately. Future studies on such patients are needed.

CONCLUSIONS

In this study, we demonstrated that diabetes was strongly and independently associated with the rapid progression of AS. Further prospective studies are needed to confirm our results.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Beijing Anzhen Hospital, Capital Medical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

KH and XM analyzed the data and drafted the manuscript. KH and MX extracted the echocardiography data from the electronic medical system. MX guided the echocardiography analysis. RZ analyzed the data and drew the figures. XM and YZ designed the study and revised the manuscript. All authors contributed to the article and approved the submitted version.

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The projections of global and regional rheumatic heart disease burden from 2020 to 2030

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Background: Rheumatic heart disease (RHD) remains the leading cause of preventable death and disability in children and young adults, killing an estimated 320,000 individuals worldwide yearly.

Materials and methods: We utilized the Bayesian age-period cohort (BAPC) model to project the change in disease burden from 2020 to 2030 using the data from the Global Burden of Disease (GBD) Study 2019. Then we described the projected epidemiological characteristics of RHD by region, sex, and age.

Results: The global age-standardized prevalence rate (ASPR) and age-standardized incidence rate (ASIR) of RHD increased from 1990 to 2019, and ASPR will increase to 559.88 per 100,000 population by 2030. The global age-standardized mortality rate (ASMR) of RHD will continue declining, while the projected death cases will increase. Furthermore, ASPR and cases of RHD-associated HF will continue rising, and there will be 2,922,840 heart failure (HF) cases in 2030 globally. Female subjects will still be the dominant population compared to male subjects, and the ASPR of RHD and the ASPR of RHD-associated HF in female subjects will continue to increase from 2020 to 2030. Young people will have the highest ASPR of RHD among all age groups globally, while the elderly will bear a greater death and HF burden.

Conclusion: In the following decade, the RHD burden will remain severe. There are large variations in the trend of RHD burden by region, sex, and age. Targeted and effective strategies are needed for the management of RHD, particularly in female subjects and young people in developing regions.

KEYWORDS

rheumatic heart disease, projections, disease burden, age-standardized prevalence rates, health policy

Introduction

Rheumatic heart disease (RHD), although regarded as a preventable disease, had affected 40.5 million individuals by 2019 (1), and had resulted in around 1,100,000 cases of heart failure (HF) as well as 320,000 death cases annually (2, 3). The improved living standards, access to healthcare, and the widespread use of penicillin-like drugs have alleviated the disease burden of RHD in the past decades (4). However, RHD is still a major cause of serious valvular heart disease and increases the health burden in some regions and populations (2, 3, 5, 6). In several developing countries, such as South Africa and India, RHD remains a public health priority (7, 8). Even in some developed countries, the case number of RHD in children has started to increase (5, 6). Those who suffer from RHD in childhood will face a significant burden of HF in future. These facts suggested that focused studies should be conducted to figure out the future trends of RHD and to guide more specified and effective policy-making. Some strategies, such as expanding echocardiographic screening and modifying perioperative penicillin use, could be implemented in high-risk locations.

In this study, we used the Global Burden of Disease (GBD) Study 2019 database to project the RHD-related disease burden from 2020 to 2030 and described the projected burden in prevalence, death, and heart failure by region, sex, and age. The results from this analysis would project longitudinal changes in RHD in the near future and guide the development of more targeted strategies to reduce the RHD burden.

Abbreviations: ASIR, age-standardized prevalence rate; ASMR, age-standardized mortality rate; ASPR, age-standardized prevalence rate; ASR, age-standardized rate; BAPC, Bayesian age-period cohort; CI, confidence interval; CODEm, Cause of Death Ensemble model; EAPC, estimated annual percentage change; GBD, Global Burden of Disease; GHDx, Global Health Data Exchange; HF, heart failure; ICD, International Classification of Diseases; MAPE, mean absolute percentage error; RHD, rheumatic heart disease; SDI, sociodemographic index; UI, uncertainty interval.

Materials and methods

Study data

The annual number of indicators of RHD burden, including prevalence, incidence, mortality, and prevalence of HF by region, sex, and age from 1990 to 2019, were extracted from the Global Health Data Exchange (GHDx) query tool.[1] The Global Burden of Diseases, Injuries, and Risk Factors Study 2019, which is supported by an ongoing multinational collaboration, comprehensively and systematically estimates 369 diseases and injuries as well as 87 behavioral, environmental, occupational, and metabolic risk factors in 204 countries and territories, 21 regions, and seven super-regions from 1990 to 2019 (1, 9). The detailed component information on data collecting and study processing used for GBD 2019 have already been thoroughly described (3). Our study complied with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) (**Supplementary Table 1**).

Definitions

Rheumatic heart disease is a heart disease mainly affecting the heart valves, especially the mitral valve. It occurs as a cardiac involvement of acute rheumatic fever caused by the infection of group A streptococcus, frequently resulting in premature death and HF (10). More detailed diagnosis information about RHD could be acquired on the website.[2] The sociodemographic index (SDI), collected from the GBD database, is a summary measure. It quantitates the average level in several basic dimensions of country and region achievement, such as incomes, educational attainments, and fertility rates (1, 9, 11, 12). The scale is limited to 0 to 1. 0 represents the lowest composite average level in all GBD countries, and 1 is in reverse. Based on SDI, all GBD countries are divided into five types (high, high-middle, middle, low-middle, and low levels). In addition, they are also divided

1 http://ghdx.healthdata.org/gbd-results-tool

2 http://www.healthdata.org/results/gbd_summaries/2019

into 21 GBD regions based on their geographic locations. In our research, we displayed the figure and table in the order of decreasing average SDI values for the 21 GBD regions. Death data were obtained from the different national vital registration databases, verbal autopsies, or household mortality survey records. The Cause of Death Ensemble model (CODEm) was used to estimate the cause-specific mortality of RHD for the region, sex, age, and year. The cause of death was coded in the International Classification of Diseases (ICD) system and then mapped to the RHD. The ICD-10 codes matched to RHD are I01-I01.9, I02.0, and I05-I09.9.

Statistical analysis

Age-standardized rate and estimated annual percentage change

Specific indicators reported by region, sex, age, and year measuring the burden of RHD in our research involved prevalence, incidence, mortality, and prevalence of HF. The RHD-associated burden was statistically estimated and modeled, utilizing an integrated and multi-parameter approach. The count, age-standardized rate (ASR) per 100,000 population, and 95% UI extracted from the database were used to quantify the burden of RHD. ASR was the rate per 100,000 people following a standardized global age structure, which could be used to exclude the effects of aging as much as possible (13).

Temporal trends of ASR from 2020 to 2030 were quantified by the estimated annual percentage change (EAPC) using least squares linear regression. The EAPC is a summative and widely used measurement for ASR trends over specified intervals (14). If the EAPC estimation and its lower limit of 95% CI were both positive, the ASR was considered to be in an increasing trend. Conversely, if the EAPC estimation and its upper limit of 95% CI were both negative, the ASR was considered to be in a downward trend. Otherwise, the ASR was deemed to be stable.

Forecasting model development

We used the GBD data from 1990 to 2019 to project the disease burden from 2020 to 2030. First, we collected the prevalence, death, and HF cases of RHD for all age groups (in 5-year intervals) at the global and regional levels from 1990 to 2019. Second, according to the formula, the cases of prevalence (or death or HF) for all age groups in a certain year/corresponding rate for all age groups in the same year, we restored the corresponding annual total populations. And then, the BAPC model was used to project the disease burden from 2020 to 2030.

The superior predictive performance of the BAPC model has been verified (15, 16). BAPC model assumed a similar effect of age, period, and cohort adjacent in time. And all unknown parameters were regarded as random with appropriate prior distributions in the BAPC model. The Bayesian inference used the second-order random walk for smoothing priors of age, period, and cohort effects. The prior knowledge combined with observed data was used to derive a posterior distribution (17). The integrated nested Laplace approximations were used with the BAPC model to approximate the marginal posterior distributions, avoiding mixing and convergence issues introduced by Markov chain Monte Carlo sampling techniques traditionally used in the Bayesian approach. We conducted the BAPC analysis using R-package BAPC (version 0.0.34).

The mean absolute percentage error (MAPE) was applied to calculate the projection deviance to evaluate model performance (18). The data on prevalence, death, and heart failure of RHD at the global level and in different SDI regions from 1990 to 2019 were retrieved and split into two periods: 1990–2013 and 2014–2019. Data from 1990 to 2013 were used to project data from 2014 to 2019 by the BAPC model, and projected data were compared with the true values. **Supplementary Table 2** shows the MAPE results at the global level and in the five SDI regions.

The R program (Version 4.1.0, R Core Team) was used to perform the statistical analysis. All graphs were drafted by GraphPad Prism (Version 8.0.2) and R program.

Results

The changes in rheumatic heart disease burden from 2020 to 2030 at the global level

There are rising trends in ASPR and ASIR of RHD from 1990 to 2019 at the global level (**Figures 1A,B**). Predictively, the ASPR will still maintain an upward trend, from 523.86 per 100,000 (95%CI, 511.92–535.81) to 559.88 per 100,000 (95%CI, 452.19–667.58), in the following decade (**Figure 1E** and **Table 1**). We could not project the future changes in incidence burden due to a lack of data (**Figures 1B,F**). Although RHD-related death cases will continue rising (**Supplementary Table 3**), the ASMR will decrease from 2020 to 2030 (**Figures 1C,G** and **Supplementary Table 5**). Heart failure is a major complication and reason for hospitalization for individuals with RHD. From 2020 to 2030, ASPR and cases of RHD-associated HF will continue increasing (**Figures 1D,H** and **Supplementary Table 6**). The ASPR and cases of HF will be 26.84 per 100,000 (95%CI, 22.09–31.59) and 2,922,840 (95%CI, 2,752,383–3,093,297) by 2030, respectively (**Supplementary Tables 3**, **6**).

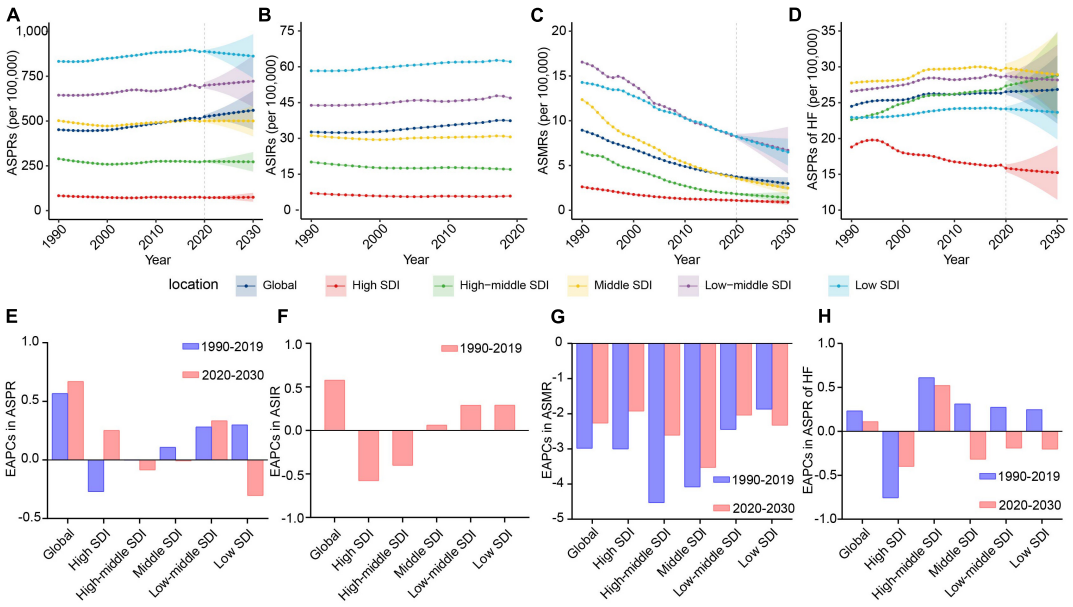

FIGURE 1
The change trends of the RHD-related disease burden at the global level and in different SDI regions. **(A)** The ASPRs from 1990 to 2030. **(B)** The ASIRs from 1990 to 2019. **(C)** The ASMRs from 1990 to 2030. **(D)** The ASPRs of HF from 1990 to 2030. **(E)** The EAPCs in ASPR between 1990–2019 and 2020–2030. **(F)** The EAPCs in ASIR between 1990 and 2019. **(G)** The EAPCs in ASMR between 1990–2019 and 2020–2030. **(H)** The EAPCs in ASPRs of HF between 1990–2019 and 2020–2030. RHD, rheumatic heart disease; SDI, sociodemographic index; ASPRs, age-standardized prevalence rates; ASIRs, age-standardized incidence rates; ASMRs, age-standardized mortality rates; HF, heart failure; EAPCs, estimated annual percentage changes.

The changes in rheumatic heart disease burden from 2020 to 2030 in different sociodemographic index regions

To assist in tailoring targeted preventive strategies for different areas, we further analyzed the RHD burden in five SDI regions. The results showed that the ASPR of RHD in low-middle and high SDI regions will increase from 2020 to 2030, while other SDI regions will experience a steady and significant decline (**Figures 1A,E** and **Table 1**). By 2030, the highest ASPR was expected to be observed in the low SDI region among five SDI regions; on the contrary, the lowest ASPR will be in the high SDI region (**Figure 1A**). Therefore, the RHD-related prevalence rate in developing regions will still be intense; the uptrend in developed regions will also merit concerns. Due to a lack of data, we could not project the future changes in incidence burden. The trend in ASIR of RHD was consistent with the trend of ASPR in the past (**Figures 1B,F** and **Supplementary Table 4**). Regarding the mortality burden, ASMR will decline in all SDI regions in the forecast period (**Figures 1C,G**). At the end of the study period, the highest ASMR will be in the low-middle SDI region, followed by the low SDI region (**Figure 1C**). When considering HF, the major complication of RHD, the ASPR of HF was projected to increase dramatically in the high-middle SDI region in the following decade, reaching 28.82 (95% CI, 22.72–34.93) per 100,000 individuals in 2030 (**Figures 1D,H** and **Supplementary Table 6**). Therefore, the ASPR of HF in the high-middle SDI region will tend to surpass that in the middle SDI area and rank first (**Figure 1D**). In contrast, the ASPR of HF in other SDI regions will experience a steady decline from 2020 to 2030 (**Figures 1D,H**). Moreover, the ASPR of HF will decline much faster in the high SDI region than in middle, low-middle, and low SDI areas (**Figure 1H**).

The changes in rheumatic heart disease burden from 2020 to 2030 in different geographic regions

Based on the epidemiologic data in 21 GBD regions, the ASPR of RHD will increase in 18 GBD regions from 2020 to 2030, with the fastest increase rate in Australasia (EAPC = 1.01 [95% CI, 0.99–1.03]) (**Figure 2A** and **Table 1**). By 2030, the highest ASPR will be in Central, Eastern, and Southern Sub-Saharan Africa among 21 GBD regions (**Supplementary Figure 1A**). The RHD-related ASIR followed a similar trend as the ASPR in the past three decades (**Figure 2B** and **Supplementary Figure 1B**). From 2020 to 2030, all GBD regions were estimated to experience declines in ASMR, while the slowest decrease rate will be in high-income North America (EAPC = −0.82 [95% CI, −0.84 to −0.81]), followed by Eastern

TABLE 1 The RHD-related ASPRs in 1990, 2020, and 2030, and their temporal trends from 1990 to 2019 and from 2020 to 2030.

	1990	2020	2030	1990–2019	2020–2030
Characteristics	**ASPRs per 100, 000 (95% UI)**	**ASPRs per 100, 000 (95% CI)**	**ASPRs per 100, 000 (95% CI)**	**EAPC of ASPRs (95% CI)**	**EAPC of ASPRs (95% CI)**
Global	451.56 (363.35,552.54)	523.86 (511.92,535.81)	559.88 (452.19,667.58)	0.57 (0.50,0.63)	0.67 (0.66,0.68)
Sex					
Female	501.56 (405.50,609.67)	582.20 (569.08,595.32)	631.51 (510.17,752.85)	0.55 (0.48,0.63)	0.82 (0.81,0.83)
Male	400.46 (321.44,492.36)	465.35 (454.84,475.86)	487.20 (394.83,579.58)	0.59 (0.53,0.65)	0.46 (0.45,0.47)
SDI					
High SDI	82.93 (71.82,93.74)	72.51 (69.45,75.58)	74.38 (49.24,99.52)	−0.27 (−0.41, −0.13)	0.25 (0.21,0.29)
High-middle SDI	289.23 (246.15,342.21)	274.56 (269.00,280.12)	272.22 (217.30,327.14)	0.00 (−0.13,0.13)	−0.09 (−0.09, −0.08)
Middle SDI	501.87 (396.81,624.96)	500.87 (491.10,510.63)	500.46 (414.40,586.52)	0.11 (0.03,0.19)	−0.01 (−0.01, −0.01)
Low-middle SDI	644.37 (503.97,805.80)	699.12 (681.18,717.06)	722.54 (578.21,866.86)	0.28 (0.25,0.31)	0.33 (0.33,0.34)
Low SDI	832.91 (648.55,1039.27)	889.00 (879.72,898.29)	862.32 (739.79,984.84)	0.30 (0.28,0.32)	−0.30 (−0.31, −0.30)
Regions					
High-income Asia Pacific	49.45 (41.49,57.17)	35.01 (33.64,36.38)	35.75 (22.83,48.66)	−1.58 (−1.69, −1.46)	0.20 (0.20,0.21)
High-income North America	123.49 (104.25,142.40)	112.41 (107.29,117.54)	114.30 (80.36,148.24)	0.02 (−0.17,0.22)	0.16 (0.14,0.19)
Western Europe	55.18 (47.96,63.00)	40.70 (39.75,41.65)	40.82 (31.92,49.71)	−1.27 (−1.34, −1.20)	0.02 (0.01,0.03)
Australasia	61.01 (51.93,70.06)	51.32 (50.15,52.49)	56.75 (43.77,69.72)	−0.76 (−0.92, −0.59)	1.01 (0.99,1.03)
Eastern Europe	215.61 (190.56,244.46)	133.72 (129.43,138.01)	137.61 (95.11,180.10)	−1.62 (−1.83, −1.41)	0.28 (0.24,0.32)
Central Europe	144.04 (129.59,160.06)	93.45 (90.35,96.56)	76.50 (55.50,97.49)	−1.29 (−1.40, −1.17)	−1.98 (−1.99, −1.97)
Southern Latin America	469.70 (374.66,582.67)	490.51 (484.78,496.23)	513.92 (437.16,590.68)	0.15 (0.12,0.18)	0.47 (0.47,0.47)
East Asia	441.29 (349.90,549.84)	388.17 (377.45,398.89)	394.11 (301.95,486.27)	−0.22 (−0.40, −0.04)	0.15 (0.15,0.15)
Central Asia	590.89 (470.83,729.78)	628.40 (617.66,639.14)	626.48 (522.89,730.07)	0.19 (0.17,0.21)	−0.03 (−0.04, −0.02)
North Africa and Middle East	368.81 (293.17,455.91)	394.27 (388.55,400.00)	415.03 (347.83,482.23)	0.22 (0.16,0.27)	0.51 (0.51,0.52)
Southeast Asia	274.88 (225.94,333.61)	287.17 (282.83,291.50)	300.84 (249.08,352.60)	0.15 (0.11,0.19)	0.47 (0.46,0.48)
Southern Sub-Saharan Africa	1071.74 (835.28,1350.28)	1091.38 (1079.84,1102.92)	1093.31 (939.03,1247.59)	0.04 (0.03,0.06)	0.02 (0.02,0.02)
Tropical Latin America	899.05 (699.28,1119.15)	917.52 (908.95,926.09)	919.65 (799.92,1039.39)	0.08 (0.07,0.09)	0.02 (0.02,0.02)
Andean Latin America	793.87 (615.64,992.80)	813.21 (804.31,822.12)	815.35 (700.40,930.29)	0.09 (0.06,0.11)	0.03 (0.02,0.03)
Caribbean	747.85 (581.94,932.43)	788.04 (779.19,796.88)	795.44 (683.47,907.41)	0.18 (0.18,0.18)	0.09 (0.09,0.10)
Central Latin America	358.19 (287.12,435.28)	355.91 (352.05,359.78)	370.99 (316.80,425.17)	−0.07 (−0.14,0.00)	0.42 (0.41,0.42)
South Asia	623.88 (481.49,781.45)	662.22 (631.56,692.88)	666.98 (500.17,833.79)	0.26 (0.21,0.31)	0.08 (0.07,0.09)
Central Sub-Saharan Africa	1184.76 (910.15,1512.89)	1196.93 (1184.56,1209.30)	1212.34 (1047.07,1377.60)	−0.03 (−0.05, −0.01)	0.13 (0.12,0.13)
Oceania	543.08 (430.73,690.95)	587.12 (577.08,597.16)	588.23 (470.59,705.86)	0.34 (0.27,0.41)	0.02 (0.02,0.02)
Western Sub-Saharan Africa	794.99 (618.33,1001.81)	839.98 (831.77,848.19)	832.77 (721.05,944.48)	0.22 (0.19,0.24)	−0.09 (−0.09, −0.08)
Eastern Sub-Saharan Africa	1093.85 (849.57,1370.07)	1179.01 (1166.38,1191.64)	1187.93 (1015.00,1360.87)	0.27 (0.25,0.28)	0.08 (0.07,0.08)

RHD, rheumatic heart disease; ASPRs, age-standardized prevalence rates; EAPC, estimated annual percentage change; UI, uncertainty interval; CI, confidence interval; SDI, sociodemographic index.

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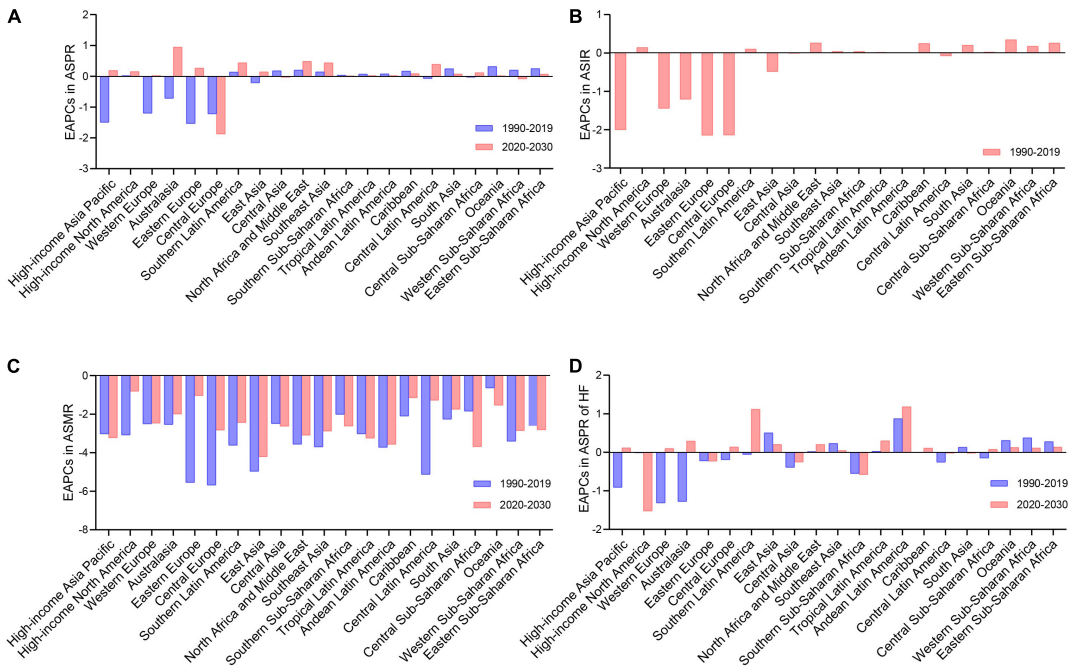

FIGURE 2
The change trends of the RHD-related disease burden in 21 GBD regions. **(A)** The EAPCs in ASPR between 1990–2019 and 2020–2030. **(B)** The EAPCs in ASIR between 1990 and 2019. **(C)** The EAPCs in ASMR between 1990–2019 and 2020–2030. **(D)** The EAPCs in ASPR of HF between 1990–2019 and 2020–2030. RHD, rheumatic heart disease; GBD, global burden of disease; EAPCs, estimated annual percentage changes; ASPR, age-standardized prevalence rate; ASIR, age-standardized incidence rate; ASMR, age-standardized mortality rate; HF, heart failure.

Europe, Caribbean and Central Latin America (EAPC: −1.05 to −1.29) (**Figure 2C** and **Supplementary Table 5**). By 2030, the highest ASMR was observed in Oceania and South Asia (**Supplementary Figure 1C**). Regarding the ASPR of RHD-associated HF, rising trends were projected to be observed in 15 GBD regions (**Figure 2D** and **Supplementary Table 6**). By 2030, the top ASPR of HF will be in East Asia, Oceania, and Western Sub-Saharan Africa, while Eastern Sub-Saharan Africa, Tropical Latin America, and Central Sub-Saharan Africa will have the lowest (**Supplementary Figure 1D**).

The changes in rheumatic heart disease burden from 2020 to 2030 in different sexes

To identify the sex group that needs focused attention regarding RHD burden, we further analyzed the sex differences in RHD-related ASPR, ASMR, and ASPR of HF at the global level and in different SDI regions. Globally, RHD-related prevalence, death, and HF burden will remain higher in female subjects than in male subjects by 2030 (**Figures 3A,C,E**), and the gap between female and male subjects will further increase from 2020 to 2030 (**Supplementary Figures 2A–C**). The ASPR and ASMR showed a similar trend in female and male subjects from 2020 to 2030 (**Supplementary Figures 3A,B**). Regarding the ASPR of HF, female subjects will sustain a rising trend in the following decade, while male subjects will have a downward trend. The increase in the ASPR of HF in female subjects will result in a growth of HF ASPR global wide (**Figure 1H** and **Supplementary Figure 3C**).

At the SDI levels, there will be a rising trend in ASPR in female subjects in the majority of SDI regions, while the declining trend will be in male subjects (**Figure 3B** and **Supplementary Figure 3A**). The descending rate of ASMR in female subjects will be slower than in male subjects in the low SDI region from 2020 to 2030 (**Figure 3D** and **Supplementary Figure 3B**). In 2030, the region with the highest ASPR of HF in female subjects will shift from the middle region to the high-middle SDI region, and the ASPR of HF in the high-middle SDI region will keep an upward trend (**Figure 3F**).

The changes in rheumatic heart disease burden from 2020 to 2030 in different age groups

We further estimated the RHD-related burden in age groups globally and in different SDI regions. Globally, the ASPR of RHD will increase in the young population (10–54 age group)

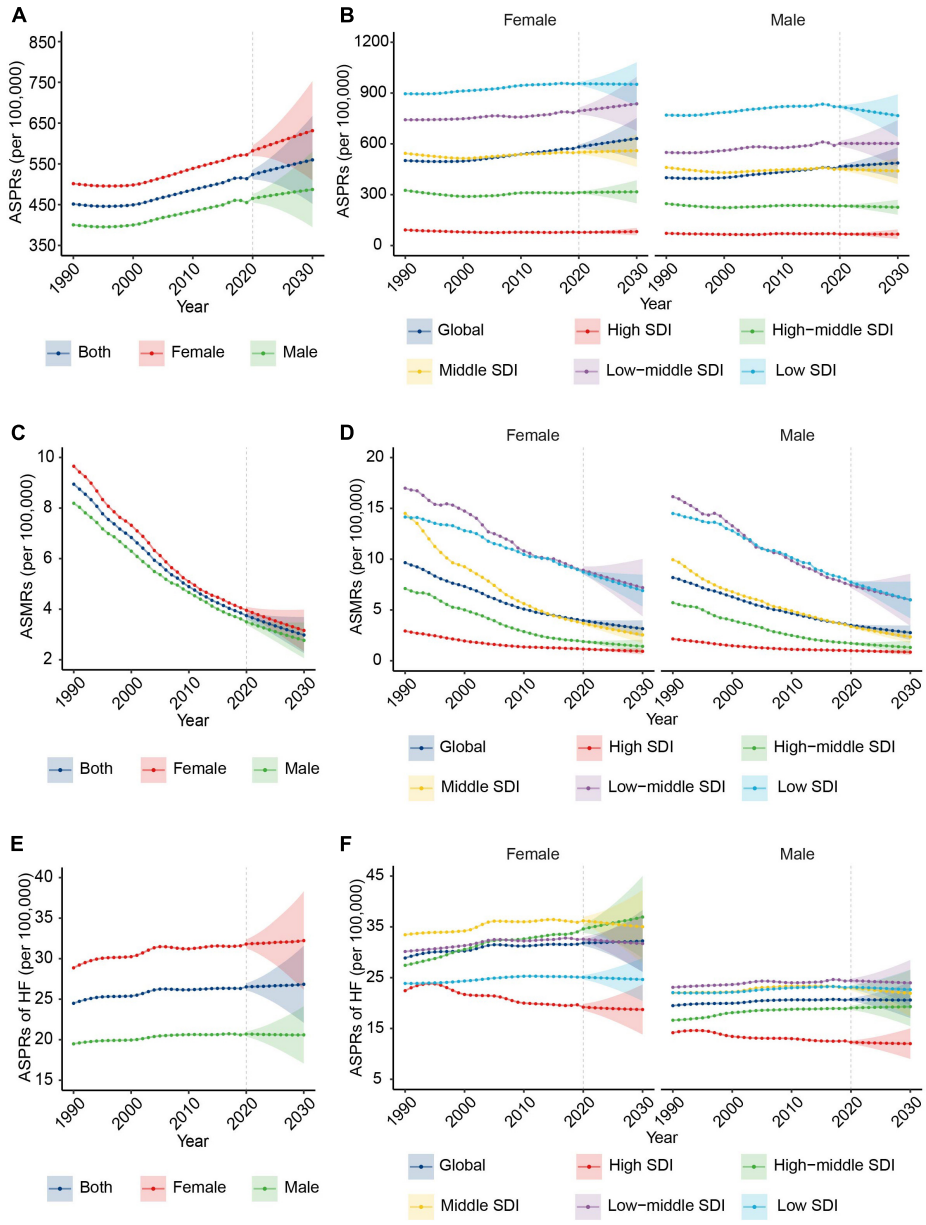

FIGURE 3
The change trends of the RHD-related disease burden by sex from 1990 to 2030. **(A)** The ASPRs from 1990 to 2030 at the global level by sex. **(B)** The ASPRs at the global level and in different SDI regions by female (the left) and male (the right) subjects. **(C)** The ASMRs from 1990 to 2030 at the global level by sex. **(D)** The ASMRs from 1990 to 2030 at the global level and in different SDI regions by female (the left) and male (the right) subjects. **(E)** The ASPRs of HF from 1990 to 2030 at the global level by sex. **(F)** The ASPRs of HF from 1990 to 2030 at the global level and in different SDI regions by female (the left) and male (the right) subjects. RHD, rheumatic heart disease; ASPRs, age-standardized prevalence rates; SDI, sociodemographic index; ASMRs, age-standardized mortality rates; HF, heart failure.

by 2030 (Figure 4A). The ASMR of RHD will decrease in all age groups (Figure 4B). The ASPR of RHD-related HF will increase in the elderly (55–84 age group) (Supplementary Figure 4).

In different SDI regions, the highest ASPR of RHD will be in the 20–34 age group among all age groups, and it will be mainly concentrated in low and low-middle SDI regions. In the high SDI region, the highest ASPR of RHD will be observed in the elderly among all age groups (Figure 4A). The ASMR of RHD will increase with age in all SDI regions. Simultaneously, the senior population will account for the majority population for RHD-related death from 2020 to 2030 (Figure 4B). For ASPR of RHD-related HF, in low and low-middle regions, the highest ASPR of HF will be in the 65–74 age group among all age groups, while in the high SDI

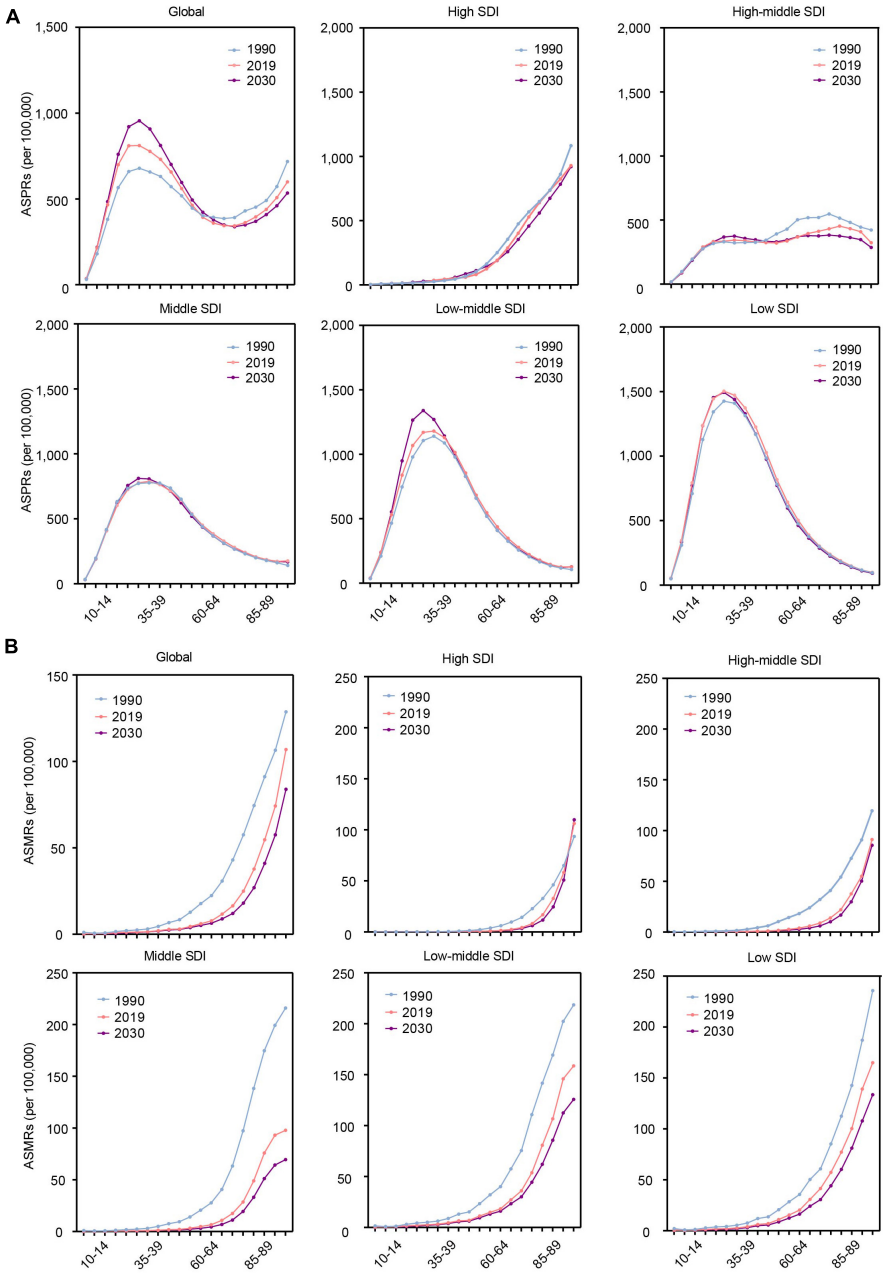

FIGURE 4
The change trends of the RHD-related disease burden at the global level and in different SDI regions by age in 1990, 2019, and 2030. **(A)** The ASPRs. **(B)** The ASMRs. RHD, rheumatic heart disease; SDI, sociodemographic index; ASPRs, age-standardized prevalence rates; ASMRs, age-standardized mortality rates.

region, it will be in the 85 plus age group (**Supplementary Figure 4**).

Discussion

Rheumatic heart disease remains the leading cause of severe valvular heart disease, with significant regional disparities. Our study is the first to project the RHD burden at global and regional levels from 2020 to 2030. According to our analysis, the ASPR of RHD and the ASPR of RHD-related HF will keep increasing globally from 2020 to 2030, although the ASMR of RHD will decline. Therefore, the global burden of RHD has not been sufficiently controlled. It is urgent to implement effective and precise strategies to control RHD and the related disease burden based on demographic characteristics.

Rheumatic heart disease results in immense medical and economic burdens (19, 20). The cost of RHD treatment was the highest among all cardiovascular diseases (averaged US $ 4710.78) (21). According to the projection of our research, the prevalence cases of RHD will exceed 48 million in 2030, continuously leading to a substantial economic burden in the near future. Premature mortality from RHD shortens life expectations significantly. Meanwhile, RHD patients with HF are more susceptible to infection, enhancing the risk of developing infective endocarditis. Moreover, increased antibiotic use in these patients raises the chance of enriching drug-resistant bacteria. Simultaneously, clinical management becomes more challenging when RHD progresses rapidly. Therefore, more attention should be paid to preventing and treating RHD and related diseases to alleviate the huge burden.

Our study indicates that the ASPR in the low SDI region will decrease from 2020 to 2030. Over the past three decades, poor sanitation, overcrowding, and limited access to healthcare have resulted in the highest prevalence and a rising trend in the low SDI area (19). Accordingly, extensive interventions to improve the efficacy of the prevention and management of RHD have been implemented in developing regions (22–26). In 2015, seven priority actions were developed in Africa. These actions include creating disease registers, ensuring the supply of benzathine penicillin, improving access to reproductive health services for female subjects, decentralizing technical expertise and technology, establishing centers for essential cardiac surgery, initiating national multi-sectoral RHD programmers, fostering international partnerships, and have been implemented in a large portion of African countries to eliminate RHD since then (26). It has been reported that RHD in African nations, such as Cameroon, Ethiopia, and Uganda, had significantly lower prevalence rates after 2015 than those counted before 2015 (27). These results indicate the success of the positive prevention in reducing the prevalence of RHD. We here project that the prevalence in the low SDI area will decrease from 2020 to 2030, further remarking the necessity of preventive efforts. Notably, our results suggest that the highest ASPR will last in the low SDI region by 2030. Therefore, developing regions should further strengthen prevention and management strategies to decrease the prevalence of RHD.

Another key finding in this study is the downward trend in ASPR of RHD in the high SDI area over the past three decades will be reversed in the following decade. In the past three decades, the prevalence of RHD in the high SDI region has decreased mainly due to improvements in the social environment and extensive use of penicillin. However, diminishing alerts of physicians in the diagnosis of RHD, lack of awareness about RHD prevention and reduced compliance with penicillin treatment have also emerged (28, 29). These issues have contributed to a rise in the prevalence of RHD in developed regions in the recent decade (30–35). Our study projects that the prevalence of RHD in developed regions will increase over the next decade if effective interventions are not fulfilled in time. In this regard, indigenous populations remain the primary concern (30, 36–38), particularly for indigenous Australians, as the highest incidence of RHD in the world was found in this population (39). This situation could be associated with the following facts. First, there is no uniform consensus in Australasia on how to improve the primary prevention of RHD (40). Second, there are disparities in diverse practices among various indigenous populations, restricting their access to healthcare, housing, and education (41–44). Third, previous health warning campaigns have triggered resistance in indigenous populations due to communication obstacles (44–46). Fourth, the ethnic background and hereditary may facilitate the development of RHD (47). These adverse rising trends in the high SDI area might constitute a major obstacle for RHD prevention and management. Therefore, effective measures should be fulfilled as soon as possible to reverse this negative tendency even in developed regions.

However, our study shows a decline in ASMR, with huge variation across all SDI regions from 2020 to 2030. The ratio of low SDI region to the high SDI region will be more than seven times. This inequality is primarily attributable to regional disparities in educational achievement and access to healthcare (48). Access to cardiac surgical therapy in developing regions is severely restricted due to the scarcity of heart surgery equipment and healthcare workforces (49–51), resulting in a much higher mortality rate in developing regions than in developed regions. It is known that the severity of valve lesions is the strongest predictor of mortality (52). The capacity to diagnose valve lesions in the early stage significantly varies and results in regional disparities in mortality rates. In this regard, echocardiography has been a cornerstone in screening programs to evaluate the prevalence of RHD and the severity of valve lesions according to multiple guidelines (53), since echocardiography could identify individuals with RHD-related valvular lesions early, confirm the severity of lesions and evaluate the prognosis to achieve early control and management of RHD (54), even in patients with RHD without overt clinical findings (subclinical carditis) (55). Therefore, significant human and material resources, additional capital investment, and extensive government efforts are required in developing regions to further decrease mortality (56, 57).

This study has several limitations. First, due to the nature of the GBD study, the data quality varies greatly between countries and regions. Our study utilized various modeling processes to compensate for this limitation and presents metrics with 95% UIs. Second, the RHD burden might be underestimated due to insufficient RHD screening in many regions, especially in low and low-middle SDI areas. Third, our study is conducted at global and regional levels without further probing the heterogeneity of endemic and non-endemic regions within

countries. Fourth, the future changes in incidence burden could not be projected due to a lack of data.

Conclusion

Rheumatic heart disease burden will still be serious in the next decade, with significant regional variability. Except for focusing on low and low-middle SDI regions with the highest prevalence rate and death burden, it is still necessary to control the rising trend in developed countries to avoid the resurgence of the diseases. Female subjects need to be particularly cared for in controlling RHD and appropriate policies and the inclination of medical resources are needed. The highest prevalence is concentrated in younger people among all age groups, while the elderly will have the highest burden of death and heart failure. To diminish the disease burden of RHD, precise and targeted strategies to control the burden of RHD need to be developed based on regional and population characteristics.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: http://ghdx.healthdata.org/gbd-results-tool.

Author contributions

YH and ZT designed the study, collected and analyzed data, and wrote the manuscript. XH, J-JQ, and LL collected and reviewed data and contributed to data analysis. FL, WW, WL, TS, and JC revised the manuscript and provided valuable suggestions for study design and data analysis. Z-GS and HL designed the project, edited the manuscript, and supervised the study. All authors have approved the final version of this article.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.941917/full#supplementary-material

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HIF1A inhibitor PX-478 reduces pathological stretch-induced calcification and collagen turnover in aortic valve

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HIF1A is significantly upregulated in calcified human aortic valves (AVs). Furthermore, HIF1A inhibitor PX-478 was shown to inhibit AV calcification under static and disturbed flow conditions. Since elevated stretch is one of the major mechanical stimuli for AV calcification, we investigated the effect of PX-478 on AV calcification and collagen turnover under a pathophysiological cyclic stretch (15%) condition. Porcine aortic valve (PAV) leaflets were cyclically (1 Hz) stretched at 15% for 24 days in osteogenic medium with or without PX-478. In addition, PAV leaflets were cyclically stretched at a physiological (10%) and 15% for 3 days in regular medium to assess its effect of on HIF1A mRNA expression. It was found that 100 μM (high concentration) PX-478 could significantly inhibit PAV calcification under 15% stretch, whereas 50 μM (moderate concentration) PX-478 showed a modest inhibitory effect on PAV calcification. Nonetheless, 50 μM PX-478 significantly reduced PAV collagen turnover under 15% stretch. Surprisingly, it was observed that cyclic stretch (15% vs. 10%) did not have any significant effect on HIF1A mRNA expression in PAV leaflets. These results suggest that HIF1A inhibitor PX-478 may impart its anti-calcific and anti-matrix remodeling effect in a stretch-independent manner.

KEYWORDS

cyclic stretch, HIF1A, PX-478, aortic valve, calcification

Introduction

Heart valve diseases are prevalent in more than 13% of the elderly population aged > 75 years old (1). Aortic stenosis (AS) is one of the most prevalent heart valve diseases, affecting more than 3.4% of the elderly population (2). When untreated, the mortality rate is about 25% per year after the onset of severe symptoms (angina, syncope,

heart failure, etc.) (3). AS is characterized by pathological narrowing of the aortic valve (AV) opening during systole, resulting in increased pressure gradient across the valve. The narrowing of AV opening is caused by significantly thicker and stiffer AV leaflets (4). The higher thickness and stiffness in AV leaflets arise from pathological fibrosis and calcification of AV tissue that take place over a period of several years (4). Unfortunately, despite its high prevalence, there is no clear understanding of the underlying mechanism of AS pathogenesis and disease progression (5). As a consequence, there are currently no therapeutic drugs available to treat AS and the only treatment options are either surgical or transcatheter AV replacement (6, 7).

Previously, it was believed that AS is a result of an age-related tissue degeneration process. However, extensive mechanobiological research in the last two decades has shown that mechanical forces play a significant role in the initiation and progression of AV fibrosis and calcification, implying that AS is not a mere manifestation of age-related passive degeneration. Rather, this disease results from an active pathological process spanning several years (8). The AV experiences different types of mechanical force during each cardiac cycle, including tensile stress, bending stress, and shear stress (9). For the healthy functioning of AV leaflets, each of these mechanical forces should remain within their respective optimal (or physiological) ranges. Any chronic (or pathological) deviation in these mechanical forces promotes AV pathogenesis, resulting in AV fibrosis and calcification. Elevated mechanical stretch and low oscillatory shear stress (i.e., disturbed flow) have been shown to promote AV pathogenesis, leading to AV fibrosis and calcification *ex vivo* (10–13). In addition, high mechanical stretch was found to induce significantly higher AV calcification compared to low oscillatory shear stress (14), indicating that elevated stretch has a more prominent effect on AV calcification compared to disturbed flow. Furthermore, elevated circumferential stretch (e.g., 15%) was shown to represent hypertensive condition for AV, whereas physiological level of stretch (e.g., 10%) corresponded to normotensive condition (15). Since hypertension is one of the major risk factors for calcific aortic valve disease (CAVD) (8), this suggests a potential causal link between elevated mechanical stretch and AV calcification.

Hypoxia Inducible Factor 1 (HIF1) is a basic-helix-loop-helix-PAS transcription factor that plays a critical role in activating homeostatic responses to hypoxia (16). HIF1 is a heterodimer consisting of two subunits, HIF1A and HIF1B. It was previously shown that HIF1A protein expression was significantly higher in the calcified areas of stenotic human AVs compared to non-calcified areas (17). In addition, low oscillatory shear stress (i.e., disturbed flow) was found to upregulate HIF1A mRNA and protein expression in human aortic valve endothelial cells (HAVECs) compared to laminar shear stress (i.e., stable flow) (18).

4-[bis(2-chloroethyl)oxidoamino]-L-phenylalanine dihydrochloride, or PX-478, is a specific inhibitor of HIF1A (19). This orally available pharmacological agent was tested in a clinical trial as a potential treatment for metastatic cancer (20). Recently, we showed that PX-478 treatment significantly inhibits AV calcification under static and disturbed flow conditions (18). Furthermore, PX-478 was found to significantly reduce aortic plaque burden in atherosclerotic mice (21).

Since elevated stretch is a more prominent inducer of AV calcification compared to disturbed flow (14), the overall objective of this study was to evaluate the effect of the HIF1A inhibitor PX-478 on AV calcification and collagen turnover, an important pathophysiological marker of AV disease, under high cyclic stretch. In addition, the effect of cyclic stretch on HIF1A mRNA expression was assessed in AV tissue samples. Results from this study could provide significant insight into the functional role of HIF1A and its inhibitor PX-478 in CAVD.

Materials and methods

Ex vivo cyclic stretch experiments

An *ex vivo* experimental approach was adopted in this study. Briefly, fresh porcine aortic valve (PAV) leaflets were collected from a local abattoir (HOLIFIELD FARMS) and transported back to the laboratory. A rectangular section of 16 mm (circumferential direction) by 8 mm (radial direction) was excised from the belly region of each leaflet, followed by insertion of stainless-steel springs at both circumferential ends. The sprung PAV tissue sections were then mounted in an *ex vivo* cyclic stretch bioreactor (**Figure 1**), which was previously validated in our laboratory (22).

To assess the effect of cyclic stretch on specific mRNA expression, sprung PAV tissue sections were cyclically (1 Hz) stretched at 10 and 15% in the circumferential direction for 3 days in regular medium. The circumferential direction was chosen for cyclic stretching since PAV tissue is known to be stiffer in the circumferential direction due to preferential alignment of the collagen fibers (23). 10 and 15% were previously shown to be the physiological and pathological levels of circumferential stretch, being representative of normotensive and hypertensive condition, respectively (15). The regular medium comprised of 13.36 g/L DMEM (FISHER SCIENTIFIC), 10% bovine calf serum (FISHER SCIENTIFIC), 3.7 g/L sodium bicarbonate (SIGMA ALDRICH), 50 mg/L ascorbic acid (SIGMA ALDRICH), 2.5% HEPES buffer (FISHER SCIENTIFIC), 1% non-essential amino acid (SIGMA ALDRICH), and 1% antibiotics (FISHER SCIENTIFIC) (10). To simulate stretch-induced calcification *ex vivo*, sprung PAV tissue sections were cyclically (1 Hz) stretched at 15% in the circumferential direction for 24 days in osteogenic medium.

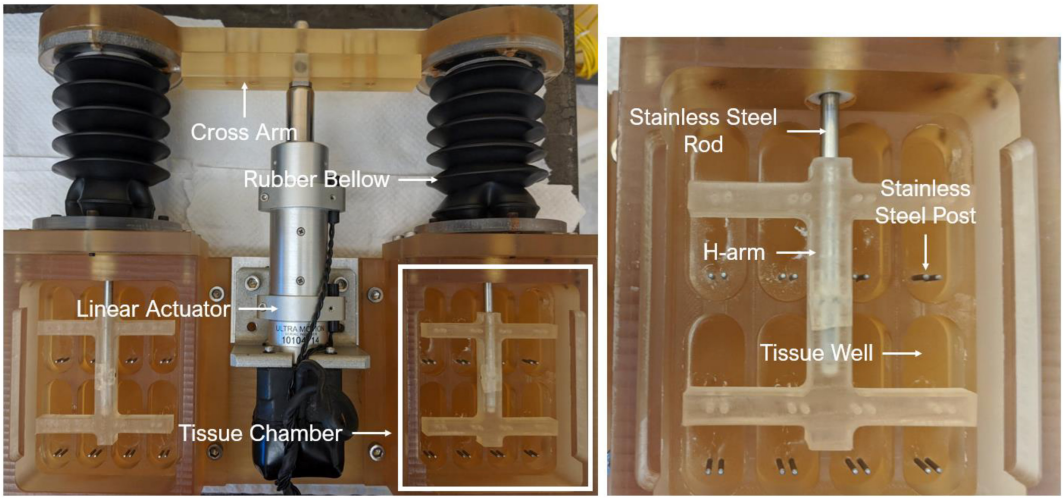

FIGURE 1
Ex vivo cyclic stretch bioreactor.

The osteogenic medium was used to accelerate the calcification process. It consisted of the regular medium supplemented with 3.8 mM monosodium phosphate (SIGMA ALDRICH), 1 mM β-glycerophosphate (SIGMA ALDRICH), and 10 μM dexamethasone (SIGMA ALDRICH) (11).

HIF1A inhibitor PX-478

HIF1A inhibitor PX-478 was obtained from MEDKOO BIOSCIENCES. PX-478 was freshly prepared in Dulbecco's phosphate buffered saline (DPBS) for each supplementation (every 2–3 days) during the course of an experiment. Two different concentrations of PX-478 were used in this study, 50 μM (moderate concentration) and 100 μM (high concentration). The maximum dosage of PX-478 (100 μM) was chosen based on the work done by Villa-Roel et al. (21) The v/v percentage, when PX-478 or PBS were added to the culture medium, was, 0.2 and 0.4% for 50 and 100 μM group, respectively. The concentration of the PX-478 stock solution was 25 mM, as described in Villa-Roel et al. (21).

Assessment of porcine aortic valve calcification

Porcine aortic valve (PAV) calcification was quantitatively assessed by Arsenazo assay. Briefly, PAV tissue samples were homogenized and digested in 1 M acetic acid (SIGMA ALDRICH) solution for 24 h. The resulting supernatant was then reacted with Arsenazo III dye (POINTE SCIENTIFIC) to determine the amount of calcium in each sample. In addition, Alizarin Red staining was used to qualitatively assess PAV calcification. Briefly, 10-μm frozen PAV tissue sections were hydrated and incubated in 2% Alizarin Red (SIGMA ALDRICH) solution (pH = 4.1–4.3) for 30 s to 1 min. Alizarin Red binds to calcium and positive staining is identified as orange or red in color. Furthermore, ImageJ software was used to quantify the amount of positively stained area as a percentage of total tissue area.

Assessment of porcine aortic valve collagen turnover

The degree of collagen turnover was assessed by quantifying the ratio of immature to mature collagen in PAV tissue samples. Picrosirius Red staining was performed to identify mature (red) and immature (green and yellow) collagen fibers (24). Briefly, 10-μm frozen PAV tissue sections were hydrated and incubated in Picrosirius Red (saturated picric acid) solution (SIGMA ALDRICH) for 1 h, followed by a wash in 0.5% acidified water. The stained PAV tissue samples were then imaged using a polarized light microscope. ImageJ software was used to quantify the amount of mature and immature collagen in PAV leaflets.

RNA isolation and quantitative polymerase chain reaction

An RNA isolation kit (ZYMO RESEARCH) was used to isolate total RNA. cDNA was synthesized using a reverse transcription kit (QIAGEN). qPCR was carried out in triplicates using a 96-well Real-Time PCR system (THERMO FISHER SCIENTIFIC) and 18S was used as the housekeeping gene.

The relative mRNA expression was calculated using the ΔCT method (25).

Statistical analysis

Data are presented as mean ± standard error of mean (SEM). Independent samples *t*-test was used to compare two independent and normally distributed data sets, whereas non-normally distributed data sets were statistically compared using non-parametric Mann-Whitney *U* test. IBM SPSS Statistics software was used to conduct all statistical comparisons. A *p*-value of 0.05 or less was considered to indicate statistical significance. In addition, effect size (Hedges' *g*-value) was calculated for each statistical comparison, where Hedges' *g*-values of 0.2, 0.5, and 0.8 were considered to indicate small, medium and large effect sizes, respectively (26).

Results

Effect of high concentration PX-478 on porcine aortic valve calcification under pathological (15%) stretch

Freshly obtained PAV leaflets were cyclically (1 Hz) stretched at pathological (15%) level for 24 days in osteogenic medium. The osteogenic medium was replaced every 2–3 days and supplemented with either DPBS or 100 μM PX-478. It was found that treatment with 100 μM PX-478 resulted in a significant decrease ($p = 0.048$) in PAV leaflet calcification (35.8% decrease with Hedges' *g*-value of 1.08) under 15% stretch in osteogenic medium compared to the control case, as determined by Arsenazo assay (**Figure 2**).

Effect of moderate concentration PX-478 on porcine aortic valve calcification under pathological (15%) stretch

To test whether a lower concentration of PX-478 could still inhibit PAV calcification, freshly obtained PAV leaflets were cyclically (1 Hz) stretched at pathological (15%) level for 24 days in osteogenic medium, supplemented with either DPBS (control) or moderate concentration (50 μM) PX-478 every 2–3 days. Treatment with 50 μM PX-478 did not have any significant effect ($p = 0.770$) on PAV leaflet calcification (6.4% increase with Hedges' *g*-value of 0.15) under 15% stretch in osteogenic medium compared to the control case, as determined by Arsenazo assay (**Figure 2**).

In addition, Alizarin Red staining was used to qualitatively assess the effect of 50 μM PX-478 on PAV leaflet calcification under 15% stretch in osteogenic medium. Interestingly, treatment with 50 μM PX-478 significantly lowered positive staining (i.e., calcification) compared to the control case [**Figure 3A**]. This was confirmed by the quantification of positively stained area as a percentage of total tissue area (using ImageJ software), which showed a significant reduction ($p = 0.025$) with 50 μM PX-478 treatment (86.3% decrease with Hedges' *g*-value of 1.43) compared to the control case

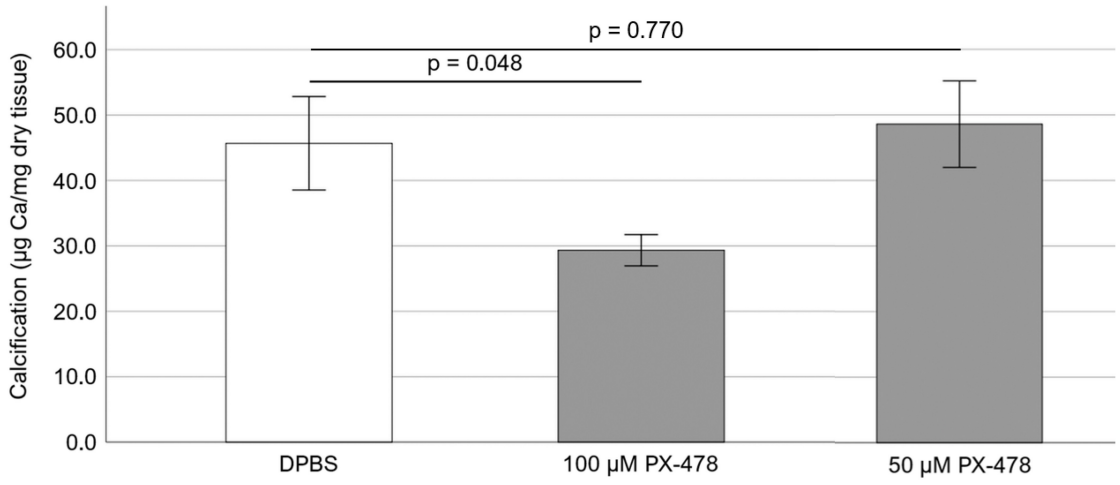

FIGURE 2
Effect of 50 and 100 μM PX-478 on porcine aortic valve (PAV) leaflet calcification after 24 days of 15% stretch in osteogenic medium, as determined by Arsenazo assay ($n = 8$).

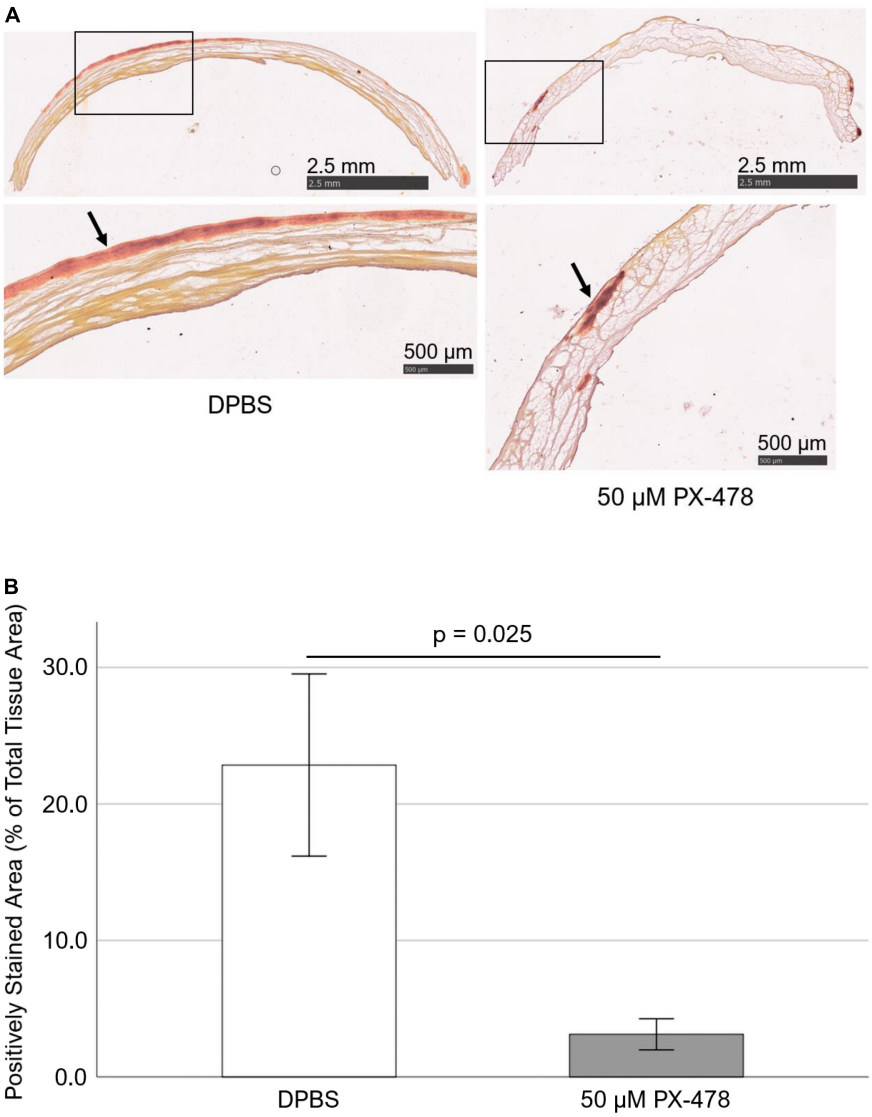

FIGURE 3
PX-478 inhibits porcine aortic valve (PAV) calcification in response to cyclic stretching. **(A)** Representative Alizarin Red staining images of PAV leaflets (top row: lower magnification, bottom row: higher magnification) after 24 days of 15% stretch in osteogenic medium. Arrows indicate areas of calcification. **(B)** Quantification of Alizarin Red staining images of PAV leaflets after 24 days of 15% stretch in osteogenic medium ($n = 5–7$).

[Figure 3B]. These results show that 50 μM PX-478 inhibits PAV leaflet calcification.

Effect of moderate concentration PX-478 on porcine aortic valve collagen turnover under pathological (15%) stretch

To investigate whether moderate concentration PX-478 could inhibit PAV collagen turnover, freshly obtained PAV leaflets were cyclically (1 Hz) stretched at pathological (15%) level for 24 days in osteogenic medium, supplemented with either DPBS (control) or moderate concentration (50 μM) PX-478 every 2–3 days. Picrosirius Red staining was performed to identify mature (red) and immature (green and yellow) collagen fibers under polarized light [Figure 4A]. ImageJ software was used to quantify PAV collagen turnover as the ratio of immature to mature collagen. It was found that treatment with 50 μM PX-478 significantly decreased ($p < 0.001$) the ratio of immature to mature collagen fibers in PAV leaflets (31.3% decrease with Hedges' g-value of 0.97) under 15% stretch in osteogenic medium compared to the control case [Figure 4B]. This result suggests that 50 μM PX-478 inhibits pathological collagen

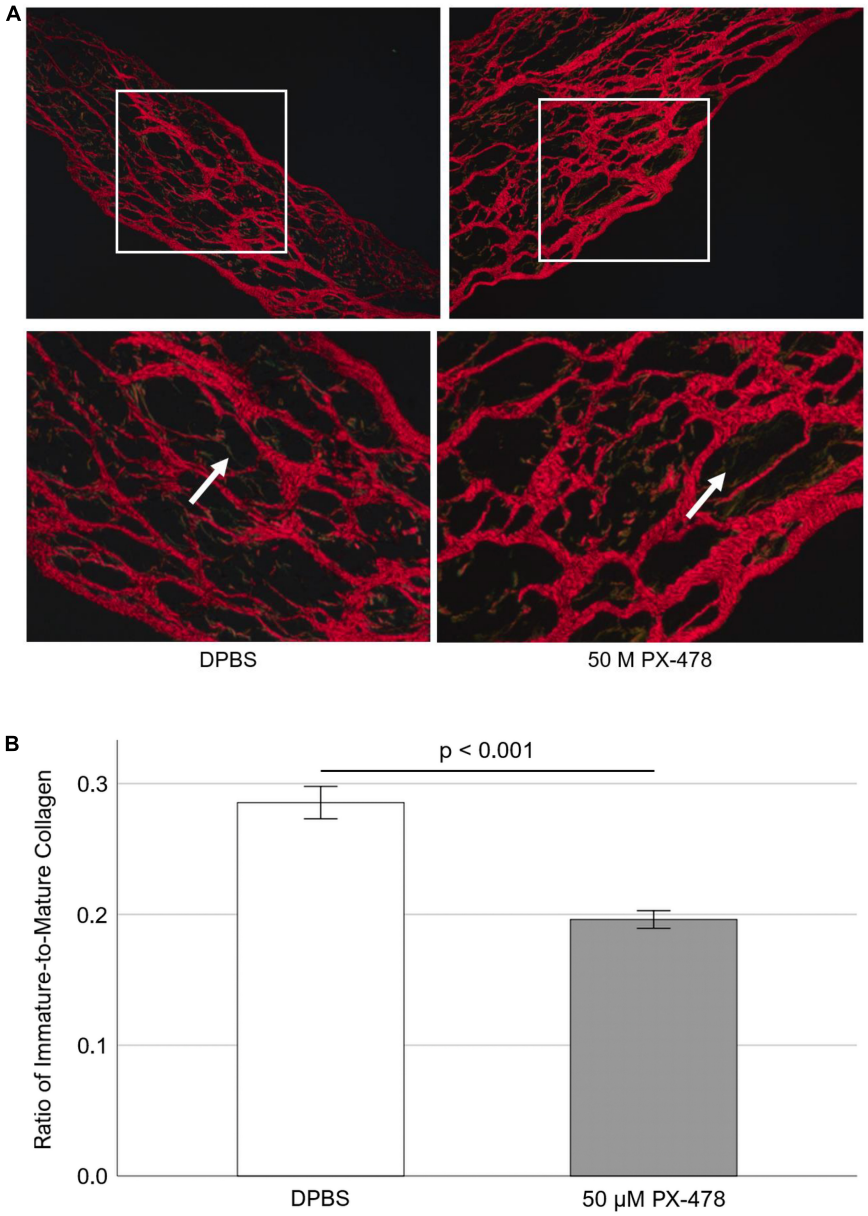

FIGURE 4
(A) Representative Picrosirius Red staining images of porcine aortic valve (PAV) leaflets after 24 days of 15% stretch in osteogenic medium. Red fibers indicate mature collagen; green and yellow fibers indicate immature collagen (white arrows). **(B)** Quantification of Picrosirius Red staining images of PAV leaflets after 24 days of 15% stretch in osteogenic medium ($n = 7$). Each sample comprises of multiple images representing multiple locations (minimum 5 images per sample).

turnover in PAV leaflets under 15% stretch in osteogenic medium.

Effect of cyclic stretch on HIF1A mRNA expression in porcine aortic valves

Since HIF1A inhibitor PX-478 could inhibit PAV leaflet calcification and collagen turnover, it was tested to see how cyclic stretch modulates HIF1A mRNA expression in PAV leaflets. Freshly obtained PAV leaflets were cyclically (1 Hz) stretched at physiological (10%) and pathological (15%) levels for 3 days in the regular medium. We found that there was no significant difference ($p = 0.244$) in HIF1A mRNA expression (32.7% decrease with Hedges' g-value of 0.54) between 10 and 15% stretch (Figure 5), which may be due to a short half-life of PX-478 in the face of its constitutively high transcription.

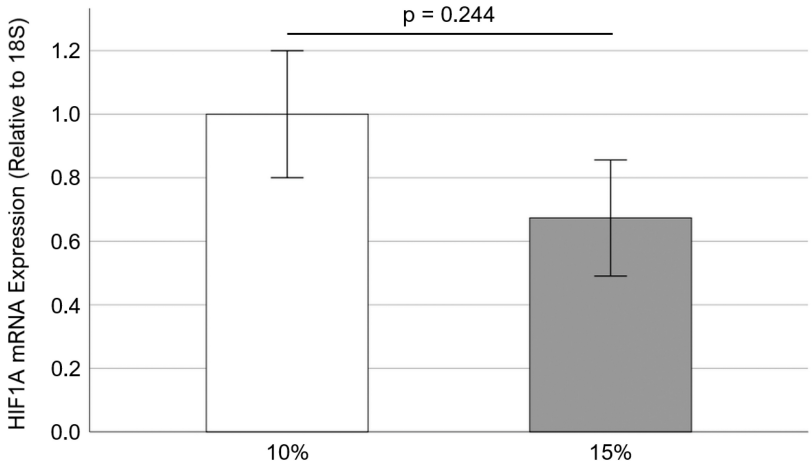

FIGURE 5
Effect of cyclic stretch on HIF1A mRNA expression in porcine aortic valve (PAV) leaflets ($n = 10$).

Discussion

In this study, we investigated the effect of HIF1A inhibitor PX-478 on PAV calcification and collagen turnover under pathological 15% stretch. We found that high concentration (100 μM) PX-478 could significantly inhibit PAV calcification under 15% stretch (**Figure 2**). However, this anti-calcific effect of PX-478 was diminished at moderate 50 μM concentration (**Figure 2**), although it could still impart some level of inhibitory effect on PAV calcification (**Figure 3**). The discrepancy between Arsenazo assay and Alizarin Red staining results may be due to the different calcification detection mechanism of these two methods. Arsenazo assay shows the degree of calcification in the whole sample quantitatively whereas Alizarin Red staining helps in detecting localized patterns of calcification qualitatively. Calcified areas of stenotic human AVs were found to express significantly higher level of HIF1A protein compared to non-calcified areas (17). HIF1A inhibitor PX-478 was previously shown to inhibit PAV calcification under static and low, oscillatory shear conditions (18). In addition, PX-478 was found to significantly reduce heterotopic ossification of soft tissue in a burn/tenotomy mouse model (27). Bone Gamma-Carboxyglutamate Protein (BGP) overexpression was shown to induce vascular calcification in a HIF1A-dependent manner (28). Similarly, it was found that HIF1A expression was significantly higher in calcifying aortas of nephrectomized male Wistar rats on high-mineral diet along with calcitriol supplementation compared to nephrectomized ones on normal diet (29). Advanced glycation end products (AGEs) were shown to enhance vascular smooth muscle cell (VSMC) calcification by activating the HIF1A-Pyruvate Dehydrogenase Kinase 4 (PDK4) pathway and inhibition of PDK4 expression significantly reduced VSMC calcification (30). Furthermore, it was found that hypoxia (5% O_2) induced osteogenic differentiation of VSMCs in a HIF1A-dependent and mitochondria-derived reactive oxygen species (ROS)-dependent manner compared to normoxic (21% O_2) condition (31). Interestingly, Interferon-γ (IFN-γ) and lipopolysaccharide (LPS), in combination, were shown to induce calcification of human aortic valve interstitial cells (HAVICs) under normoxic condition by activating the Signal Transducer and Activator of Transcription 1 (STAT1)/HIF1A pathway (32). Hypoxic (13% O_2) culture of aged (> 2 years) PAV tissue resulted in significant upregulation of the expression of Matrix Metalloproteinase 9 (MMP9)-Neutrophil Gelatinase-Associated Lipocalin (NGAL) complex and fragmentation of elastic fibers (in the ventricularis layer) compared to fresh ones (33). In addition, hypoxia (13% O_2) induced the formation of ectopic, nascent elastic fibers in the fibrosa layer of aged (> 2 years) PAV tissue compared to fresh and normoxic (20% O_2) ones, implying pathological alteration in elastic matrix composition (33).

Moderate concentration (50 μM) PX-478 was found to significantly inhibit PAV collagen turnover under 15% stretch in osteogenic medium (**Figure 4**). The collagen fiber architecture was previously shown to be significantly altered in calcified human AVs compared to healthy ones (34). Furthermore, immature collagen was found to be associated with regions of microcalcification in atherosclerotic plaques (35). In a recent study (21), it was shown that PX-478 significantly reduced aortic plaque burden in two chronic mouse models of atherosclerosis.

Interestingly, it was observed that there was no significant difference in HIF1A mRNA expression in PAV leaflets between 10 and 15% stretch (**Figure 5**). Low, oscillatory shear stress (i.e., disturbed flow) was previously shown to upregulate HIF1A mRNA and protein expression in HAVECs compared to laminar shear stress (i.e., stable flow) (18). However, it was found that O_2 diffusion coefficient was essentially similar in PAV leaflets between 4.5 and 10.5 kPa (i.e., different degree of

leaflet stretching) under normoxic (20% O_2) condition (36). Furthermore, it was shown that there was no significant difference in local O_2 diffusion within the PAV tissue under 4.5 and 10.5 kPa pressure (36). As HIF1A expression is directly related to O_2 diffusion (16), it can be argued that no significant difference in HIF1A mRNA expression between 10 and 15% was possibly due to similar O_2 diffusion under these stretch conditions. Specifically, elevated cyclic stretch (15% vs. 10%) would result in higher tissue thinning, leading to a lower O_2 diffusion path and lower HIF1A expression in PAV tissue. This was possibly observed as non-significant 32.7% decrease in HIF1A mRNA expression at 15% stretch compared to 10% in PAV leaflets (**Figure 5**).

Hence, these results indicate that high concentration (100 μM) PX-478 significantly inhibits PAV calcification under 15% stretch in osteogenic medium, while moderate concentration (50 μM) PX-478 imparts some inhibitory effect on PAV calcification. Nevertheless, 50 μM PX-478 can significantly reduce PAV collagen turnover under 15% stretch in osteogenic medium. Since cyclic stretch (10 and 15%) does not significantly affect HIF1A mRNA expression in PAV leaflets, this implies that HIF1A inhibitor PX-478 may inhibit PAV calcification and collagen turnover in a stretch-independent manner (at least within the range of 10–15% stretch). Unfortunately, as HIF1A protein is highly unstable under normal oxygen condition, it could not be measured by western blot. In addition, HIF1A mRNA was not measurable after 24 days of cyclic stretching. Further studies need to be conducted to investigate the functional role of HIF1A and its inhibitor PX-478 in modulating and potentially mitigating CAVD.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

MTS: executed the study, conducted all experiments, experimental and data analysis, and prepared the manuscript. NV-R: helped in experimental analysis and manuscript preparation. BV: helped in experimental analysis. HJ: co-principal investigator and provided supervision in all aspects of the study. AY: principal investigator and provided supervision in all aspects of the study. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Impact of severe valvular heart disease in adult congenital heart disease patients

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Background: The clinical impact of valvular heart disease (VHD) in adult congenital heart disease (ACHD) patients is unascertained. Aim of our study was to assess the prevalence and clinical impact of severe VHD (S-VHD) in a real-world contemporary cohort of ACHD patients.

Materials and methods: Consecutive patients followed-up at our ACHD Outpatient Clinic from September 2014 to February 2021 were enrolled. Clinical characteristics and echocardiographic data were prospectively entered into a digitalized medical records database. VHD at the first evaluation was assessed and graded according to VHD guidelines. Clinical data at follow-up were collected. The study endpoint was the occurrence of cardiac mortality and/or unplanned cardiac hospitalization during follow-up.

Results: A total of 390 patients (median age 34 years, 49% males) were included and S-VHD was present in 101 (25.9%) patients. Over a median follow-up time of 26 months (IQR: 12–48), the study composite endpoint occurred in 76 patients (19.5%). The cumulative endpoint-free survival was significantly lower in patients with S-VHD *vs.* patients with non-severe VHD (Log rank $p < 0.001$). At multivariable analysis, age and atrial fibrillation at first visit ($p = 0.029$ and $p = 0.006$ respectively), lower %Sat O_2, higher NYHA class ($p = 0.005$ for both), lower LVEF ($p = 0.008$), and S-VHD ($p = 0.015$) were independently associated to the study endpoint. The likelihood ratio test demonstrated that S-VHD added significant prognostic value ($p = 0.017$) to a multivariate model including age, severe CHD, atrial fibrillation, %Sat O2, NYHA, LVEF, and right ventricle systolic pressure > 45 mmHg.

Conclusion: In ACHD patients, the presence of S-VHD is independently associated with the occurrence of cardiovascular mortality and hospitalization. The prognostic value of S-VHD is incremental above other established prognostic markers.

KEYWORDS

valvular heart disease, adult congenital heart disease (ACHD), prognosis, hospitalization, mortality

Background

The improvement of neonatal and pediatric cardiac care have led to the progressive increase of children with congenital heart disease (CHD) surviving to late adulthood (1), with a significant increase in the healthcare burden worldwide (2). Most adults with CHD (ACHD) retain a lifelong risk of cardiovascular complications, which is related both to the original defects and the possible sequelae of the cardiac surgery performed in childhood. Consequently, the risk of hospitalizations and mortality in ACHD patients remains higher than that of the general population (3, 4). Arrhythmias, heart failure (HF) and need for interventions on valvular heart diseases (VHD) are often part of the ACHD clinical history (5). Notably, in the large spectrum of ACHD, VHD are frequently encountered as primitive congenital lesions, post-surgery sequelae or as acquired new lesions (5).

Although the presence of VHD in ACHD represents a clinical challenge, most data on their relevance come from registries (6) and surveys (7) where the characterization of VHD was limited and their prognostic impact was not ascertained.

In the present study, we assessed the prevalence and clinical impact of severe VHD (S-VHD) in a real-world contemporary cohort of ACHD patients.

Materials and methods

Study design and population

This is a single center observational clinical study reporting data that have been prospectively collected within the framework of clinical pathway dedicated to ACHD patients at Fondazione Policlinico Universitario "A. Gemelli," which is a surgical/interventional tertiary Center and represents a national referral for ACHD patients and for heart valve disease.

For the present study, all patients evaluated in our ACHD outpatient clinic from September 2014 to February 2021 were screened. Patients with a patent foramen ovale, cardiomyopathies and congenital arrhythmias without any structural abnormalities were excluded. CHD distribution across patients population is depicted in **Supplementary Table 1**. Among the remaining ACHD patients, those who were treated by other Institutions and referred to our center just for a single consultation were also excluded.

Baseline clinical and echocardiographic data

Clinical, imaging and operation details were prospectively entered into a digitalized medical records database dedicated to cardiovascular patients (SI-cardio, GESI, Rome, Italy). From the above-mentioned database, we obtained the report of the first clinical outpatient evaluation that included complete medical history, vital signs, electrocardiogram (ECG), complete echocardiography. According to our institutional clinical pathway dedicated to ACHD patients (8), clinical assessment, ECG reading, and echocardiograms are directly performed and reported from experienced cardiologists specialized in the imaging and care of this patients' population (FG, AD, and RL) and all patients that require an intervention are discussed in Heart Team, as previously described (9).

Comphrensive echocardiography was performed using commercially available ultrasound systems (Toshiba Artida, Tokyo, Japan; Philips Epiq 7, Amsterdam, Netherlands) equipped with 3.5 MHz or M5S transducers as previously reported (10) and was also used to record the presence and degree of VHD.

For each enrolled patient the clinical records were revised to extract the following data:

- Clinical findings: age, gender, CHD diagnosis at birth, number of cardiac interventions performed before our first evaluation, age at cardiac intervention(s), presence of genetic syndrome, severity of the CHD lesion (assessed according to the classification proposed in the latest ESC Guidelines) (11), previous pacemaker or implantable cardioverter defibrillator (PM/ICD) implantation, O_2 saturation at rest (%Sat O_2), New York Heart Association (NYHA) functional class, symptoms.
- ECG findings: rhythm; PR interval (msec); presence of right or left bundle branch block; QRS interval (msec).

- Echocardiographic findings: left ventricle ejection fraction (LVEF) assessed with biplane Simpson's method (applied also for the evaluation of the systemic right ventricular function and the systolic function of single ventricle physiology patients), right ventricle systolic function expressed by tricuspid annular plane systolic excursion (TAPSE), parameters of diastolic function (E/A; E/e', left atrium volume index, LAVi), right ventricle systolic pressure (RVSP), degree of valvular stenosis or regurgitation as defined by a multiparametric approach according to the current best practices recommended for VHD patients (12–15).

All forms of VHD were included: primary valvular disease (bicuspid aortic valve, Ebstein's anomaly, etc.), valvular lesions secondary to the sequelae of the intervention performed for CHD (pulmonary regurgitation from repaired Tetralogy of Fallot, valvular insufficiency from previous valvulotomy etc.) as well as functional VHD (atrioventricular valve regurgitation from systemic right ventricle, univentricular heart or Fontan repair etc.) and percutaneous/surgical prosthesis dysfunction (11).

Severe valvular heart disease (S-VHD) was defined as the presence of at least one valve with severe dysfunction according to the latest guidelines. The grading of the severity of VHD is reported in **Supplementary Table 2**. Multiple VHD was defined as the presence of more than one valve with severe lesion. Severe VHD distribution according to the etiology has been depicted in **Supplementary Table 3**.

Clinical follow-up and study endpoints

Clinical data at follow-up were collected through the medical records of the last evaluation at our ACHD Outpatient Clinic, or at the last hospital admission or by phone contact.

The endpoint of the study was the composite of cardiac death and/or cardiac hospitalization. Cardiac death was defined as any death without clear non-cardiac cause. Cardiac hospitalization was defined as any hospitalization due to heart failure and/or arrhythmias.

The occurrence of major arrhytmias not requiring hospitalization as well as the rate of cardiac interventions (percutaneous or surgical) were also recorded.

The study conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Ethical Committee (protocol number 4742).

Statistical analysis

Continuous variables normally distributed are presented as mean ± standard deviation whereas non-normally distributed data are presented as median and interquartile range (IQR). Categorical variables are expressed as frequencies and percentages.

The comparison of baseline characteristics between patients with S-VHD (no severe VHD: NS-VHD) was performed by the unpaired Student's *T* test (for normally distributed continuous variables), Mann–Whitney *U* test (for non-normally distributed continuous variables) and Chi-square test or Fisher's exact test, as appropriate (for categorical variables).

Cumulative event-free survival rates for the population, stratified by the presence of severe VHD, were calculated using the Kaplan–Meier method. The log-rank test was used to compare the two groups. Cox proportional hazards regression analysis was used to assess the association between clinical and echocardiographic parameters with the composite study endpoint. Exposure to percutaneous or surgical interventions was included in the analysis as a binary time-dependent term. The hazard ratio (HR) and 95% confidence intervals (CIs) were calculated for each variable. The proportional hazards assumption was verified based on Schoenfeld residuals. The entry criteria for the multivariate regression analysis were a significant association in univariate analysis ($p < 0.05$) and an amount of missing values that did not exceed 5% of the total study population. A minimum tolerance level of 0.5 was established to avoid multicollinearity between covariates. Moreover, to investigate the incremental prognostic value of S-VHD on the top of variables included in the multivariate analysis, the likelihood ratio test for nested models was performed. The change in global Chi-square was calculated and reported.

As secondary analysis, the occurrence of cardiovascular mortality and cardiovascular hospitalization under medical management (censoring patients at the time of interventions) was also performed, using Cox proportional hazard regression analysis.

All tests were two-sided and *p*-values < 0.05 were considered statistically significant. Statistical analysis was performed using SPSS version 25.0 (IBM Corporation, Armonk, NY, USA) and R version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Characteristics of the study population

During the study period, 596 patients were evaluated in our ACHD Outpatient Clinic. After exclusion of patients with patent foramen ovale, cardiomyopathies or congenital arrhythmias, and of those who had a single consultation, 422 ACHD patients were eligible for the study. Out of them, 32 patients had a follow-up time < 12 months and were excluded from the

present study. Thus, a total of 390 patients constituted the study population. The flow chart of the study is graphically summarized in Figure 1.

The clinical characteristics of the study population are reported in Table 1. Overall, median age was 34 years (range 26–46) and 189 (49%) patients were male. Most patients (n = 256, 66%) underwent corrective or palliative procedure during childhood and 30 (8%) had a PM/ICD implantation. At our first evaluation, 146 (37%) patients presented with NYHA functional class > II and 22 (6%) had atrial flutter/atrial fibrillation (Af/Afib).

Nearby half of the population had moderate CHD (191 patients, 49%) and CHD was graded as severe in 40 patients (10%). Supplementary Figure 1 shows the distribution of severe CHD.

Severe valvular heart disease (S-VHD) was present in 101 patients (25.9%). The pulmonary valve was the valve more frequently affected by severe stenosis and/or regurgitation (n = 42, 40.5%), while the single most common valve lesion was severe tricuspid regurgitation (n = 31, 30.7%). The distribution of severe valvular lesions is illustrated in Figure 2. Among patients with S-VHD, 36 underwent a surgical procedure and 6 patients a percutaneous intervention.

Characteristics of patients with severe valvular heart disease

Table 2 shows the comparison between patents with S-VHD and those with NS-VHD. Age at first visit was significantly higher in S-VHD patients ($p < 0.001$), who also were more likely to have a moderate or severe underlying CHD ($p < 0.001$) and to have undergone corrective or palliative surgery in pediatric age ($p = 0.014$). S-VHD patients had statistically significant lower %Sat O_2 ($p < 0.011$) and were more often in NYHA functional class > II ($p < 0.001$).

At ECG, S-VHD patients presented more frequently with Af/Afib rhythm at first evaluation ($p < 0.001$) and had longer QRS duration ($p < 0.001$) as compared to NS-VHD patients.

At echocardiography, patients with S-VHD had lower LVEF ($p = 0.027$), lower TAPSE ($p < 0.006$), larger LAVi ($p < 0.001$), and increased RVSP ($p < 0.001$) as compared to NS-VHD patients.

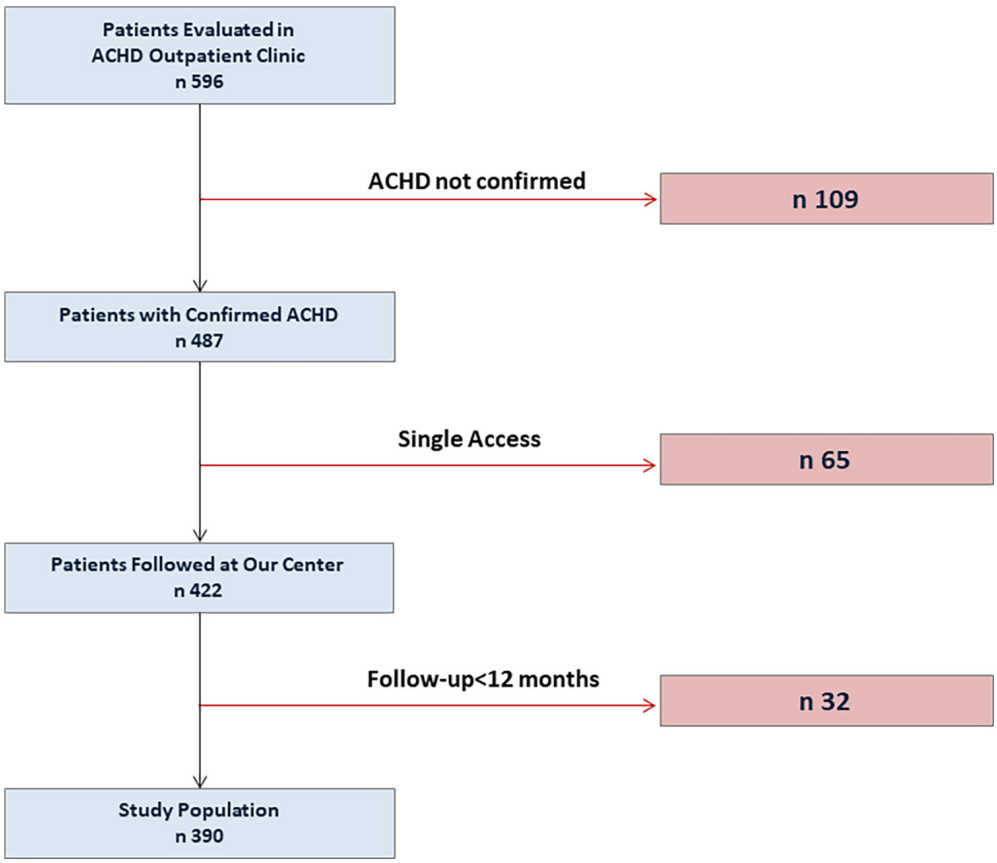

FIGURE 1
Study flow-chart. ACHD, Adult congenital heart disease.

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TABLE 1 Baseline characteristics of the study population.

Variables	Total ($n = 390$)
Age (years)	34 (26–46)
Male (n, %)	189 (49)
Complexity of CHD (n, %)	
Mild	159 (41)
Moderate	191 (49)
Severe	40 (10)
Surgery in pediatric age (n, %)	
None	184 (47)
Corrective surgery	179 (46)
Palliative surgery	27 (7)
Previous implantation of PM/ICD (n, %)	30 (8)
Af/Afib (n, %)	22 (6)
HR (bpm)	73 ± 13
QRS (ms)	105 (94–126)
Sat O_2(%)	97 ± 5
NYHA class II-IV	146 (37)
LVEF (%)	61 ± 7
LAVi (ml/m2)	31 (24–43)
E/E′ ratio	7 (5–8)
S-VHD (n, %)	101 (26)
TAPSE (mm)	22 ± 5
RVSP (mmHg)	30 (25–40)
RVSP > 45 mmHg (n, %)	29 (7)

Values are expressed ad mean ± SD, median (IQR) or n (%).
Af/Afib, atrial flutter/atrial fibrillation; CHD, congenital heart disease; HR, heart rate; ICD, implantable cardioverter defibrillator; LAVi, left atrium volume index; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PM, pacemaker; RVSP, right ventricle systolic pressure; Sat O_2, oxygen saturation; TAPSE, tricuspid annular plane systolic excursion.

Impact of severe valvular heart disease on outcome

Over a median follow-up time of 26 months (IQR: 12–48), the study endpoint occurred in a total of 76 patients (19.5%). Cardiovascular death occurred in 8 patients with 2 cases of sudden cardiac death. A cardiac intervention was performed in 78 patients (median time to intervention being 10 months, range 4–29). Patients with S-VHD underwent more frequently percutaneous or surgical intervention, as compared with NS-VHD (41.6 vs. 12.5%, $p < 0.001$).

Arrhythmias occurred more often in patients with S-VHD than NS-VHD (32.7 vs. 15.2%, $p < 0.001$).

The cumulative endpoint-free survival was significantly lower in patients with S-VHD *vs.* NS-VHD [**Figure 3**, 59 vs. 83% (Log rank $p < 0.001$)]. **Supplementary Table 4** summarizes the prevalence of the single endpoints in the overall population as well as in S-VHD and NS-VHD groups.

At univariable Cox regression analysis (**Table 3**), S-VHD was significantly associated with an increased risk of the study endpoint [3.483 (2.086–5.816); $p < 0.001$]. In addition, age, severe CHD, Af/Afib at first visit, %Sat O2, NYHA class ≥ II, LVEF, TAPSE and increased RVSP (> 45 mmHg) were also associated with the study endpoint. On multivariable analysis (**Table 3**), the association between S-VHD and the study endpoint remained significant [HR: 1.925 (1.133–3.271); $p = 0.015$], after adjustment for age, severe CHD, Af/Afib at first visit, %Sat O_2, NYHA class ≥ II, LVEF and increased RVSP. Notably, the likelihood ratio test demonstrated an incremental prognostic value by incorporating S-VHD in the multivariable model (changes in $X^2 = 5.70$; $p = 0.017$) (**Supplementary Figure 2**).

The association of each subgroup of S-VHD (defined according to the affected valve and the type of valvular lesion), with outcomes is reported in **Supplementary Figure 3**. Each type of S-VHD was individually associated with the endpoint. After adjustment for significant clinical and echocardiographic variables (age, severe CHD, Af/Afib, NYHA ≥ II, Sat O_2, LVEF and RVSP > 45 mmHg), isolated S-VHD ($p = 0.049$), left-sided VHD ($p = 0.007$), and regurgitant S-VHD ($p = 0.016$) retained their independent association with outcomes.

There was no significant difference in adverse outcomes occurrence between S-VHD patients who received corrective intervention during follow-up and those who did not [14 (33%) vs. 23 (39%), respectively, $p = 0.56$]. However, in the subgroup of the S-VHD population that underwent surgical/percutaneous procedure, most of the events [10, (71%)] occurred before the intervention.

To further confirm the prognostic value of S-VHD on the clinical evolution, the occurrence of cardiac mortality or cardiac hospitalization without cardiac operations was examined. After a median follow-up of 23 months (range: 9–44), 68 events occurred. At univariable Cox regression analysis, S-VHD was significantly associated with outcomes in patients medically treated [HR: 3.473 (2.144–5.627); $p < 0.001$]. The adjustment for significant clinical and echocardiographic variables (age, severe CHD, Af/Afib, NYHA class ≥ II, LVEF and increased RVSP) did not affect the powerful association of S-VHD with the occurrence of the composite endpoint under medical management [HR: 1.920 (1.093–3.373); $p = 0.023$].

The **Figure 4** is an illustrative example of four patients included in our study, coupled according to the ACHD.

Discussion

The major and novel finding of our study in a contemporary real-world ACHD population is that the presence of severe VHD impacts prognosis, being independently associated with the risk of cardiac mortality and hospitalization. This highlights the need for careful VHD characterization in ACHD outpatient clinics and call for improvement in their management.

The management of patients with ACHD represents an expanding clinical field, with constantly increasing numbers, mainly due to the success of cardiac surgery and interventions in children (16).

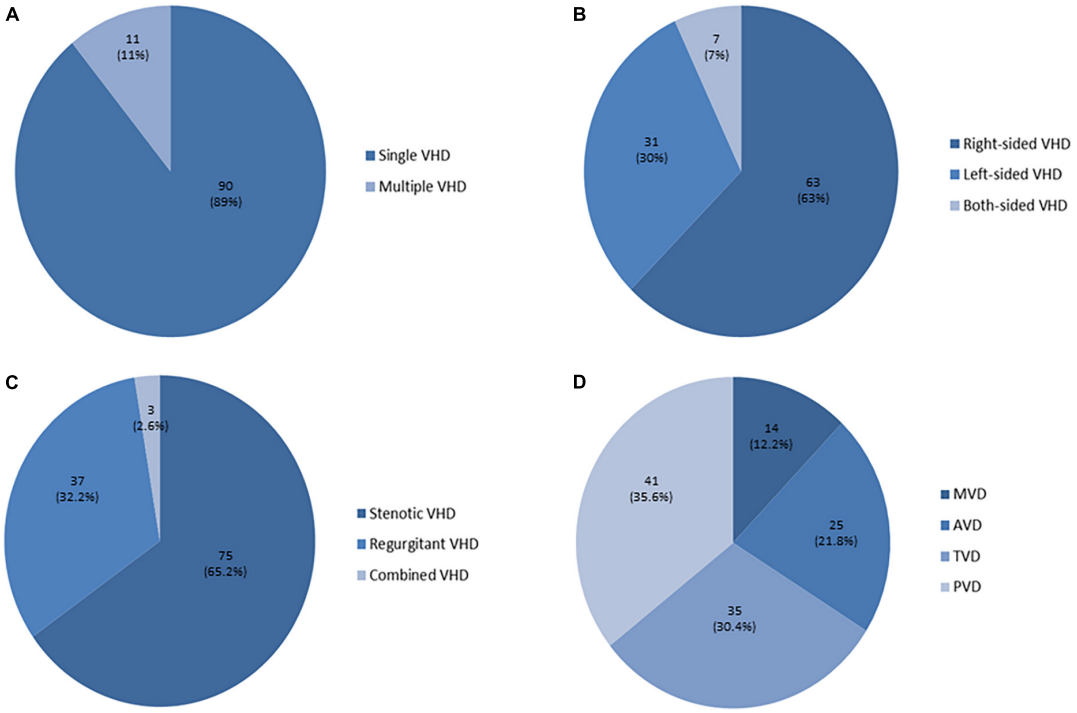

FIGURE 2
Distribution of severe heart valve lesions. **(A)** Among patients with severe valvular heart disease (S-VHD), 90 (89%) had single S-VHD (= 1 valve with severe dysfunction), while 11 (11%) had multiple S-VHD (≥ 2 valves with severe lesions). **(B)** Right-sided S-VHD (63 patients, 63%) were prevalent as compared to left-sided S-VHD (31 patients, 30%), while in few cases both-sided S-VHD were detected (7 patients, 7%). **(C)** When considering patients with multiple VHD (= more than one valve with severe dysfunction in the same patient), a total of 115 severe valvular dysfunctions were detected among the 101 patients with S-VHD. Severe regurgitant lesions were prevalent (75) as compared to severe stenotic lesions (37), while in three cases severe combined VHD was present (2 patients with severe pulmonary valve steno-insufficiency and 1 with severe mitral valve steno-insufficiency). **(D)** The pulmonary valve was the most frequently affected by severe stenosis and/or regurgitation (S-PVD, $n = 41$), followed by the tricuspid valve (S-TVD, $n = 35$). Severe aortic valve (S–AV) and mitral valve (S–MV) stenosis and/or regurgitation were less common (25 and 14 respectively).

These patients, however, cannot be considered cured, as most of them will suffer the long-term sequelae of their birth defect and/or the surgical interventions performed in childhood, which can take decades to manifest (17). The clinical complexity of the ACHD population, indeed, is increasing over time (1, 4, 18), with HF and arrhythmias representing the major causes of death or re-admission for these patients during adult life (18–20) and VHD are commonly found and frequently require an intervention (21, 22). To date, however, most data come from registries or surveys (based on large administrative databases, general electronic health records and death certificates) that cannot provide detailed information about important clinical features regarding baseline disease severity characterization and outcome measures. More importantly, these are frequently descriptive analyses in which factors often associated to ACHD, as the presence of VHD, are not evaluated as covariates. All these limits make the real burden of VHD on ACHD difficult to ascertain.

In this context, the major strength of our study is that we carefully collected clinical, ECG and echocardiographic data in a contemporary real-world population of ACHD patients followed at our dedicated outpatient clinic, with the specific aim to assess the role of severe VHD on prognosis. We found that half of the population had a VHD at least moderate at the first evaluation in our center. This is of particular importance, as moderate valve dysfunction has been shown to be detrimental in other clinical settings (23) as well as in ACHD (24). Moreover, the median age of our population at first visit was 34 years, thus the chance of progression of the VHD is expected to be high. As much as a quarter of patients presented at their first evaluation in our dedicated adult outpatient clinic with a severe valve dysfunction, that is expected to determine a major impact on the overall CHD hemodynamics. These patients were older, presented with more advanced NYHA functional class and more often had an underlying moderate or severe CHD, in line with recent studies reporting the increasing complexity of ACHD patients (1, 4–17). Moreover, patients with severe VHD were more prone to develop arrhythmias and more often required interventions/reinterventions, confirming previous observations (25–27).

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TABLE 2 Comparison between severe valvular heart disease (S-VHD) vs. NS-VHD patients.

Variables	S-VHD ($n = 101$)	NS-VHD ($n = 289$)	*P*-value
Age (years)	40 (30–54)	33 (24–44)	<**0.001**
Male (n, %)	49 (49)	140 (48)	0.990
Complexity of CHD (n, %)			
Mild	23 (23)	136 (47)	<**0.001**
Moderate	63 (62)	128 (44)	
Severe	15 (15)	25 (9)	
Surgery in pediatric age (n, %)			
None	37 (37)	147 (51)	**0.0014**
Corrective surgery	53 (53)	127 (44)	
Palliative surgery	11 (10)	15 (5)	
Age at first surgery	5 (1.0–13.25)	3 (0.0–10.5)	0.11
Previous implantation of PM/ICD (n, %)	10 (10)	20 (7)	0.343
Af/Afib (n, %)	15 (15)	7 (3)	<**0.001**
HR (bpm)	73 ± 15	72 ± 12	0.49
QRS (ms)	117 (101–149)	103 (93–119)	<**0.001**
Sat O_2(%)	95 ± 6	97 ± 4	**0.011**
NYHA class II-IV (n, %)	57 (57)	89 (31)	<**0.001**
LVEF (%)	60 ± 6	62 ± 7	**0.027**
LAVi (ml/m2)	41 (27–61)	29 (23–40)	<**0.001**
E/E′ ratio	7 (5–10)	6 (5–8)	0.344
TAPSE* (mm)	20 ± 6	22 ± 5	**0.006**
RVSP (mmHg)	40 (30–55)	30 (25–35)	<**0.001**
RVSP > 45 mmHg (n, %)	17 (17)	12 (4)	<**0.001**

Values are expressed ad mean ± SD, median (IQR) or n (%).
Bold values indicate statistical significance at the $p < 0.05$ level.
*TAPSE was available in 326 patients (84% of the overall population).
Af/Afib, atrial flutter/atrial fibrillation; CHD, congenital heart disease; HR, heart rate; ICD, implantable cardioverter defibrillator; LAVi, left atrium volume index; LVEF, left ventricular ejection fraction; NS-VHD, non-severe valvular heart disease; NYHA, New York Heart Association; PM, pacemaker; RVSP, right ventricle systolic pressure; Sat O_2, oxygen saturation; S-VHD, severe valvular heart disease; TAPSE, tricuspid annular plane systolic excursion.

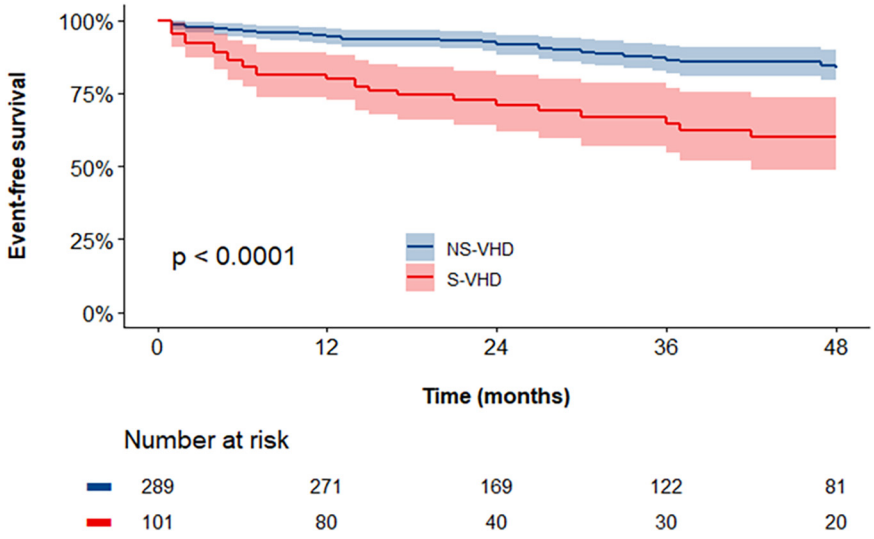

FIGURE 3
Kaplan–Meier curves assessing the cumulative event-free survival rates in severe valvular heart disease (S-VHD) and NS-VHD populations. S-VHD, severe valvular heart disease; NS-VHD, non-severe valvular heart disease.

TABLE 3 Univariable and multivariable Cox regression analysis.

	Univariable analysis		Multivariable analysis	
Variables	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Age (years)	1.037 (1.020–1.054)	<**0.001**	1.022 (1.002–1.041)	**0.029**
Male	0.981 (0.623–1.546)	0.935		
Severe CHD	3.483 (2.086–5.816)	<**0.001**	1.332 (0.663–2.673)	0.421
Surgery in pediatric age	1.376 (0.865–2.186)	0.177		
Af/Afib	6.444 (3.224–12.877)	<**0.001**	3.214 (1.408–7.333)	**0.006**
HR (bpm)	1.011 (0.994–1.029)	0.209		
QRS duration (ms)	1.007 (0.999–1.014)	0.075		
Sat O_2 (%)	0.934 (0.914–0.955)	<**0.001**	0.956 (0.926–0.986)	**0.005**
NYHA class II–IV	4.224 (2.613–6.827)	<**0.001**	2.246 (1.270–3.974)	**0.005**
Surgical or percutaneous intervention *(time-dependent)*	1.503 (0.745–3.031)	0.255		
LVEF (%)	0.922 (0.896–0.948)	<**0.001**	0.952 (0.918–0.987)	**0.008**
LAVi (ml/m2)	1.000 (0.998–1.003)	0.657		
E/E′ ratio	1.049 (0.932–1.181)	0.426		
S-VHD	3.258 (2.073–5.121)	<**0.001**	1.925 (1.133–3.271)	**0.015**
TAPSE (mm)	0.901 (0.856–0.949)	<**0.001**		
RVSP > 45 mmHg	1.029 (1.017–1.040)	<**0.001**	2.023 (0.955–4.286)	0.066

Bold values indicate statistical significance at the $p < 0.05$ level.
Af/Afib, atrial flutter/atrial fibrillation; CHD, congenital heart disease; HR, heart rate; LAVi, left atrium volume index; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; Sat O_2, oxygen saturation; S-VHD, severe valvular heart disease; TAPSE, tricuspid annular plane systolic excursion; RVSP, right ventricle systolic pressure.

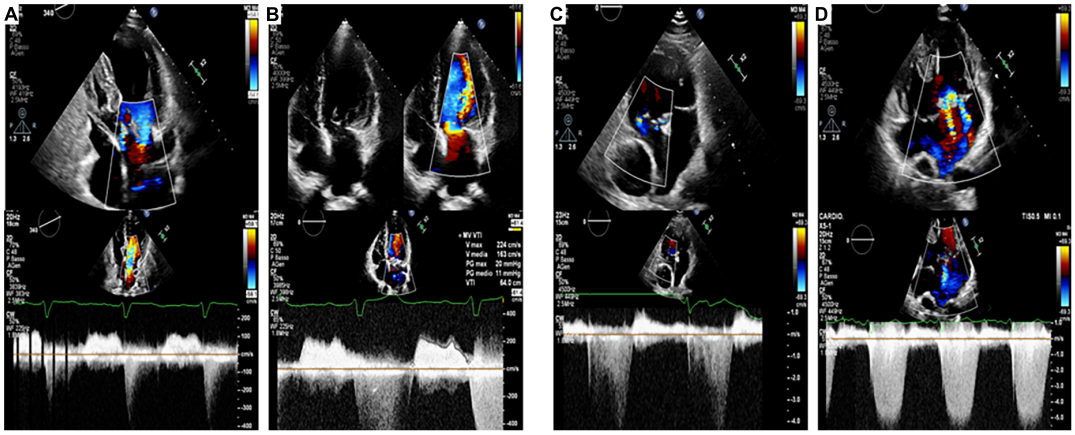

FIGURE 4
Echocardiographic images (Top: apical 4-chamber views, Bottom: CW Doppler through mitral valve and systemic AV valve) of four patients included in our study, coupled according to the ACHD [**(A,B)**: repaired partial atrioventricular septal defect; **(C,D)**: Fontan circulation], with (Panel **B,D**) and without (Panel **A,C**) associated S-VHD. This is illustrative of our findings, since patients **(B–D)** experienced hospitalization for heart failure. while patients **(A–C)** had an unremarkable clinical course.

The major finding of our study is that severe VHD at presentation was independently associated with an adverse outcome during the clinical course. S-VHD adds strong prognostic value to the multivariate model including significant clinical and echocardiographic variables. In particular, S-VHD had an independent prognostic impact on outcome while severe CHD did not. This is worth noting, since most data suggest that cardiovascular death and complications are associated with the severity of underlying CHD (21, 28, 29). A study (21) evaluating the trends in hospitalizations for ACHD (2003–2012), stratified into simple and complex disorder, showed that HF, respiratory disorders, and arrhythmias were the top three reasons for admission among patients with complex ACHD while VHD was among the three top causes for admission among patients with simple ACHD without atrial septal defect/patent foramen ovale.

However, these studies did not stratify patients for the degree of VHD while our study showed the relevance of the severity of the valvular heart lesion on ACHD outcome. This

data is of particular importance as most studies reporting on VHD in CHD patients comes from national registries and surveys with the valve dysfunction often reported as a dichotomous variable and no mention on the type and degree of valvular lesion, or the affected valve or the underlying etiology. Of note, our study reveals the striking difference between the typical scenario of adult cardiology, in which VHD poses a significant burden dominated by far by aortic stenosis and mitral regurgitation (30) and ACHD valvular abnormalities. In fact, ACHD comprise a wide spectrum, with extremely heterogeneous anatomy, physiology and surgical history, including systemic right ventricles, systemic single ventricle and Fontan palliation. Due to this complexity, ACHD-related VHD are difficult to categorize as primary, post-surgical or functional lesions. Indeed, on an individual basis, patients often fall in more than one category. Thus, whether there is a different prognostic role for primitive vs. post-surgical or functional VHD cannot be deduced from our study.

In this context, right-sided valvular lesions were prevalent in our study but left-sided VHD (including all systemic atrio-ventricular valves) retained their independent association with outcomes. These findings highlight the importance of considering valvular heart lesions in ACHD according to the functional, rather than the anatomical classification.

Limitations

Some limitations of the present study should be acknowledged. Firstly, we included a wide spectrum of congenital heart diseases patients with heterogeneous valvular lesions. However, this is a problem commonly encountered in studies on ACHD, considering that most CHD are rare diseases. In addition, this is an observational study conducted in a tertiary referral center for ACHD and VHD, thus our population could not be representative of average ACHD patients. Moreover, we did not systematically collect cardiac magnetic resonance (CMR) data that is the gold standard for the assessment of most ACHD patients. However, the presence and degree of VHD was carefully established according to the most recent echocardiography guidelines and echo studies were personally performed by experienced team in the imaging and care of VHD and ACHD. Moreover we did perform CMR in every patient with pulmonary regurgitation to quantify its severity by means of regurgitant fraction. It is also worth noting that echocardiography is still the gold standard for the assessment of valvular stenosis.

Conclusion

Our study shows that the occurrence of S-VHD in ACHD patients is a major threat, being a significant independent predictor of hospitalization or death. The prognostic value of severe valve dysfunction is incremental above other established prognostic markers and consistent independently from CHD severity.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethic Committee Fondazione Policlinico Universitario Agostino Gemelli, n°4742. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

FG, GI, MCM, and RL: study design, data collection, and statistical analysis. All authors contributed to the drafting and revision of the manuscript, to data analysis improvement and discussion development.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.983308/full#supplementary-material

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Left ventricular hypertrophy, diastolic dysfunction and right ventricular load predict outcome in moderate aortic stenosis

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Aims: Predictors of progression of moderate aortic valve stenosis (AS) are incompletely understood. The objective of this study was to evaluate the prognostic value of left ventricular hypertrophy (LVH), diastolic dysfunction, and right ventricular (RV) load in moderate AS.

Methods and results: Moderate AS was defined by aortic valve area (AVA), peak transvalvular velocity (V_{max}) or mean pressure gradient (PG_{mean}). A total of 131 Patients were divided into two groups according to the number of pathophysiological changes (LVH, diastolic dysfunction with increased LV filling pressures and/or RV load): <2 (group 1); ≥2 (group 2). The primary outcome was survival without aortic valve replacement (AVR). After follow-up of 30 months, the reduction of AVA (−0.06 ± 0.16 vs. −0.24 ± 0.19 cm^2, $P < 0.001$), the increase of PG_{mean} (2.89 ± 6.35 vs 6.29 ± 7.13 mmHg, $P < 0.001$) and the decrease of the global longitudinal strain (0.8 ± 2.56 vs. 1.57 ± 3.42%, $P < 0.001$) from baseline to follow-up were significantly more pronounced in group 2. Survival without AVR was 82% (group 1) and 56% (group 2) [HR 3.94 (1.74–8.94), $P < 0.001$]. Survival without AVR or progression of AS was 77% (group 1) and 46% (group 2) [HR 3.80 (1.84–7.86), $P < 0.001$]. The presence of ≥2 pathophysiological changes predicted outcome whereas age, comorbidities, LDL-cholesterol did not.

Conclusion: The presence of ≥2 pathophysiological changes is a strong predictor of outcome in moderate AS and may be useful for risk stratification, particularly for scheduling follow-up time intervals and deciding the timing of AVR.

KEYWORDS

valvular heart disease, aortic stenosis (AS), echocardiography, outcome, longitudinal strain

Introduction

Patients with severe symptomatic aortic stenosis (AS) have a poor prognosis and benefit from aortic valve replacement (AVR) (1–3). In contrast, the natural history and clinical outcome of patients with moderate AS are incompletely described and parameters for risk stratification are sparse. Moderate AS is defined by echocardiography on the basis of aortic valve area (AVA), peak transvalvular velocity (V_{max}) and mean pressure gradient (PG_{mean}) (3, 4). The importance of V_{max}, PG_{mean}, and valve calcification on clinical outcome is not clear (5–8). Most of the studies on progression of moderate AS are limited by small study populations, do not include echocardiographic assessment and/or were performed 20–30 years ago (9).

There is no specific therapy available to prevent moderate AS progression. The treatment focuses on the prevention of atherosclerosis including optimal treatment of comorbidities and risk factors. Patients with moderate AS are recommended to be regularly monitored by echocardiography but individual AS progression varies widely causing difficulties to implement general recommendations of risk stratification (3, 8).

Considering the pathophysiology of AS, left ventricular hypertrophy (LVH), diastolic dysfunction (DD) with increased LV filling pressures, and/or right ventricular (RV) load are characteristics of patients with advanced stages of AS. Recently, we assessed the presence of LVH, DD (E/e'), and RV load (maximum tricuspid regurgitation velocity, TR_{Vmax}) in patients with severe AS (10). We observed that severe AS is highly unlikely without the presence of LVH including normal values for E/e' and TR_{Vmax} (10).

Based on these findings we hypothesized that LVH, E/e' and TR_{Vmax} may have a prognostic value in moderate AS.

Materials and methods

Study population

Between 2016 and 2019 patients with moderate AS meeting the following inclusion criteria were included: AVA 1.0–1.5cm^2 and V_{max} > 2.9 m/s (<4.0 m/s), or PG_{mean} > 20 mmHg (<40 mmHg) (3, 4). Patients with concomitant moderate or severe valvular disease, already confirmed cardiac amyloidosis, hypertrophic obstructive cardiomyopathy, acute myocarditis, LV ejection fraction (EF) <45% or/and LV stroke volume index (SVi) <35 ml/m^2, pulmonary hypertension due to pulmonary disease and/or acute pulmonary embolism, body mass index ≥35 kg/m^2, prior heart surgery or valvular intervention were excluded. The prospective study was conducted in accordance with the Declaration of Helsinki and was approved by the ethical committee of the University of Leipzig (041/19-ek). All included patients provided informed consent.

Clinical follow-up was available in 131 of 157 patients. All patients were monitored clinically and by echocardiography every 6 months. The inclusion date corresponds to the date of baseline transthoracic echocardiography (TTE). Transesophageal echocardiography (TEE) was performed in cases of uncertain findings by TTE. Moderate AS patients were divided into two groups according to the number of pathophysiological changes [LVH: increased left ventricular mass index (LVMi), DD: increased E/e' and/or RV load: increased TR_{Vmax}]: group 1: <2 changes (n = 79); group 2: ≥2 changes (n = 52). The primary outcome was survival without AVR. The secondary outcome was survival without AVR or progression from moderate to severe AS based on current recommendations (3). Clinical decisions on referral for AVR were made by heart team decisions.

Patient characteristics were collected from the patients and from medical records. At baseline, all patients were asymptomatic or presented with unspecific and/or only mild symptoms. N-terminal pro-B-type natriuretic peptide (NT pro-BNP), low-density lipoprotein-(LDL)-cholesterol, and lipoprotein(a) [Lp(a)] (cut-off value of > 58.5 mg/dl/140 nmol/l) were assessed (11).

Echocardiography

Transthoracic echocardiography was performed using a Vivid E9 or E95 ultrasound system with a M5-S or a 4Vc phased array probe and echocardiographic analyses were performed with the EchoPac software version 203 or 204 (GE Healthcare Vingmed Ultrasound AS, Horten, Norway).

Evaluation of aortic valve stenosis

Effective AVA was calculated by the continuity equation. The diameter of the left ventricular outflow tract (D_{LVOT}) was determined by TTE in the parasternal long axis view in the LVOT at a distance of 5–10 mm from the aortic valve during mid-systole. Only in a few exceptional cases D_{LVOT} was measured by TEE in the mid-esophageal long axis view. LVOT blood flow velocities were assessed by pulsed wave (PW) Doppler echocardiography in the apical long axis view by placing the sample volume at the position corresponding to the position of D_{LVOT} measurements. V_{max} was determined by continuous wave (CW) Doppler echocardiography either in the apical long axis or 5-chamber view. PG_{mean} was calculated by the (simplified: if pre-stenotic velocities were in normal ranges) Bernoulli equation (3, 4). Progression from moderate to severe AS was assessed by AVA, V_{max} and PG_{mean} by experienced cardiologists based on current recommendations (3, 4).

Left ventricular volumes/function and pathophysiological changes

left ventricular hypertrophy was defined by LVMi (males: ≥115 g/m^2; females: ≥95 g/m^2) using the Devereux formula (12, 13). LV mass was assessed by M-Mode measurements using parasternal short axis views. LV volumes and LVEF were assessed by biplane LV planimetry using the modified Simpson's rule (13). Myocardial deformation was characterized by global longitudinal peak systolic strain (GLS) by 2D speckle tracking analysis in the apical long axis-, 2- and 4-chamber-view (14, 15). Endocardial contours and tracking areas were adjusted manually to enable full myocardial tracking. Only segments with accurate tracking were accepted.

Valvulo-arterial impedance (Z_{VA}) was calculated by PG_{mean}, systolic blood pressure (sBP) and LVSVi by the following equation: $Z_{VA} = (PG_{mean} + sBP)/LVSVi$ (16). sBP was measured in supine position at the time of TTE using an automatic arm-cuff blood pressure monitor.

Diastolic dysfunction was assessed according to current recommendations (17). Mild DD in terms of LV relaxation disorder was not considered sufficient, so relevant DD was defined by DD with an increase of LV filling pressures (increased E/e'): ≥14 (sinus rhythm) or ≥11 (atrial fibrillation, AF) (17).

Right ventricular load was defined by an increase of TR_{Vmax} ≥2.8 m/s in the apical 4-chamber-view (17). RV systolic function was evaluated by tricuspid annular plane systolic excursion (TAPSE). Normal RV function was defined by TAPSE >17 mm (13).

Statistical analysis

Statistical analyses were performed using SPSS Statistics (version 24.0, IBM, Armonk, NY, USA). Kolmogorov–Smirnov was used to test normal data distribution. Continuous variables are expressed as mean ± standard deviation (SD) and differences between two groups were analyzed by student's *t*-test. Follow-up period was expressed by median ± interquartile range. All categorical variables were expressed as numbers and/or percentages. Chi-squared or Fisher's exact test were used to analyze categorical variables as appropriate. Kappa coefficient (κ) was used to assess interrater reliability for LVH, E/e' and TR_{Vmax} in 20 randomly selected patients. Kaplan-Meier time-to-event analyses were performed and compared by log-rank test. Multivariate analysis was done by cox proportional-hazards model. A *P*-value < 0.05 was considered to indicate statistical significance.

Results

Baseline characteristics were balanced between both groups, except for a higher percentage of patients with coronary heart disease (CHD) in group 2 and a slightly higher percentage of patients with bicuspid AS in group 1 (Table 1).

Echocardiographic parameters

An increase of LVMi was the most common echocardiographic finding in both groups (group 1: 48%; group 2: 92%), followed by increase of TR_{Vmax} (group 1: 14%; group 2: 69%) and E/e' (group 1: 6%; group 2: 63%). Based on this classification, LVMi, E/e' and TR_{Vmax} were higher in group 2 ($P < 0.001^{\dagger, \ddagger}$). However, a significant increase between baseline and follow-up was only observed for LVMi (both groups, $P < 0.05^{*}$) and TR_{Vmax} (group 2, $P < 0.05^{*}$; Table 2). Interrater variability revealed high agreement for LVH, E/e', and TR_{Vmax} (LVH: κ = 0.74 (z = 3.42, $P < 0.001$); E/e': κ = 0.90 (z = 3.66, $P < 0.001$); TR_{Vmax} κ = 0.80 (z = 3.66, $P < 0.001$).

AVA and PG_{mean} were similar at baseline. After 30 months of follow-up (30 ± 5 months) AVA was significantly lower and PG_{mean} was significantly higher in both groups. Changes in AVA ($P < 0.001^{\ddagger}$) and PG_{mean} ($P < 0.05^{\ddagger}$) were more pronounced in patients with ≥2 pathophysiological changes (Table 2).

Almost all patients had a LVEF >50% (95%; 5% had an LVEF between 45 and 49%) and a normal TAPSE (100%) at baseline and follow-up (Table 2). GLS was significantly lower at follow-up, which was even more pronounced in group 2 (group 1: Δ −0.83 ± 0.18 vs. group 2: Δ −1.72 ± 0.04, $P < 0.05^{\ddagger}$; Table 2). Z_{VA} did not differ between both groups neither at baseline nor at follow-up (Table 2).

Predictors of outcome

Survival without AVR was 99% at 12, 90% at 24, and 82% at 30 months (group 1) vs. 90, 73, and 56% (group 2) [HR 3.94 (1.74–8.94), $P < 0.001$, Table 3 and Figure 1]. Survival without AVR or progression of AS was 99% at 12, 86% at 24, and 77% at 30 months (group 1) vs. 90, 67, and 46% (group 2) [HR 3.80 (1.84–7.86), $P < 0.001$, Table 3 and Figure 2].

During the follow-up period 20 (15%) patients received AVR. AVR or progression of AS were observed in 31 (24%) patients (Table 3). Both AVR and AVR or progression of AS were more frequently observed in patients with ≥2 pathophysiological changes ($P < 0.001$; Table 3 and Figures 1, 2). Most patients ($n = 17$, 85%) underwent transcatheter aortic valve implantation (TAVI). Surgery was performed in three (15%) patients due to younger age or indication for coronary artery bypass grafting.

Seventeen patients (13%) died during follow-up. The number of deaths did not differ between both groups (Table 3). Cardiovascular deaths were observed in four (24%) patients: endocarditis ($n = 1$), acute pulmonary embolism ($n = 1$) and cardiogenic shock due to acute myocardial infarction ($n = 2$). Non-cardiac deaths ($n = 13$, 76%) involved pneumonia,

TABLE 1 Baseline characteristics of patients with moderate aortic valve stenosis (AS).

Variables	All patients (n = 131)	Group 1: <2 (n = 79)	Group 2: ≥2 (n = 52)	P-value
Age, years	72 ± 9.90	72 ± 9.38	73 ± 9.31	0.79
Female	43 (33%)	25 (32%)	18 (35%)	0.89
BMI, kg/m^2	28.56 ± 5.09	28.29 ± 4.71	28.73 ± 5.08	0.43
sBP, mmHg dBP, mmHg	140 ± 17 77 ± 11	141 ± 17 79 ± 11	139 ± 19 75 ± 11	0.20 0.08
Hypertension	103 (79%)	61 (77%)	42 (81%)	0.62
Diabetes mellitus	44 (34%)	26 (33%)	18 (34%)	0.84
Hypercholesterolemia	66 (51%)	42 (53%)	24 (47%)	0.44
Peripheral vascular disease	14 (11%)	7 (9%)	7 (13%)	0.43
CHD	47 (36%)	23 (29%)	24 (46%)	**<0.05**
Bicuspid valve	8 (6%)	6 (8%)	2 (3%)	**<0.05**
Atrial fibrillation	35 (27%)	21 (26%)	14 (27%)	0.97
Stroke	23 (18%)	15 (19%)	8 (15%)	0.59
COPD	9 (7%)	5 (7%)	4 (8%)	0.78
Smoker	37 (28%)	24 (30%)	13 (26%)	0.52
CKD ≥ 3	53 (40%)	30 (38%)	23 (45%)	0.92
NYHA	1.5 ± 0.6	1.5 ± 0.6	1.5 ± 0.6	0.28
Angina pectoris	19 (14%)	12 (15%)	7 (13%)	0.23
Previous syncope	5 (4%)	4 (5%)	1 (2%)	0.33
Statins	86 (66%)	50 (63%)	36 (69%)	0.79
LDL-Cholesterol, mmol/l	2.96 ± 1.02	2.94 ± 0.95	2.98 ± 1.15	0.84
NT pro-BNP, pg/ml	470 ± 251	386 ± 233	695 ± 284	0.20

Data are expressed as mean ± SD or as n (%), P-value < 0.05 (bold) was considered to indicate statistical significance. BMI, body mass index; s/dBP, systolic/diastolic blood pressure; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; NYHA, New York Heart Association; LDL, low-density lipoprotein; NT pro-BNP, N-terminal pro-B-type natriuretic peptide.

stroke, kidney failure, intracranial hemorrhage, sepsis, and post-operative complications after non-cardiac surgery. In two patients the reason of death remained undetermined.

Multivariate analysis revealed that the presence of ≥2 pathophysiological changes was the only predictor of outcome in moderate AS ($P < 0.001$). Age, comorbidities, $V_{max} > 3.5$ m/s etc., were not associated with the outcome of moderate AS (Table 4). These results were consistent, irrespective of whether the endpoint was defined as survival without AVR or survival without AVR or progression of AS.

In addition to LDL-cholesterol level, Lp(a) was available in nearly half of the patients (n = 57, 44%, mean 87 ± 121 nmol/l). On third (n = 17, 30%) had elevated Lp(a) plasma levels. Two patients (12%) with elevated Lp(a) received AVR, whereas AVR or AS progression were observed in five patients (29%). Progression rate of AVA and V_{max} per year did not differ between patients with non-elevated (AVA: −0.12 ± 0.08; V_{max}: 0.19 ± 0.11) or elevated (AVA: −0.13 ± 0.06; V_{max}: 0.20 ± 0.13) Lp(a) plasma levels ($P > 0.05$).

Discussion

The main novel observation of the study is that three well-validated echocardiographic parameters which characterize AS pathophysiology, namely LVH, E/e' and TR_{Vmax}, predict clinical outcome in patients with moderate AS.

Pathophysiology and echocardiographic findings in moderate AS

The natural history of AS is accompanied by pathophysiological changes of the left and right ventricle. A progressive narrowing of the aortic valve leads to a chronic increase of LV pressures resulting in concentric LVH. Concentric LVH induces a shift of the diastolic pressure-volume relationship followed by increasing DD with an increase of left ventricular end-diastolic filling pressure (LVEDP) which favors the development of post-capillary pulmonary

TABLE 2 Echocardiographic results of patients with moderate aortic valve stenosis (AS).

Variables	Group 1: <2 (*n* = 79)			Group 2: ≥2 (*n* = 52)		
	Baseline	Follow-up	*P*-value	Baseline	Follow-up	*P*-value
AVA, cm^2	1.21 ± 0.16*	1.16 ± 0.18*‡	<**0.05***	1.23 ± 0.15*	1.00 ± 0.21*‡	<**0.001*** 0.28† <**0.001**‡
PG_{mean}, mmHg	24.45 ± 6.11*	27.14 ± 6.84*‡	<**0.05***	25.41 ± 6.99*	31.74 ± 9.21*‡	< **0.001*** 0.55† < **0.05**‡
LVMi, g/m^2	105.98 ± 16.90*†	110.52 ± 17.63*‡	<**0.05***	124.14 ± 17.43*†	132.72 ± 18.63*‡	<**0.05*** <**0.001**† <**0.001**‡
E/e'	10.72 ± 2.44†	11.37 ± 3.39‡	0.11	16.01 ± 4.09†	17.07 ± 4.87‡	0.09* <**0.001**† <**0.001**‡
TR_{Vmax}, m/s	2.63 ± 0.35†	2.69 ± 0.30‡	0.06	2.97 ± 0.32*†	3.16 ± 0.40*‡	<**0.05*** <**0.001**† <**0.001**‡
LVEF, %	59.70 ± 5.36	59.62 ± 5.27	0.26	59.80 ± 5.83	59.37 ± 5.96	0.76* 0.95† 0.82‡
GLS, %	−18.59 ± 3.12*	−17.76 ± 2.94*‡	<**0.05***	−17.71 ± 3.35*	−16.14 ± 3.91*‡	<**0.05*** 0.18† <**0.05**‡
Z_{VA}, $mmHg/ml/m^2$	3.96 ± 0.92	3.76 ± 0.79	0.14	3.95 ± 0.72	4.01 ± 0.80	0.38* 0.94† 0.09‡
TAPSE, mm	20.51 ± 3.92	20.25 ± 3.66	0.55	20.64 ± 3.85	19.80 ± 3.26	0.26* 0.86† 0.51‡

Data are expressed as mean ± SD or as *n* (%), *P*-value < 0.05 (bold) was considered to indicate statistical significance (*statistically significant between baseline and follow-up, †statistically significant between baseline group 1 and baseline group 2, ‡statistically significant between follow-up group 1 and follow-up group 2). AVA, aortic valve area; PG, pressure gradient; LVMi, left ventricular mass index; TR, tricuspid regurgitation; V_{max}, maximum velocity; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; Z_{VA}, Valvulo-Arterial impedance; TAPSE, tricuspid annular plane systolic excursion.

TABLE 3 Outcomes in moderate aortic stenosis (AS).

Outcome	Group 1: <2 (*n* = 79)	Group 2: ≥2 (*n* = 52)	HR (95% CI)	*P*-value
	No. (%)	No. (%)		
Primary outcome				
Survival without AVR	65 (82.3)	29 (55.8)	3.94 (1.74–8.94)	<**0.001**
AVR	4 (5.1)	16 (30.8)	7.68 (2.49–23.68)	<**0.001**
Death from any cause	10 (12.6)	7 (13.5)	0.89 (0.23–3.45)	0.87
Secondary outcome				
Survival without AVR or AS progression	60 (75.9)	23 (44.2)	3.80 (1.84–7.86)	<**0.001**
AVR orAS progression	9 (11.4)	22 (42.3)	5.35 (2.33–12.28)	<**0.001**
Death from any cause	10 (12.6)	7 (13.5)	0.79 (0.22–2.82)	0.72

Primary (survival without AVR) and secondary (survival without AVR or AS progression) outcomes are shown for patients with moderate AS. HR and CI confidence interval were calculated by cox proportional-hazards model (log-rank test). A *P*-value < 0.05 (bold) was considered to indicate statistical significance. AS, aortic stenosis; AVR, aortic valve replacement; CI, confidence interval; HR, hazard ratio.

hypertension (1, 4). Increases of LVMi, TR_{Vmax} and E/e' are less frequent in moderate AS (LVMi: 66%, TR_{Vmax} ≥ 2.8 m/s: 36%, E/e' ≥ 14: 28%) compared to patients with severe AS (TR_{Vmax} ≥ 2.8 m/s: 80%, LVMi: 79%, E/e' ≥ 14: 69%) (10). Recently, we reported that the combination of all three parameters were detected in >50% of severe AS patients. Thus,

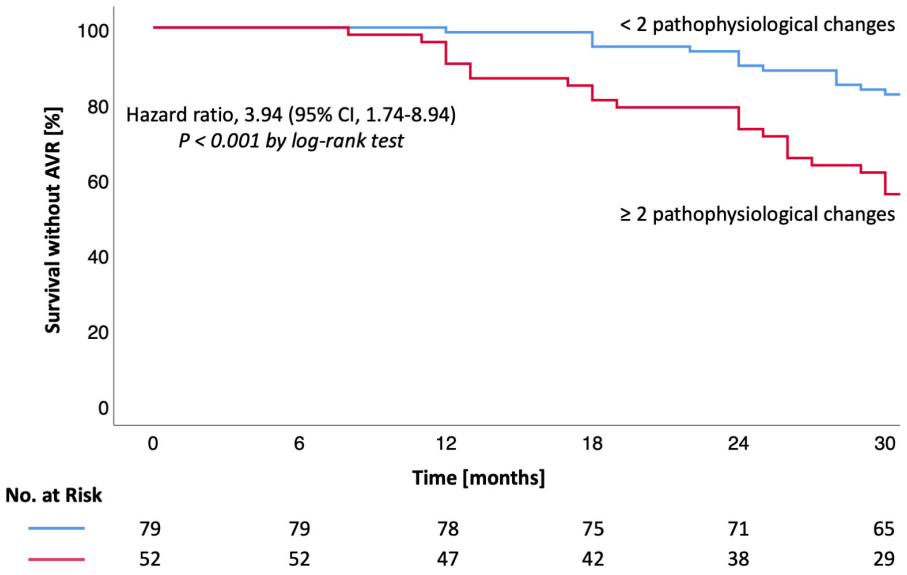

FIGURE 1
Kaplan-Meier estimates for survival without AVR in moderate AS. Kaplan-Meier estimates are shown for the primary outcome (survival without AVR). CI denotes confidence interval. Hazard ratio and CI were calculated by cox proportional-hazards model (log-rank test). A *P*-value < 0.05 was considered to indicate statistical significance. AS, aortic valve stenosis; AVR, aortic valve replacement.

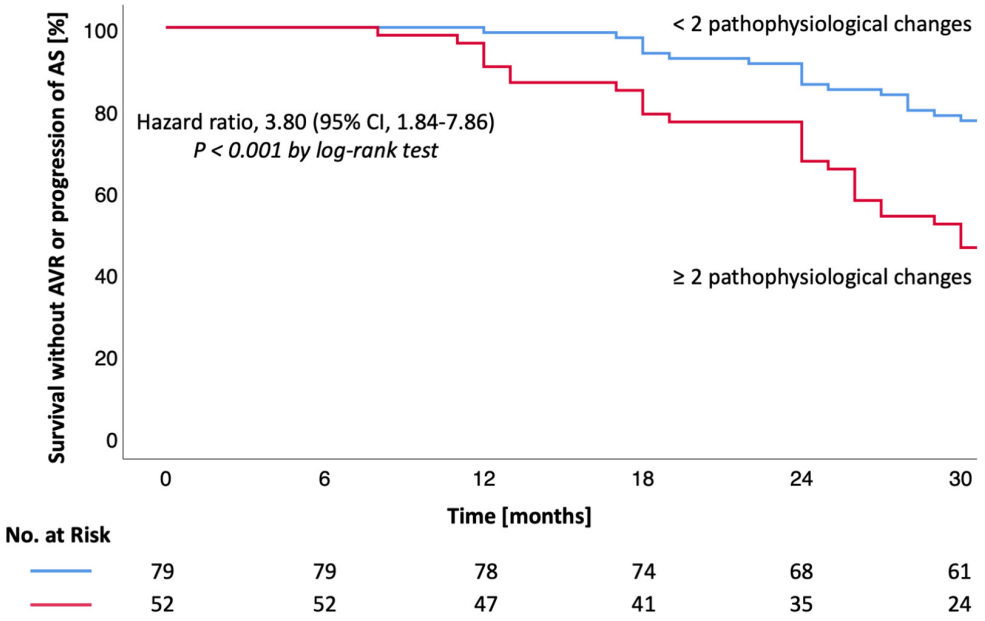

FIGURE 2
Kaplan-Meier estimates for survival without AVR or AS progression in moderate AS. Kaplan-Meier estimates are shown for the secondary outcome (survival without AVR or AS progression). CI denotes confidence interval. Hazard ratio and CI were calculated by cox proportional-hazards model (log-rank test). A *P*-value < 0.05 was considered to indicate statistical significance. AS, aortic valve stenosis; AVR, aortic valve replacement.

severe AS without at least one of these pathophysiological changes is highly unlikely (10). In moderate AS, the presence of all three echocardiographic findings was only found in 18%, whereas none of those changes were found in at least 20% confirming that changes in LVMi, E/e', and TR_{Vmax} correlate with AS progression.

Valvulo-arterial impedance has been reported to predict prognosis in moderate AS (18, 19). Despite methodological

TABLE 4 Multivariate analysis of potential predictors of outcome in moderate aortic stenosis (AS).

Outcome	Survival without AVR		Survival without AVR or AS progression	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age > 70 years	1.01 (0.97–1.05)	0.62	1.02 (0.98–1.06)	0.39
≥2 pathophysiological changes	3.94 (1.74–8.94)	**<0.001**	3.80 (1.84–7.86)	**<0.001**
GLS > −16.5%	1.18 (0.55–2.51)	0.67	1.05 (0.53–2.06)	0.89
V_{max} > 3.5 m/s	0.54 (0.23–1.24)	0.14	0.54 (0.25–1.13)	0.10
Hypertension	1.77 (0.66–4.75)	0.27	1.31 (0.51–3.37)	0.58
CHD	0.88 (0.39–1.99)	0.77	1.09 (0.53–2.23)	0.82
LDL-cholesterol > 3 mmol/l	1.15 (0.52–2.53)	0.734	1.18 (0.59–2.37)	0.64

Multivariant analysis is shown for the primary (survival without AVR) and secondary (survival without AVR or AS progression) outcome. HR and CI were calculated by cox proportional-hazards model (log-rank test). A *P*-value < 0.05 (bold) was considered to indicate statistical significance. AS, aortic stenosis; AVR, aortic valve replacement; CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; LDL, low-density lipoprotein; V_{max}, peak transvalvular velocity; GLS, global longitudinal strain.

disadvantages, e.g., dependence on Doppler angle, or possible errors in BP measurement, studies have reported its usefulness as a parameter of "global hemodynamic afterload" in AS assessment (20). The mortality risk was increased 2.8-fold in patients with Z_{VA} > 4.5 mmHg·ml^{-1}·m^2 (18). Lancellotti and Magne (21) reported poor outcome in patients with moderate to severe AS with Z_{VA} > 5.5 mmHg·ml^{-1}·m^2 and reduced GLS. In the present cohort Z_{VA} was neither associated with GLS decrease nor with a poorer prognosis. However, Z_{VA} seems promising to reconcile the discordance between moderate AS and the symptomatic status. In our study, lower Z_{VA} values may indicate, that unspecific symptoms might be related to another concomitant disease. Contrary, in patients with higher Z_{VA}, symptoms could reflect additive effects of moderate AS and reduced arterial compliance.

Impact of comorbidities on AS pathophysiology

Comorbidities were mainly balanced between both groups and consistent with patient characteristics of other studies (7, 8, 10). In 2017 Genereux et al. (22) introduced a classification system describing different stages of cardiac damage being probably associated with severe AS. The extent of cardiac damage was independently associated with an increased mortality after AVR due to severe AS. As mentioned in the limitations it can be criticized that the cardiac damage detected, due to the partly serious comorbidities (e.g., moderate/severe MR, advanced chronic obstructive pulmonary disease), may not be entirely attributable to AS (22). For this reason, patients with such severe comorbidities were excluded in the present study.

In contrast, very common comorbidities, e.g., arterial hypertension (AHT) or CHD could not simply be excluded due to their high prevalence in developed countries as well as, in patients with AS. Although LV wall thickening is most commonly caused by AHT, it may also be caused by AS, edema and/or non-muscular depositions in storage diseases (23). AHT is one of the most relevant cardiovascular risk factors favoring comorbidities such as CHD and AF, which in turn may be associated with LVH (24). CHD was more prevalent in group 2 but did not reveal to be associated with the outcome of moderate AS patients. In contrast, patients with heart failure with significantly reduced LVEF and/or LVSVi were excluded because an increase in E/e' and/or TR_{Vmax} is usually observed due to the presence of heart failure *per se* rather than due to consequences of AS in these patients.

Predictors of outcome

Data on the outcome of patients with moderate AS have been inconsistent to some extent. Mortality rates range from 8 to 20% in moderate AS, which is consistent with the results of the present study (5, 7). In contrast, a more unfavorable prognosis with remarkably higher mortality rates was reported by other studies (6, 8). In the present study, the number of moderate AS patients who underwent AVR (15%) was significantly lower compared to other studies (19–28%) (5–8). Lower event and mortality rates in the present study could be explained by the preselected cohort, the intensive monitoring at a specialized outpatient department including optimal treatment of comorbidities and a shorter follow-up duration.

Transvalvular velocity, pressure gradient, and valve calcification

Previous studies showed that V_{max} and AV calcification were associated with outcomes in AS. Event-free survival was significantly lower in patients with moderate and/or severe calcification (described by visual assessment) compared to patients with only mild or no calcification (2, 5). In contrast, a recent prospective study has shown that PG_{mean} and moderate-to-severe AV calcification were not associated with increased mortality in moderate AS (8). The extent of

AV calcification was not assessed in the present study because visual assessment of the degree of AV calcification is associated with high interobserver variability (25). Computer tomography (CT) was not performed to avoid radiation exposure in predominantly asymptomatic patients. In addition, repeated CT examinations are difficult to integrate in the routine care of patients with moderate AS. Nevertheless, calcium scoring is recommended as a part of an integrated approach especially in AS with conflicting echocardiographic results (3, 26).

Left ventricular ejection fraction, stroke volume, and diastolic dysfunction

Ito et al. has shown that patients ($n = 696$) with moderate AS and reduced LVEF, and/or SVi, and elevated E/e' had a poorer prognosis, even if only E/e' was elevated and LVEF and SVi were preserved (27). The main challenge is that patients with AS usually have many comorbidities leading to pathophysiological changes (e.g., LV hypertrophy or increase of LV filling pressure). Despite a higher proportion of patients with CHD by Ito et al. (27) the distribution of comorbidities was similar to our study and the majority of patients had preserved LVEF (>80%) or SVi $\geq$ 35 ml/m^2 (>90%), respectively. Moreover, in both studies, a relevant diastolic dysfunction was considered only insofar as an increase of E/e' was present. In general, an elevation of E/e' can probably be attributed to ischemic or non-ischemic cardiomyopathy with reduced LVEF. However, more than 50% of the patients by Ito et al. (27) showed elevated E/e' values although LVEF and/or SVi were normal. Similarly, patients with significantly reduced LVEF and/or SVi were excluded in the preset study. Hence, both studies suggest that especially E/e' must be given high importance in risk stratification of patients with moderate AS. Nevertheless, more complementary data is needed in this area of moderate AS. Another study has proven that higher NT pro-BNP levels were associated with higher mortality rates in patients with moderate AS (28). In the present study no significant differences for NT pro-BNP levels were observed between both cohorts, mainly due to the smaller study population and because patients with significantly reduced LVEF and/or SVi were excluded. Although NT pro-BNP is not a specific biomarker to directly quantify AS severity, it is helpful for further risk stratification to verify cardiopulmonary congestion probably due to relevant AS (3, 28).

LDL-cholesterol and Lp(a) plasma levels

Low-density lipoprotein-cholesterol and Lp(a) are causally associated with atherosclerotic cardiovascular diseases (29, 30). Contrary, studies found out that the natural history of AS cannot directly be influenced by medical therapy (31). In a subanalysis of the ASTRONOMER trial higher Lp(a) plasma levels (>58.5 mg/dl; >140 nmol/l) were associated with a faster progression rate of V_{max} in mild-to-moderate AS (11). We also observed slightly higher progression rates of AVA and V_{max} in patients with elevated Lp(a) plasma levels although these differences did not reach statistical significance. Presumably, this might be due to the shorter follow-up period and the small number of patients with elevated Lp(a) plasma levels in our cohort (11).

Deformation imaging in moderate AS

Several studies have proven the prognostic value of GLS mainly by detecting subclinical LV dysfunction due to myocardial fibrosis (32, 33). Zhu et al. (33) reported significantly higher mortality rates in moderate AS with preserved LVEF and GLS > −15.2%. A difference of almost Δ −5% between both groups indicates that some patients had remarkably low GLS values. Further, patients with an GLS > −15.2% were older, had higher NT pro-BNP and more often CHD and/or myocardial infarction (33). A GLS decrease can probably be attributed to an increase of LV afterload even in moderate AS (32). Further, comorbidities and age contribute to an impairment of GLS (34, 35).

Although a GLS > −16.5% turned not out to be a predictor of outcome, a GLS decrease from baseline to follow-up indicates subclinical impairment of longitudinal LV deformation which can be attributed to AS progression. These considerations were supported by significantly lower GLS at follow-up in patients with ≥2 pathophysiological changes.

Limitations

Although we aimed to characterize our population of moderate AS patients as well as possible, it cannot be ruled out, that pathophysiological changes (e.g., left ventricular hypertrophy) may also be proportionally caused by comorbidities, e.g., arterial hypertension. Although patients with ischemic cardiomyopathy (CHD) or patients with non-ischemic cardiomyopathy with significantly reduced LVEF (<45%) were excluded, patients with AHT could not simply be excluded due to its high prevalence. Due to the strict exclusion criteria results of the present study cannot generally be applied to all patients with AS. The data analysis deliberately focused on the distinction between moderate AS patients with <2 and ≥2 pathophysiological changes, because there were no differences between subgroups with no, only 1, 2, or 3 pathophysiological changes, respectively. Death may be a competing event for AVR. However, the number of deaths were not different between both groups and cardiovascular deaths did only occur in four

patients. Further studies are needed to quantify the quality of life and physical capacity of patients with moderate AS.

Conclusion

The presence of ≥2 pathophysiological changes (LVH, increased E/e' and/or TR_{Vmax}) is a strong predictor of outcome in patients with moderate AS. Considering these changes may be useful for risk stratification, particularly for scheduling follow-up time intervals and deciding the timing of AVR, which is still challenging based on current recommendations.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Universität Leipzig, Medizinische Fakultät, Ethik-Kommission, Liebigstraße, 18, Leipzig. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SS and JK: substantial contribution to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work. MM, AH, BT, and UL: drafting the work, or revising it critically for important intellectual content provide approval for publication of the content. All authors agreed to be 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, resolved, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1101493/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Flow chart of patients with moderate aortic valve stenosis (AS) with assignment to the respective study cohorts.

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Racial disparities in characteristics and outcomes of patients undergoing mitral transcatheter edge-to-edge repair

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Background: There are scarce data regarding the post-mitral transcatheter edge-to-edger repair (TEER) course in different racial groups.

Objective: To assess the impact of race on outcomes following TEER for mitral regurgitation (MR).

Methods: This is a single-center, retrospective analysis of consecutive TEER procedures performed during 2013–2020. The primary outcome was the composite of all-cause mortality or heart failure (HF) hospitalizations along the first postprocedural year. Secondary outcomes included individual components of the primary outcome, New York Heart Association (NYHA) class, MR grade, and left ventricular mass index (LVMi).

Results: Out of 964 cases, 751 (77.9%), 88 (9.1%), 68 (7.1%), and 57 (5.9%) were whites, blacks, Asians, and Hispanics, respectively. At baseline, non-whites and blacks were younger and more likely be female, based in lower socioeconomic areas, not fully insured, diagnosed with functional MR, and affected by biventricular dysfunction. Intra-procedurally, more devices were implanted in blacks. At 1-year, non-whites (vs. whites) and blacks (vs. non-blacks or whites) experienced higher cumulative incidence of the primary outcome (32.9% vs. 22.5%, p =0.002 and 38.6% vs. 23.4% or 22.5%, p =0.002 or p =0.001, respectively), which were accounted for by hospitalizations in the functional MR sub-cohort (n =494). NYHA class improved less among blacks with functional MR. MR severity and LVMi equally regressed in all groups. White race (HR 0.62, 95% CI 0.39–0.99, p =0.047) and black race (HR 2.07, 95% CI 1.28–3.35, p =0.003) were independently associated with the primary outcome in functional MR patients only.

Conclusion: Mitral TEER patients of different racial backgrounds exhibit major differences in baseline characteristics. Among those with functional MR, non-whites and blacks also experience a less favorable 1-year clinical outcome.

KEYWORDS

mitral regurgitation, mitral transcatheter edge-to-edge repair, transcatheter mitral valve repair, MitraClip, racial disparities

Introduction

Transcatheter edge-to-edge repair (TEER) is an effective therapy for both functional (1) and primary (2) forms of mitral regurgitation (MR). Consequently, it has a central role in the management of these conditions according to the most recent North American (3) and European (4) practice guidelines. Lately, there has been increased recognition of the interaction between race/ethnicity and numerous disease states and therapies, including percutaneous structural heart interventions (5, 6). While not explicitly assessed in the pivotal randomized controlled trials, racial disparities affecting the mitral TEER arena were found in real-world reports that examined short-term, namely in-hospital, outcomes (7–10). Although plausible in theory, the association between race and longer-term course following mitral TEER has not been explored. Using a contemporary, large database, we evaluated the characteristics and 1-year clinical and echocardiographic outcomes of patients undergoing mitral TEER according to race. In addition, we assessed whether race was an independent predictor for mortality or heart failure (HF) hospitalizations.

Methods

Study population and outcomes

Our study is the product of an observational analysis of the Cedars-Sinai Medical Center (CSMC) registry of consecutive mitral TEER procedures performed on adult patients between January 1st, 2013 and December 31st, 2020. Constructed using an electronic medical chart platform (CS-Link™, Epic, Verona, WI, United States), the registry contained information regarding demographic background, medical conditions, therapeutics, electrocardiographic, laboratory and imaging studies, procedures, hospitalizations, and deaths – all as entered by medical providers and state authorities in real-time. While insurance coverage data were taken directly from patient files, income and level of education were estimated based on the 2020 United States (US) Census Report (11) according to address zip codes.

Patients included in the study underwent an isolated, first-ever mitral TEER. Formal assessment was carried per protocol at baseline, hospital discharge, 1-month and 1-year post-procedure. Stratification was made according to self-reported racial background. The primary outcome was the combined 1-year rate of all-cause mortality or HF hospitalizations. Secondary outcomes consisted of the separate endpoints of death and HF hospitalizations, as well as the achievement of New York Heart Association (NYHA) functional class I-II and/or MR grade of mild or moderate and less at 1-month and 1-year. Left ventricular mass index (LVMi) by echocardiography, as a surrogate of remodeling, was also assessed. One-month adverse events were defined as any of the following: cardiac tamponade, cardiac arrest, myocardial infarction, stroke, transient ischemic attack, Mitral Valve Academic Research Consortium (MVARC) bleeding, and vascular complications. All medical diagnoses were made in accordance with accepted criteria, such as those of the MVARC (12).

This project complied with the Declaration of Helsinki and was approved by the Cedars-Sinai Institutional Review Board (IRB), which waived the need for informed consent.

Procedural and echocardiographic aspects

Mitral TEER followed a Heart Team discussion that included at least one interventional cardiologist, one cardiac surgeon, one echocardiologist, and one HF specialist. Patient-, disease-, and institution-related aspects, as well as perceived risks and benefits according to the best scientific evidence at the time, were all considered in the decision process. All procedures used the MitraClip™ system (Abbott Vascular Inc., Santa Clara, CA, United States) and were performed under general anesthesia, *via* a femoral venous access, and with echocardiographic and fluoroscopic guidance. Monitoring by simultaneous right heart catheterization (RHC) was utilized as well.

Echocardiograms were carried out pre-, intra-, and post-procedure using the EPIQ ultrasound system (Philips, Amsterdam, Netherlands) and the PICOM365 software for post-test processing (SciImage, Los Altos, CA, United States), and conformed to the relevant American Society of Echocardiography (ASE) guidelines (13–15). MR severity was assessed using integration of qualitative and semi-quantitative measures, whenever applicable. MR Etiology was determined according to the valve leaflet morphology, as visualized on the intraprocedural transesophageal echocardiogram (TEE). Pulmonary venous flow pattern (PVFP) was evaluated on TEE by a pulsed-wave (PW) Doppler beam placed within 1 cm of the PV ostia. Normalization in the PV flow after clip deployment required the emergence of a peak systolic (S) to peak diastolic (D) velocity ratio of $\geq$1 on either side. LVMi calculation was applied on transthoracic echocardiograms (TTEs) using the ASE formula. Global right ventricular (RV) function was determined by qualitative assessment.

Statistical analysis

The study cohort was split into 4 groups based on race – white, black, Asian, and Hispanic. For each group, variables were reported as frequencies and percentages, medians and interquartile ranges (IQR), or means and standard deviations, as appropriate. Inter-group comparisons incorporated two racial groups at a time (mostly whites vs. non-whites, blacks vs. non-blacks, Asians vs. non-Asians, Hispanics vs. non-Hispanics, and whites vs. blacks) and utilized Pearson's Chi-Square, Fisher's exact, Student's *t*, or Mann–Whitney *U* tests. Evaluation of change over time in variables within each group was based on paired-sample t, Wilcoxon, or McNemaer tests.

The risk for death and/or HF hospitalizations as a function of race was graphically displayed according to the Kaplan–Meier method, with comparisons of cumulative event-free survival times across strata by the Log-Rank test. To identify associations between baseline and procedural factors and the primary outcome, a multivariable Cox regression analysis was employed that integrated variables demonstrating a value of p of <0.1 on a preliminary univariable model.

Abbreviations: BNP, B-type natriuretic peptide; HF, Heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, Left ventricular ejection fraction; MR, Mitral regurgitation; NYHA, New York Heart Association; TEER, Transcatheter edge-to-edge repair.

Parameters included in this first step were chosen based their perceived prognostic implication, as judged by clinical reasoning, published data (16, 17), and results of the comparison between the various racial groups.

Lastly, descriptive and survival analyses were repeated on two matched cohorts that were created by means of propensity score matching – the first comparing whites and non-whites and the second comparing blacks and non-blacks. In each cohort, cases were matched according to the probability of belonging to either white or black racial group, in a 1:1 fashion, and by using a match tolerance of ≤0.1. A multivariable binary logistic regression was employed for calculating this probability, which included baseline parameters of perceived and/or proved prognostic implication regarding the primary outcome: age, sex, regular/full insurance, median yearly income and percentage of adults with academic degrees according to area of residence, chronic obstructive pulmonary disease (COPD), peripheral arterial disease (PAD), blood hemoglobin level, estimated glomerular filtration rate, no use of renin angiotensin system (RAS) inhibitors, high-dose diuretics (i.e., ≥80 mg of furosemide per day or use of ≥2 diuretics excluding mineralocorticoid receptor antagonists (MRAs)), NYHA class, functional MR, left ventricular ejection fraction (LVEF), and low tricuspid annular plane systolic excursion (TAPSE) to pulmonary arterial systolic pressure (PASP) ratio according to the total cohort's median.

Cases with missing data were censored from the relevant analyses. A two-sided value of p of <0.05 defined statistical significance. All analyses were performed using SPSS, version 24 (IBM Corporation, Armonk, NY, United States).

Results

Baseline characteristics of the study population

A total of 964 patients were identified that underwent an isolated, first-time mitral TEER at CSMC between 2013 and 2020. Of these, 751 (77.9%), 88 (9.1%), 68 (7.1%), and 57 (5.9%) were whites, blacks, Asians, and Hispanics, respectively. Among patients aged 65 or 75 years and over, the figures were 667 (81.3%) or 503 (84.7%) for whites, 51 (6.2%) or 27 (4.5%) for blacks, 60 (7.3%) or 41 (6.9%) for Asians, and 42 (5.1%) or 23 (3.9%) for Hispanics. The follow-up duration was 468 (IQR, 106–1,034) days. Baseline, 1-month, and 1-year echocardiograms were performed on day 19 (IQR, 5–46) before, day 33 (IQR, 29–36) after, and day 370 (IQR, 351–403) following the intervention, respectively.

Pre-procedural clinical characteristics of the four racial groups are summarized in Table 1. A significant inter-racial variation in demographics and comorbidities was evident. Notably, whites were the oldest [median age 80 (IQR, 72–87) years] and most often male (n = 469, 62.5%), as well as the most fully insured (n = 677, 90.4%), highest paid, and most academically educated group. In blacks, on the other hand, the median age, proportion of males to females, full coverage percentage, median household income, and fraction of adults with academic degrees were lowest [67 (IQR, 58–77) years, 40 (45.5%) males, 67 (76.1%) with regular insurance]. Blacks were more likely to have a cardiac implantable electronic device (CIED) or non-ischemic cardiomyopathy. Indices of functional and symptomatic status, including the NYHA class, the Kansas City Cardiomyopathy Questionnaire (KCCQ) 12 score, and the 6-min walk test distance, were comparable; B-type natriuretic peptide (BNP) levels, however, were highest within the black group and lowest in whites. Surgical and percutaneous risk were not significantly different. While most of the medical treatment prior to mitral TEER was comparable, whites were prescribed less MRAs and more oral anticoagulants and blacks received more often a hydralazine-nitrates combination.

Echocardiographic parameters are presented in detail in Table 2. Functional MR was observed more commonly in blacks (n = 71, 80.7%) and Hispanics (n = 40, 70.2%), while primary MR – in whites (n = 399, 53.1%). Apart from effective regurgitant orifice area (EROA), which was lowest in blacks, most indices of MR severity, as well as left atrial volume index (LAVi), were comparable across the various racial groups. Blacks displayed the lowest LVEF and the highest prevalence of ≥moderate RV dysfunction. By contrast, whites exhibited the highest LVEF and RV-pulmonary arterial (PA) coupling values and harbored the lowest frequencies of significant RV dysfunction and tricuspid regurgitation (TR). Baseline LVMi was lower among whites and higher among blacks and Hispanics.

Procedural details and short-term results

Supplementary Table 1 summarizes aspects pertaining to the mitral TEER procedure itself and its immediate and short-term results. Whites were less likely to present to the intervention with acute decompensated heart failure or to require hemodynamic support. Intra-procedurally, black patients had more devices implanted. Clipping was mostly applied to the A2P2 segment, with no major differences in total procedure or fluoroscopy times across the races. While immediate reduction in MR severity to mild or less and PVFP normalization on either side were similarly achieved in the four racial groups, fewer black and Asian patients maintained an up to mild MR upon hospital discharge (n = 61, 69.3% and n = 45, 69.2%, respectively). Further, blacks experienced the highest rate of in-hospital blood transfusion or any 1-month adverse events (n = 17, 19.3%), the lengthiest duration of hospitalization [3 (IQR, 1–9) days], and the highest 1-month transmitral mean pressure gradient (TMPG) [5 (IQR, 3–6) mmHg].

Mortality and heart failure hospitalizations

By the end of the first postprocedural year, the primary outcome, a composite of all-cause mortality or HF hospitalizations, was experienced by a total of 239 (24.8%) patients. Considering race, it occurred earlier and more frequently in non-whites vs. whites (n = 70, 32.9% vs. n = 169, 22.5%, p = 0.002), blacks vs. non-blacks (n = 34, 38.6% vs. n = 205, 23.4%, p = 0.002), and blacks vs. whites (p = 0.001) (Table 3; Figure 1). Event rates in Asians (n = 18, 26.5%) and Hispanics (n = 18, 31.6%) were similar to the ones in non-Asians (n = 221, 24.7%, p = 0.740) and non-Hispanics (n = 221, 24.4%, p = 0.221), respectively. Notably, the differences in the primary outcome incidence were accounted for by hospitalizations only (Supplementary Figures 1, 2). According to a multivariable analysis, no race was found to independently predict the primary outcome, although black race did impose a trend toward a higher risk (HR 1.61, 95% CI 0.93–2.78, p = 0.088) (Supplementary Tables 2, 4).

TABLE 1 Baseline clinical characteristics of the total cohort according to race.

					p-value				
	Whites (*N* =751)	Blacks (*N* =88)	Asians (*N* =68)	Hispanics (*N* =57)	Whites vs. non-whites	Blacks vs. non-blacks	Asians vs. non-Asians	Hispanics vs. non-Hispanics	Whites vs. blacks
Demographic details									
Age (years)	80 (72–87)	67 (58–77)	78 (68–84)	73 (63–82)	**<0.001**	**<0.001**	0.291	**0.002**	**<0.001**
Sex Male	469 (62.5)	40 (45.5)	37 (54.4)	32 (56.1)	**0.003**	**0.004**	0.333	0.544	**0.002**
Insurance									
None	5 (0.7)	0 (0.0)	0 (0.0)	1 (1.8)	0.746	0.436	0.498	0.264	0.442
Low-income	67 (8.9)	21 (23.9)	14 (20.6)	24 (42.1)	**<0.001**	**0.002**	0.058	**<0.001**	**<0.001**
Regular / full	677 (90.4)	67 (76.1)	54 (79.4)	32 (56.1)	**<0.001**	**0.004**	0.088	**<0.001**	**<0.001**
Median yearly household income* (K USD)	84.9 (64.4–103.0)	58.3 (52.3–72.2)	78.9 (59.3–97.8)	70.6 (55.1–95.1)	**<0.001**	**<0.001**	0.334	**0.018**	**<0.001**
Percentage of adults with academic degree*	44.0 (28.1–61.9)	24.0 (16.0–35.0)	39.3 (27.0–48.1)	28.8 (18.9–46.4)	**<0.001**	**<0.001**	0.174	**<0.001**	**<0.001**
Comorbidities									
Obesity (Body mass index ≥30 kg/m^2)	127 (16.9)	21 (23.9)	6 (8.8)	12 (21.1)	0.633	0.083	0.057	0.429	0.105
Diabetes mellitus	175 (23.4)	28 (31.8)	27 (39.7)	25 (43.9)	**<0.001**	0.239	**0.011**	**0.002**	0.081
Hypertension	627 (83.5)	75 (86.2)	49 (72.1)	50 (87.7)	0.627	0.428	**0.011**	0.345	0.515
Smoking history	32 (4.3)	3 (3.4)	0 (0.0)	3 (5.3)	0.341	0.783	0.103	0.488	0.702
Previous MI, PCI, or CABG	330 (43.9)	26 (29.5)	28 (41.2)	33 (57.9)	0.421	**0.006**	0.719	**0.021**	**0.010**
Prior stroke or transient ischemic attack (TIA)	99 (13.2)	13 (14.8)	13 (19.1)	4 (7.0)	0.733	0.688	0.150	0.146	0.678
Peripheral arterial disease (PAD)	60 (8.0)	8 (9.1)	4 (5.9)	4 (7.0)	0.816	0.662	0.524	0.801	0.723
Atrial fibrillation / flutter	424 (56.5)	33 (37.5)	31 (45.6)	26 (45.6)	**<0.001**	**0.002**	0.185	0.229	**0.001**
Chronic obstructive pulmonary disease (COPD)	101 (13.4)	17 (19.3)	6 (8.8)	4 (7.0)	0.769	0.080	0.262	0.151	0.134
Anemia+	459 (61.1)	63 (71.6)	41 (60.3)	44 (77.2)	**0.026**	0.079	0.636	**0.022**	0.055
Stage ≥III chronic kidney disease	534 (73.0)	61 (70.1)	59 (88.1)	39 (69.6)	0.423	0.443	**0.005**	0.492	0.575
Heart failure indices									
New York Heart Association (NYHA) Class									
II	53 (7.1)	3 (3.4)	4 (5.9)	1 (1.8)	0.081	0.238	0.876	0.254	0.195
III	310 (41.4)	32 (36.4)	24 (35.3)	30 (52.6)	0.813	0.346	0.315	0.068	0.375
IV	385 (51.4)	53 (60.2)	40 (58.8)	26 (45.6)	0.235	0.118	0.263	0.299	0.111
Kansas city cardiomyopathy questionnaire 12 score	39.1 (18.8–62.0)	36.5 (13.0–52.1)	38.0 (17.7–69.3)	26.3 (6.8–51.0)	0.092	0.370	0.751	**0.033**	0.279
6-Minute walk test distance (m)	244 (122–335)	183 (61–305)	274 (187–366)	219 (122–354)	0.865	0.092	0.106	0.803	0.106
Serum B-type natriuretic peptide (pg/mL)	466 (221–1,104)	1,180 (494–2,088)	615 (284–1,470)	486 (255–1,553)	**<0.001**	**<0.001**	0.219	0.535	**<0.001**
Risk status									
STS score for mitral valve repair	5.5 (3.0–8.7)	5.9 (2.1–9.0)	6.2 (3.7–10.4)	5.5 (2.1–9.8)	0.929	0.313	0.136	0.828	0.365

(Continued)

TABLE 1 (Continued)

					p-value				
	Whites (*N* =751)	Blacks (*N* =88)	Asians (*N* =68)	Hispanics (*N* =57)	Whites vs. non-whites	Blacks vs. non-blacks	Asians vs. non-Asians	Hispanics vs. non-Hispanics	Whites vs. blacks
MitraScore	3 (2–4)	4 (3–4)	3 (2–4)	4 (3–4)	0.622	0.256	0.378	0.663	0.280
Treatment									
Medications									
Beta Blockers	514 (68.4)	68 (77.3)	42 (61.8)	43 (75.4)	0.344	0.085	0.169	0.292	0.089
Renin angiotensin system (RAS) inhibitors	367 (48.9)	49 (55.7)	33 (48.5)	27 (47.4)	0.552	0.25	0.985	0.754	0.226
Mineralocorticoid receptor antagonists (MRAs)	135 (18.0)	29 (33.0)	12 (17.6)	18 (31.6)	**0.002**	**0.002**	0.597	**0.026**	**0.001**
Loop diuretics									
Frequency	557 (74.2)	73 (83.0)	55 (80.9)	39 (68.4)	0.207	0.074	0.253	0.229	0.071
Furosemide-equivalent dose (mg/day)	40 (20–80)	40 (40–80)	40 (40–40)	60 (40–80)	0.085	0.067	0.086	**0.006**	0.058
Anti-arrhythmics	159 (21.2)	20 (22.7)	14 (20.6)	11 (19.3)	0.982	0.710	0.901	0.79	0.741
Hydralazine + nitrates	16 (2.1)	7 (8.0)	1 (1.5)	2 (3.5)	**0.039**	**0.006**	0.533	0.685	**0.006**
Oral anticoagulants	355 (47.3)	35 (39.8)	30 (44.1)	16 (28.1)	**0.017**	0.281	0.849	**0.007**	0.182
Cardiac implantable electronic device (CIED)									
Total	237 (31.6)	49 (55.7)	16 (23.5)	17 (29.8)	0.057	**<0.001**	0.082	0.589	**<0.001**
Pacemaker	95 (12.6)	9 (10.2)	5 (7.4)	3 (5.3)	0.061	0.669	0.265	0.123	0.514
Implantable cardioverter defibrillator (ICD)	40 (5.3)	17 (19.3)	2 (2.9)	6 (10.5)	**0.001**	**<0.001**	0.311	0.268	**<0.001**
CRT/defibrillator (CRT/D)	102 (13.6)	23 (26.1)	9 (13.2)	8 (14.0)	0.059	**0.002**	0.718	0.879	**0.002**

Data are presented as number (percentage) or median (interquartile range), where appropriate. Figures in bold denote statistical significance. *Per zip code. + Anemia was defined as a blood hemoglobin of <13 mg/dL in men or < 12 mg/dL in women. CABG, coronary bypass artery grafting; CRT, cardiac resynchronization therapy; GFR, glomerular filtration rate; MI, myocardial infarction; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons; USD, United States Dollars.

Functional status

One-year NYHA class was significantly improved compared to baseline in all groups. However, the magnitude of change was modest in blacks vs. non-blacks or whites (−1.1 ± 0.7 vs. −1.4 ± 0.9 or − 1.4 ± 0.9 classes, $p = 0.005$ and $p = 0.008$, respectively) and more prominent in Asians vs. non-Asians (−1.7 ± 0.7 vs. −1.4 ± 0.9 classes, $p = 0.021$) (Table 3). Consequently, whites and non-blacks exhibited a better functional status at 1 year compared to non-whites ($p = 0.045$) and blacks ($p < 0.001$), respectively (Figure 2). Of note, the difference between non-blacks and blacks was evident also at 1-month ($p = 0.015$).

Mitral regurgitation severity and reverse remodeling

MR of up to mild or up to moderate degree was equally maintained in the four racial groups at the 1-month and 1-year marks (Table 3). Nevertheless, 1-month MR was generally more severe in non-whites vs. whites ($p = 0.012$) and in blacks vs. non-blacks ($p = 0.049$) (Figure 3). Concurrently, 1-year LVMi proved lower in whites vs. non-whites (110.0 (IQR, 90.1–133.9) vs. 125.8 (IQR, 103.6–152.0) gr/m^2, $p = 0.001$) and higher in Hispanics vs. non-Hispanics (140.5 (IQR, 116.4–165.8) vs. 111.0 (IQR, 91.1–137.1) gr/m^2, $p = 0.001$) (Table 3). The relative reduction (i.e., improvement) in LVMi from baseline and over the span of a year, however, was unaffected by race.

Overall, whites ($n = 324$, 90%) and non-blacks ($n = 377$, 90.0%) enjoyed higher rates of freedom from either >mild MR or a NYHA class III-IV by 1-year compared to blacks ($n = 29$, 78.4%) ($p = 0.049$ for both comparisons) (Table 3).

Subgroup analysis for functional and primary mitral regurgitation

Most race-related differences in baseline and procedural features, as observed in the entire cohort, were evident within the functional MR subgroup, which included 494 (51.2%) of the study patients

TABLE 2 Baseline echocardiographic data of the total cohort according to race.

					P-value				
	Whites (*N* =751)	Blacks (*N* =88)	Asians (*N* =68)	Hispanics (*N* =57)	Whites vs. non-whites	Blacks vs. non-blacks	Asians vs. non-Asians	Hispanics vs. non-Hispanics	Whites vs. blacks
Mitral valve									
Mitral regurgitation etiology					**<0.001**	**<0.001**	0.333	**0.003**	**<0.001**
Functional	352 (46.9)	71 (80.7)	31 (45.6)	40 (70.2)					
Primary	399 (53.1)	17 (19.3)	37 (54.4)	17 (29.8)					
Mitral regurgitation severity									
Moderate–severe	152 (20.3)	14 (15.9)	5 (7.4)	12 (21.1)	0.058	0.429	**0.011**	0.693	0.324
Severe	589 (78.8)	73 (83.0)	63 (92.6)	44 (77.2)	0.068	0.482	**0.007**	0.570	0.369
Mitral regurgitation PISA EROA (cm^2)	0.37 (0.27–0.50)	0.34 (0.25–0.40)	0.38 (0.27–0.42)	0.30 (0.22–0.43)	**0.020**	0.260	0.543	**0.044**	0.167
Mitral regurgitation PISA RVol (mL)	51.8 (36.9–69.5)	48.4 (36.8–60.8)	50.2 (41.0–66.8)	44.8 (31.2–56.1)	0.119	0.387	0.813	0.053	0.306
Transmitral mean pressure gradient (TMPG) (mmHg)	3 (2–4)	3 (2–4)	3 (2–4)	3 (2–4)	0.396	0.595	0.174	0.525	0.544
≥Moderate mitral annulus calcification (MAC)	83 (11.1)	4 (4.5)	5 (7.4)	5 (8.8)	0.055	0.071	0.441	0.738	0.058
Left heart									
Left ventricular ejection fraction (LVEF) (%)	55 (34–64)	29 (18–45)	58 (33–66)	40 (25–60)	**<0.001**	**<0.001**	0.122	**0.041**	**<0.001**
Left ventricular end-systolic diameter (LVESD) (cm)	3.7 (3.0–4.8)	5.3 (3.9–6.2)	3.8 (3.0–4.9)	4.2 (3.4–5.6)	**<0.001**	**<0.001**	0.398	0.054	**<0.001**
Left ventricular mass index, ASE formula (gr/m^2)	124.7 (98.3–151.3)	131.3 (110.4–153.6)	130.0 (107.4–168.8)	136.7 (111.5–158.8)	**<0.001**	**0.047**	0.099	**0.041**	**0.019**
Left atrial volume index (LAVi) (cm^3/m^2)	57.2 (43.2–75.0)	52.0 (40.2–72.8)	56.8 (46.1–71.8)	60.5 (50.1–75.2)	0.916	0.147	0.897	0.140	0.199
Right heart									
≥Moderate right ventricular dysfunction	115 (17.9)	26 (34.2)	15 (24.6)	13 (22.8)	**0.003**	**0.001**	0.380	0.617	**0.001**
≥Moderate–severe tricuspid regurgitation	144 (19.3)	25 (28.4)	23 (34.3)	24 (42.1)	**<0.001**	0.164	**0.016**	**<0.001**	**0.043**

(Continued)

TABLE 2 (Continued)

					P-value				
	Whites (*N* =751)	Blacks (*N* =88)	Asians (*N* =68)	Hispanics (*N* =57)	Whites vs. non-whites	Blacks vs. non-blacks	Asians vs. non-Asians	Hispanics vs. non-Hispanics	Whites vs. blacks
Right ventricular (RV)-pulmonary arterial (PA) coupling									
Tricuspid annular plane systolic excursion (TAPSE) (mm)	17 (14–20)	16 (14–22)	17 (13–20)	15 (13–20)	0.698	0.716	0.942	0.259	0.809
Pulmonary arterial systolic pressure (PASP) (mmHg)	44 (34–57)	53 (35–64)	45 (33–60)	48 (37–63)	**0.006**	**0.022**	0.573	0.149	**0.013**
TAPSE/PASP (mm/mmHg)	0.39 (0.27–0.56)	0.34 (0.23–0.50)	0.35 (0.29–0.54)	0.31 (0.22–0.44)	**0.018**	0.129	0.925	**0.025**	0.085

Data are presented as number (percentage) or median (interquartile range), where appropriate. Figures in bold denote statistical significance. ASE, American Society of Echocardiography; EROA, effective regurgitant orifice area; PISA, proximal isovelocity surface area; RVol, regurgitant volume.

(Supplementary Tables 3–5). However, RV dysfunction at baseline, hemodynamic status at presentation, and MR severity at hospital discharge were similar in the four racial groups. Hospitalization was still the lengthiest in blacks, but not statistically significant.

As in the total cohort, non-whites (vs. whites) and blacks (vs. non-blacks or whites) experienced higher cumulative incidence of the primary outcome, which again were accounted for by HF hospitalization events (Supplementary Table 6 and Supplementary Figures 3–5). Also, blacks faced less improvement in NYHA functional class (Supplementary Table 6 and Supplementary Figure 6). Other than a lower LVMi in whites vs. non-whites, no differences were noted in echocardiographic measures at 1 year (Supplementary Table 6 and Supplementary Figure 7). The combined 1-year rates of NYHA class I-II or MR of up to mild degree were non-significantly highest among whites and Asians and lowest in blacks and Hispanics.

Within the primary MR sub-cohort, there were fewer differences in baseline characteristics between the races (Supplementary Tables 7, 8). Still, whites were the oldest, most fully insured, highest-paid, most educated, and least diabetic. Also, they were less likely to present with acute HF or hemodynamic instability. Blacks had the lowest LVEF and highest PASP values, received more clips per procedure, and experienced the lowest rate of up to mild MR at discharge (Supplementary Table 9).

Overall, 1-year clinical and echocardiographic outcomes, as well as periprocedural adverse events, were non-different across different racial groups with primary MR (Supplementary Table 10 and Supplementary Figures 8–12). Notably, the primary MR subgroup as a whole exhibited significantly fewer primary outcome events compared to the functional MR subgroup (78/470, 16.6% vs. 161/494, 32.6%, $p < 0.001$). While 1-month MR was generally less severe in whites (vs. non-whites) and in non-blacks (vs. blacks), up to moderate MR was equally achieved.

A Cox regression analysis performed separately in each of the two main MR etiologic subgroups identified white race as an independent protective factor and black race as an independent risk factor for the primary outcome – but only in patients with functional MR (HR for white race 0.62, 95% CI 0.39–0.99, $p = 0.047$; HR for black race 2.07, 95% CI 1.28–3.35, $p = 0.003$) (Supplementary Table 2 and Table 4). Conversely, no race was associated with the risk for the combined endpoint of death or HF hospitalizations among primary MR patients.

Propensity score matching

Within the 2 matched cohorts – one with 147 patients of either white or non-white race and one with 65 patients of either black or non-black race – most inter-racial differences in baseline characteristics and periprocedural aspects vanished (Supplementary Tables 11–14). Yet, non-whites (vs. whites) and blacks (vs. non-blacks) again experienced higher cumulative incidence of all-cause mortality, HF hospitalizations, and the composite of both, reaching statistical significance for HF hospitalizations and in blacks also for the primary outcome (Supplementary Table 14). Moreover, these two subgroups exhibited numerically lower rates of non-significant MR following TEER. After multivariable analysis, black race remained associated with a higher risk for the primary outcome in the blacks vs. non-blacks matched cohort (HR 1.73, 95% CI 1.02–3.33, $p = 0.044$), while in the whites vs. non-whites matched cohort its presence imposed a trend toward worse outcome (HR 1.84, 95% CI 0.99–3.42, $p = 0.055$); Non-white race did not demonstrate an independent predictive significance anymore (Supplementary Table 15).

Discussion

Our study evaluated the characteristics and 1-year outcomes of patients referred to mitral TEER according to their race. Based on a large, contemporary, real-world registry, we made the following observations (Figure 4, CENTRAL ILLUSTRATION): (1) Non-whites were under-represented in the cohort; (2) Pre-, intra-, and

TABLE 3 Outcomes and trends following mitral transcatheter edge-to-edge repair in the total cohort according to race.

					P-value				
	Whites (*N* =751)	Blacks (*N* =88)	Asians (*N* =68)	Hispanics (*N* =57)	Whites vs. non-whites	Blacks vs. non-blacks	Asians vs. non-Asians	Hispanics vs. non-Hispanics	Whites vs. blacks
Primary outcome									
All-cause mortality or heart failure hospitalizations at 1-year	169 (22.5)	34 (38.6)	18 (26.5)	18 (31.6)	**0.002**	**0.002**	0.740	0.221	**0.001**
Event-free survival time at 1-year (days)	300 ± 5	252 ± 16	286 ± 17	285 ± 17	**0.003**	**0.002**	0.591	0.406	**0.001**
Secondary outcomes									
Clinical									
All-cause mortality at 1-year	84 (11.2)	15 (17.0)	8 (11.8)	8 (14.0)	0.181	0.120	0.965	0.613	0.107
Heart failure hospitalizations at 1-year	101 (13.4)	26 (29.5)	13 (19.1)	13 (22.8)	**<0.001**	**<0.001**	0.447	0.140	**<0.001**
New York Heart Association Class ≤II									
At 1-month	448 (80.1)	46 (70.8)	35 (68.6)	36 (83.7)	0.075	0.102	0.069	0.406	0.078
At 1-year	294 (78.4)	22 (56.4)	32 (91.4)	19 (67.9)	0.194	**0.001**	**0.014**	0.230	**0.002**
Echocardiographic									
Mitral regurgitation severity ≤mild									
At 1-month	344 (64.1)	33 (53.2)	26 (53.1)	25 (62.5)	0.059	0.126	0.171	0.969	0.094
At 1-year	158 (53.7)	17 (53.1)	12 (42.9)	12 (46.2)	0.322	0.929	0.295	0.511	0.947
Mitral regurgitation severity ≤moderate									
At 1-month	496 (94.5)	53 (89.8)	48 (98.0)	38 (95.0)	0.795	0.133	0.513	0.855	0.151
At 1-year	274 (93.2)	29 (90.6)	26 (92.9)	23 (88.5)	0.435	0.719	0.962	0.425	0.483
Left ventricular mass index (gr/m^2)									
At 1-month	115.3 (93.5–145.7)	127.9 (105.4–176.5)	139.0 (109.5–158.6)	122.3 (106.8–150.7)	**<0.001**	**0.030**	**0.026**	0.269	**0.015**
At 1-year	110.0 (90.1–133.9)	125.7 (94.9–146.8)	120.6 (94.4–146.5)	140.5 (116.4–165.8)	**0.001**	0.192	0.521	**0.001**	0.096
Combined clinical and echocardiographic									
New York Heart Association Class ≤II or mitral regurgitation severity ≤mild									
At 1-month	505 (92.0)	54 (84.4)	40 (80.0)	39 (92.9)	**0.011**	0.080	**0.020**	0.788	**0.042**
At 1-year	324 (90.0)	29 (78.4)	32 (100.0)	21 (77.8)	0.202	**0.049**	**0.037**	0.102	**0.049**
Trends									
Absolute change in New York Heart Association Class									

(Continued)

TABLE 3 (Continued)

					P-value				
	Whites (*N* =751)	Blacks (*N* =88)	Asians (*N* =68)	Hispanics (*N* =57)	Whites vs. non-whites	Blacks vs. non-blacks	Asians vs. non-Asians	Hispanics vs. non-Hispanics	Whites vs. blacks
At 1-month	−1.4 ± 0.8	−1.3 ± 0.8	−1.5 ± 0.8	−1.5 ± 0.8	0.704	0.142	0.768	0.429	0.171
At 1-year	−1.4 ± 0.9	−1.1 ± 0.7	−1.7 ± 0.7	−1.3 ± 0.9	0.424	**0.005**	**0.021**	0.485	**0.008**
P-value for 1-year vs. baseline	**<0.001**	**<0.001**	**<0.001**	**<0.001**	NA	NA	NA	NA	NA
Relative change in left ventricular mass index (%)									
At 1-month	−2.7 (−19.6–14.5)	5.2 (−10.7–25.8)	−1.6 (−19.1–15.7)	−3.8 (−22.6–13.0)	0.251	**0.018**	0.966	0.430	**0.021**
At 1-year	−4.3 (−21.7–17.3)	−0.2 (−20.9–22.8)	−16.3 (−30.5– −2.7)	0.1 (−17.2–27.5)	0.747	0.744	0.073	0.355	0.785

Data are presented as number (percentage), median (interquartile range), or mean ± standard deviation, where appropriate. Figures in bold denote statistical significance. NA, not applicable.

post-procedural features, including demographics, comorbidities, baseline echocardiographic parameters, hemodynamic status at presentation, number of deployed clips, hospitalization length, and 1-month course differed substantially between races; (3) Non-whites (vs. whites) and blacks (vs. non-blacks or whites) experienced similar death rates but earlier, more frequent HF hospitalizations during the first postprocedural year; (4) One-year functional status was worse in blacks (vs. non-blacks) and in non-Asians (vs. Asians), however MR severity and reverse LV remodeling by TTE were comparable across races; (5) Non-white and black races independently imposed a higher risk for the combined outcome of 1-year all-cause mortality or HF hospitalizations; and (6) The prognostic implication and predictive ability of racial background were confined to the functional MR sub-cohort.

To the best of our knowledge, this is the first study to report on mitral TEER outcomes in various racial groups beyond the index hospitalization. Furthermore, it is among the first to explicitly consider in this context all four major races residing in the US, particularly Hispanics, who are increasingly being recognized as a distinct racial/ethnic group (18, 19). While previous studies (7–9) relied on an administrative, billing-focused database – the National Inpatient Sample (NIS) – we used a clinical, patient-level registry that was prospectively constructed by physicians, thus reinforcing clinical relevance which allowed for a pioneering MR etiology-based subgroup analysis. Also, our cohort consisted of patients undergoing an isolated mitral TEER for the first time and in one center, thus eliminating possible interactions with non-mitral procedures and with institution and operator-related factors, all of which may have been presented in the earlier nationwide works.

As previously shown in both mitral TEER (8, 9) and non-mitral TEER populations (5, 6), our findings demonstrated a discrepancy between racial segmentation of the general public and that of an interventional cardiology cohort, which further expanded as patients aged. While non-white individuals comprised 22.1% of patients who underwent mitral TEER at our institution between 2013 and 2020, their percentage among those aged ≥65 or ≥75 years was 18.7% or 15.3%, respectively. At the same time, the national percentage of non-whites steadily rose from 36.3% in 2010 to 42.2% in 2020 (19). Moreover, within the senior US population, non-whites constituted 22.8 and 24.0% of ≥65 and ≥75-year-old individuals in 2016, respectively (20), and by 2019, as high as 24% of elderly Americans were non-white (21). Compared to the State of California, in which (non-Hispanic) whites are a minority (19), our registry probably under-represented non-whites even further. As the prevalence of ≥moderate MR has been shown to be comparable between races (22), the disparities in mitral TEER utilization in the present study could have reflected gaps in access to medical care, and specifically high-volume centers as ours (23). Consistent with this assumption were the significant inter-racial differences in insurance coverage, as well as income and level of academic education, making whites the highest-paid, most educated and fully-insured group, and blacks and Hispanics – the least ones. Such differences, too, have been previously observed (24).

Further consistent with published data (6–9, 22, 25), blacks treated at our institution were relatively younger and more likely to be women compared to patients of other racial origins. As in those previous reports, they had an overall higher burden of comorbidities and biventricular dysfunction and suffered more commonly from functional MR. The earlier presentation, worse medical condition, and increased prevalence of functional MR within the black group possibly mirrored and accounted for one another. Considering the female predominance observed in blacks undergoing TEER, they could also have been brought about by prior peripartum cardiomyopathy, which is known to primarily affect young black women, and which may transform later in life to a chronic HF condition. Although not directly explored in our registry, and not clearly associated with outcomes according to a Cox regression model, non-ischemic cardiomyopathy did prove more common among blacks, and particularly in black females with functional MR (28/42, 66.7% vs. 75/90, 45.5%, $p = 0.014$). Apart from representing genuine medical interactions, the higher disease burden experienced by blacks may have implied a delay in diagnosis and treatment, which could again reflect inequality in access to medical care. While reasonable, this last notion remained hypothetical as our registry did not include information about the timing of mitral TEER in relation to the emergence of overt indications for intervention.

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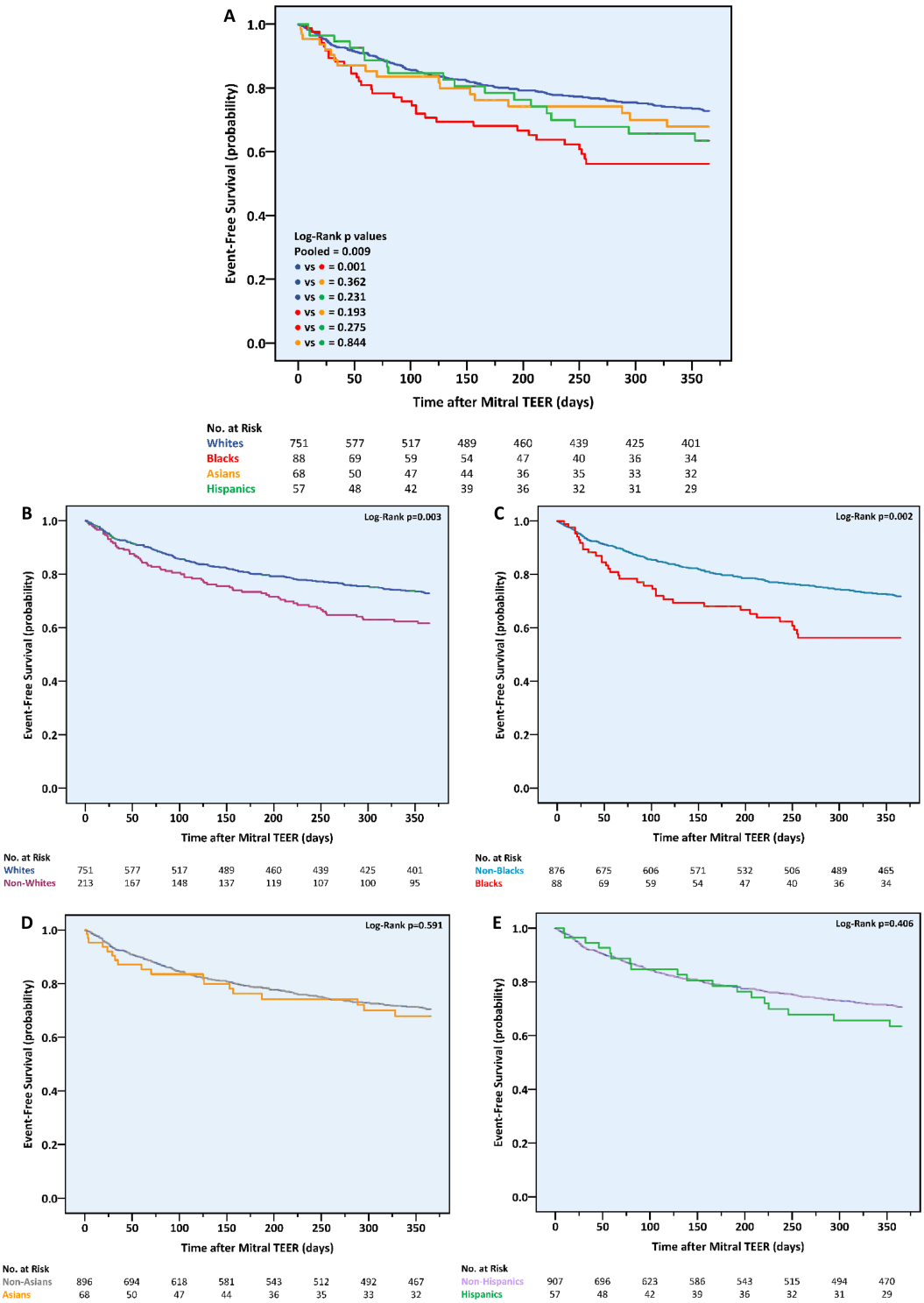

FIGURE 1
One-year cumulative incidence of the combined outcome of all-cause mortality or heart failure hospitalizations following mitral transcatheter edge-to-edge repair according to race. **(A)** All races, **(B)** whites vs. non-whites, **(C)** blacks vs. non-blacks, **(D)** Asians vs. non-Asians, **(E)** Hispanics vs. non-Hispanics. TEER, transcatheter edge-to-edge repair.

Adding to present-day evidence of a higher incidence of in-hospital complications (9) in non-whites and lower odds of next-day discharge (10) in black patients following mitral TEER, our study demonstrated a more complex course affecting these racial groups up to 1 year after the procedure, as well. This was likely the result of the worse health status, the more advanced HF and LV dysfunction, the increased prevalence of functional MR, and the lower socioeconomic indices that characterized non-whites and blacks prior

TABLE 4 Multivariable Cox proportional hazard model for the combined outcome of all-cause mortality or heart failure hospitalizations at 1year following mitral transcatheter edge-to-edge repair.

	Total cohort				Functional mitral regurgitation			
	White race considered		Black race considered		White race considered		Black race considered	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Baseline clinical variables								
Age (continuous)	0.98 (0.96–1.01)	0.064	0.99 (0.97–1.00)	0.103	NA	NA	NA	NA
Race								
White vs. non-White	0.99 (0.69–1.66)	0.776	NA	NA	0.62 (0.39–0.99)	**0.047**	NA	NA
Black vs. non-Black	NA	NA	1.61 (0.93–2.78)	0.088	NA	NA	2.07 (1.28–3.35)	**0.003**
None or low-income vs. regular / full insurance	1.04 (0.63–1.72)	0.529	1.14 (0.68–1.89)	0.625	1.15 (0.69–1.91)	0.591	1.28 (0.78–2.09)	0.332
Median yearly household income* (continuous)	1.00 (0.99–1.01)	0.259	1.00 (0.99–1.01)	0.329	NA	NA	NA	NA
Percentage of adults with academic degree* (continuous)	1.00 (0.99–1.02)	0.463	1.01 (0.99–1.02)	0.350	NA	NA	NA	NA
Diabetes mellitus	1.66 (1.07–2.56)	**0.023**	1.62 (1.05–2.50)	**0.044**	1.30 (0.82–2.07)	0.265	1.27 (0.80–2.02)	0.308
Previous MI, PCI, or CABG	0.81 (0.53–1.23)	0.322	0.88 (0.58–1.35)	0.558	NA	NA	NA	NA
Chronic obstructive pulmonary disease (COPD)	1.60 (0.94–2.71)	0.081	1.53 (0.90–2.58)	0.113	NA	NA	NA	NA
Anemia+	2.37 (1.43–3.93)	**<0.001**	2.29 (1.38–3.81)	**0.001**	3.22 (1.70–6.12)	**<0.001**	3.16 (1.66–6.01)	**<0.001**
Stage ≥III chronic kidney disease	1.36 (0.77–2.42)	0.288	1.21 (0.70–2.11)	0.497	1.27 (0.73–2.20)	0.404	1.24 (0.72–2.16)	0.438
New York Heart Association (NYHA) Class IV	1.66 (1.09–2.53)	**0.017**	1.65 (1.09–2.51)	**0.019**	1.83 (1.13–2.96)	**0.014**	1.84 (1.14–2.98)	**0.013**
Serum B-type natriuretic peptide level (continuous)	1.00 (0.98–1.01)	0.177	1.01 (0.99–1.03)	0.129	1.00 (0.99–1.01)	0.299	1.00 (0.99–1.01)	0.191
No use of renin angiotensin system (RAS) inhibitors	1.69 (1.12–2.56)	**0.013**	1.71 (1.13–2.59)	**0.010**	1.93 (1.43–2.96)	**0.012**	1.84 (1.15–2.95)	**0.012**
Furosemide-equivalent dose (continuous)	1.00 (0.99–1.04)	0.824	1.00 (0.99–1.04)	0.879	NA	NA	NA	NA
Oral anticoagulants prescription	NA	NA	NA	NA	0.90 (0.57–1.41)	0.641	0.96 (0.61–1.51)	0.859
Cardiac implantable electronic device (CIED)	1.29 (0.83–1.99)	0.262	1.22 (0.78–1.90)	0.389	NA	NA	NA	NA
Baseline echocardiographic variables								
Functional mitral regurgitation	1.89 (1.08–3.30)	**0.025**	1.94 (1.10–3.40)	**0.022**	NA	NA	NA	NA
Mitral regurgitation PISA EROA (continuous)	2.50 (0.79–7.69)	0.117	1.85 (0.62–5.56)	0.265	NA	NA	NA	NA
Left ventricular ejection fraction (LVEF)								
Continuous	NA	NA	NA	NA	1.01 (0.99–1.02)	0.139	1.01 (0.99–1.03)	0.103
<60%	1.60 (0.88–2.90)	0.121	1.55 (0.85–2.81)	0.152	NA	NA	NA	NA
Left ventricular end-systolic diameter (LVESD) ≥0.4 cm	2.19 (1.29–3.72)	**0.004**	2.05 (1.21–3.48)	**0.008**	NA	NA	NA	NA
Left atrial volume index (LAVi) (continuous)	1.08 (1.02–1.14)	**0.008**	1.06 (1.01–1.12)	**0.027**	1.07 (1.02–1.13)	**0.010**	1.07 (1.02–1.13)	**0.010**
≥Moderate right ventricular dysfunction	1.20 (0.75–1.93)	0.454	1.21 (0.75–1.96)	0.432	1.14 (0.69–1.88)	0.609	1.13 (0.69–1.85)	0.628
≥Moderate–severe tricuspid regurgitation	1.02 (0.65–1.61)	0.920	1.07 (0.68–1.68)	0.775	1.04 (0.64–1.69)	0.881	1.08 (0.66–1.77)	0.752

(Continued)

TABLE 4 (Continued)

	Total cohort				Functional mitral regurgitation			
	White race considered		Black race considered		White race considered		Black race considered	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
TAPSE/PASP ≤0.37 mm/mmHg (total cohort median)	1.99 (1.60–2.59)	**0.027**	1.96 (1.57–2.58)	**0.042**	1.97 (1.68–2.91)	**0.036**	1.95 (1.65–2.88)	**0.046**
Procedural variables								
Acute heart failure presentation, cardiogenic shock, hemodynamic support, or urgent procedure	1.86 (1.20–2.87)	**0.005**	1.82 (1.18–2.80)	**0.007**	1.92 (1.32–2.99)	**0.009**	1.87 (1.33–2.64)	**0.011**
Number of clips deployed (continuous)	1.39 (1.08–1.79)	**0.010**	1.39 (1.08–1.78)	**0.010**	1.38 (1.03–1.86)	**0.032**	1.31 (0.98–1.76)	0.069

*Per zip code. + Anemia was defined as a blood hemoglobin of <13 mg/dL in men or < 12 mg/dL in women. Figures in bold denote statistical significance. CABG, coronary artery bypass grafting; CI, confidence interval; EROA, effective regurgitant orifice area; HR, hazard ratio; MI, myocardial infarction; NA, not applicable; PASP, pulmonary arterial systolic pressure; PCI, percutaneous coronary intervention; PISA, proximal isovelocity surface area; TAPSE, tricuspid annular plane systolic excursion.

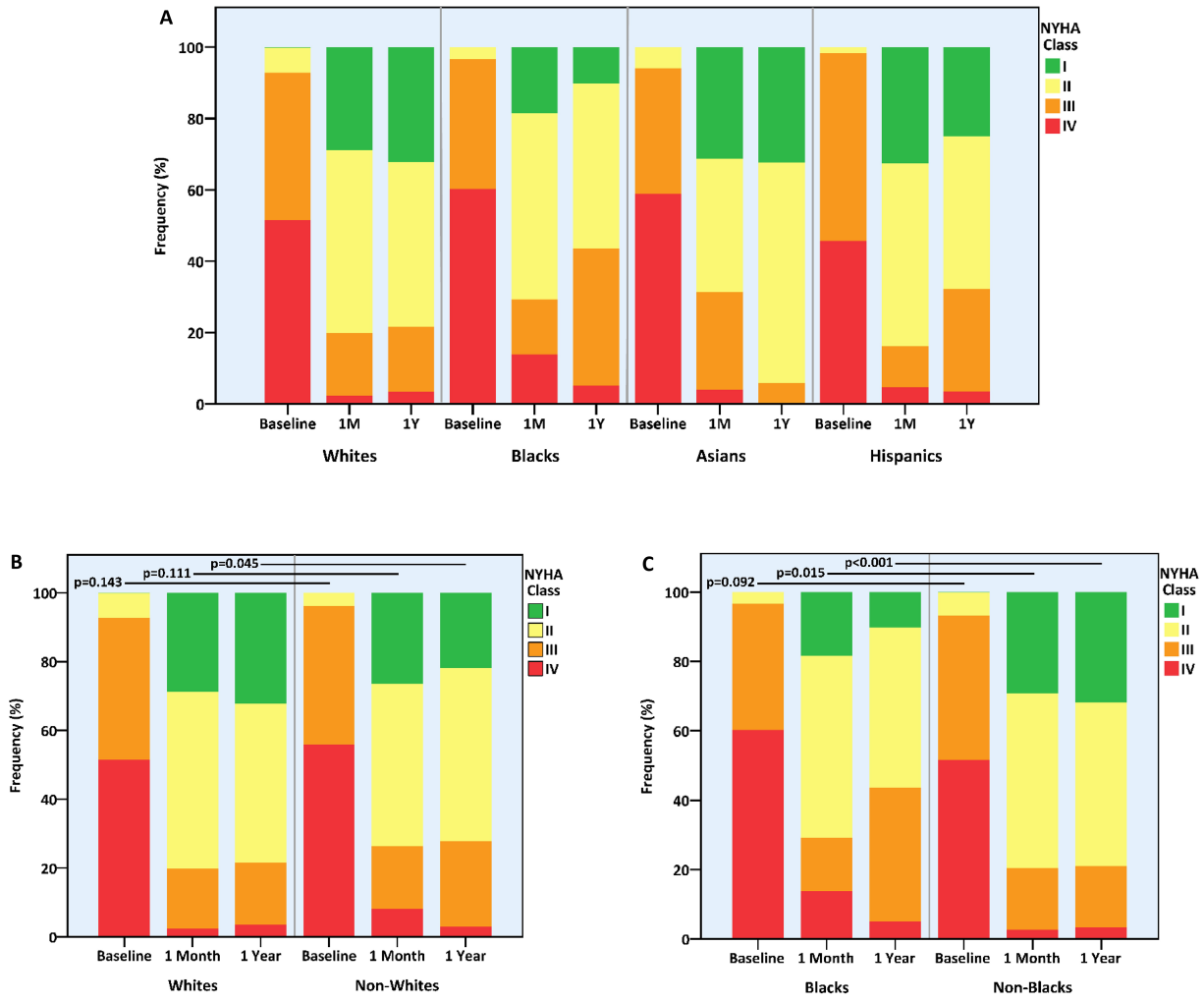

FIGURE 2
Functional status at baseline and following mitral transcatheter edge-to-edge repair according to race. **(A)** All races, **(B)** whites vs. non-whites, **(C)** blacks vs. non-blacks. NYHA, New York Heart Association.

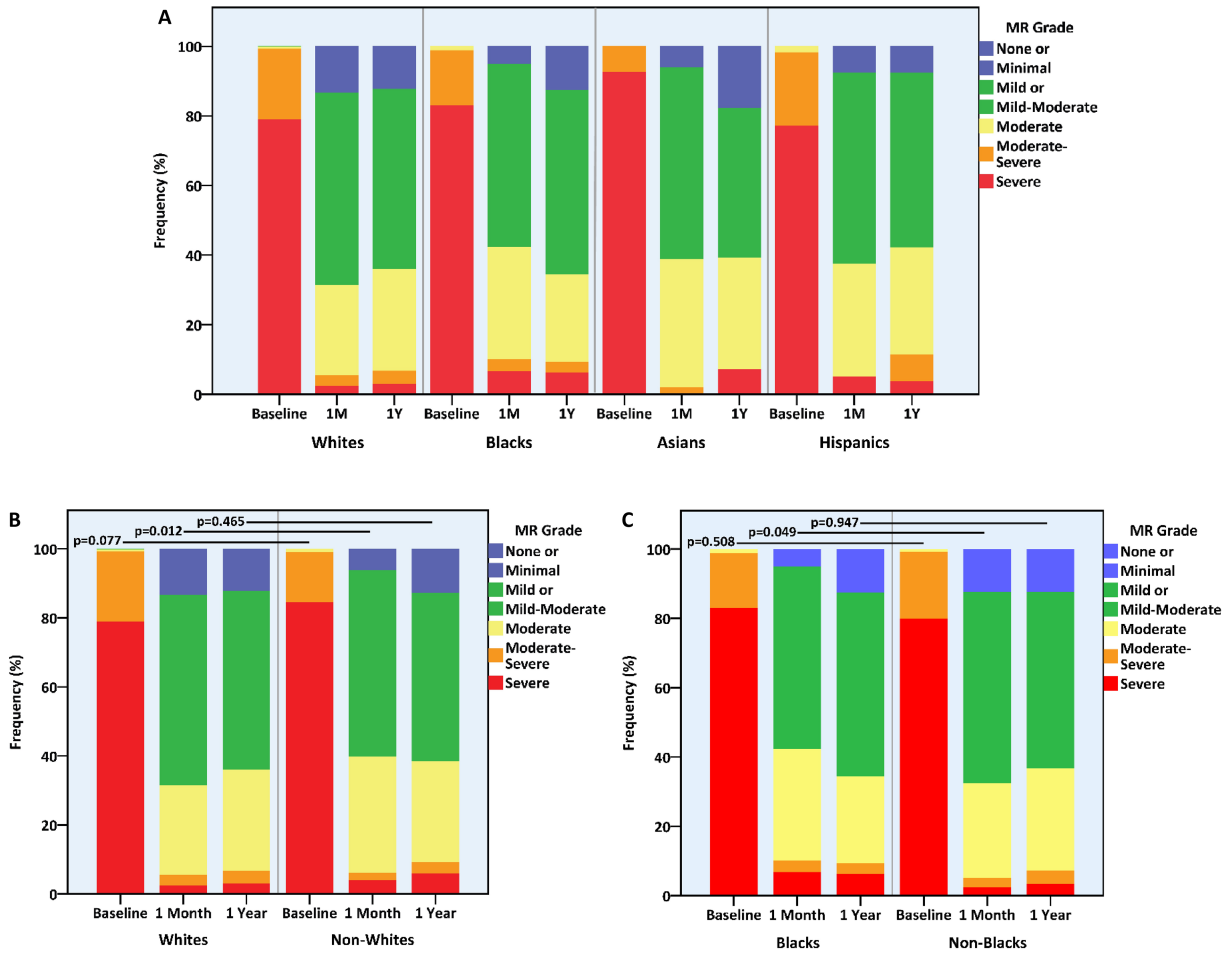

FIGURE 3
Mitral regurgitation grade at baseline and following mitral transcatheter edge-to-edge repair according to race. **(A)** All races, **(B)** whites vs. non-whites, **(C)** blacks vs. non-blacks. MR, mitral regurgitation.

to the procedure. In blacks, the less favorable outcome also could have represented the increased number of clips used and a possible attenuated effect of RAS inhibitors (26–28). Indeed, our comprehensive multivariable analysis suggested several comorbidities, as well as LV enlargement, functional MR, higher number of deployed clips, and no use of RAS inhibitors as independent risk factors for the 1-year composite endpoint of death or HF hospitalizations, similar to earlier works (17, 29–31). Yet, blacks received more clips regardless of MR etiology, were similarly hypertensive as non-blacks, and utilized comparable medical prescriptions in the periprocedural period. Furthermore, non-white and black races remained prognostically meaningful after adjusting for inter-racial differing parameters, all implying the presence of additional race-related factors not measured in our study that could have determined the post-TEER course. Some of these variables, such as more distant post-interventional management and adherence to treatment, also could have interacted with socioeconomic parameters discussed earlier. Importantly, MR severity itself did not play a role in this regard, as it was comparable across races and did not possess any association with the primary outcome.

Interestingly, racial disparities in patient outcomes were mainly observed between whites and non-whites and between blacks and non-blacks. Also, they were limited to the functional MR sub-cohort, in which non-white and black races independently conferred a higher risk for the primary outcome. One explanation for these findings may lie in statistical power, as racial groups other than whites and blacks were relatively small. Similarly, although comparable in size, the primary MR subgroup experienced fewer composite events of death or hospitalizations, again signifying a lower power that could have masked inter-racial differences. Besides statistical considerations, baseline and procedural characteristics, and specifically age, sex, and insurance, were less varied among patients of different races who had primary MR, potentially contributing to a more balanced and homogenous downstream course. The reason underlying the association between race and demographics specifically within the functional MR sub-cohort was unclear, and may again relate to the possibly different prevalence of non-ischemic cardiomyopathy.

Limitations

First, our study represents a retrospective analysis from one center which did not employ an external core laboratory. Second, missing data regarding functional status and echocardiographic

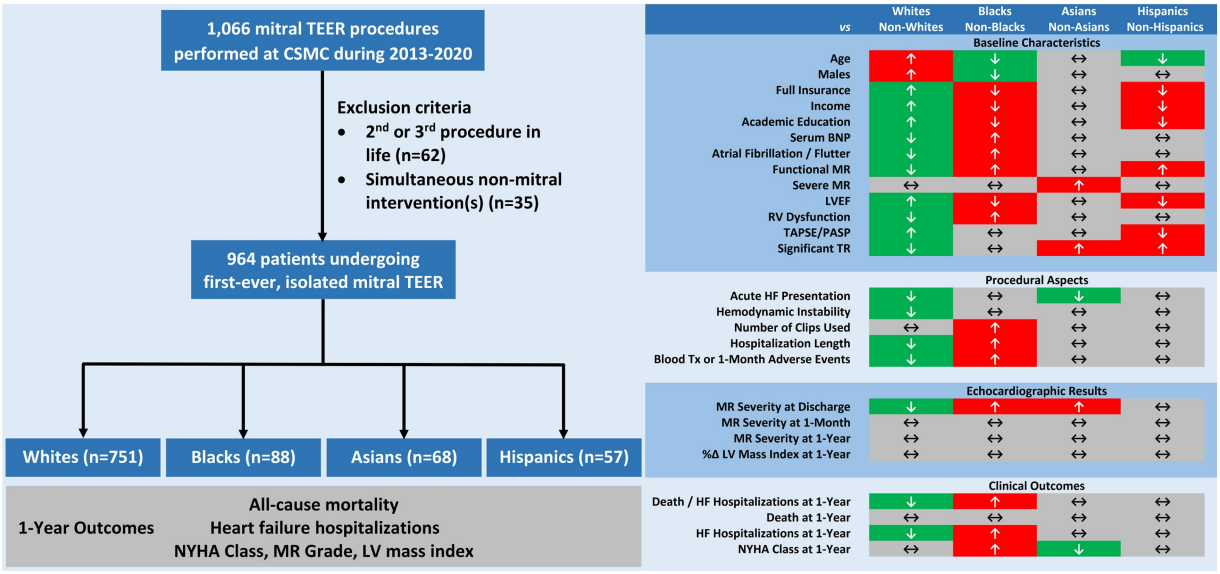

FIGURE 4
CENTRAL ILLUSTRATION Racial disparities in characteristics and outcomes of patients undergoing mitral transcatheter edge-to-edge repair. Among 964 patients undergoing isolated, first-time mitral transcatheter edge-to-edge repair, major inter-racial differences were note in pre-, intra-, and post-procedural features. At 1-year, non-whites and blacks experienced higher rates of all-cause mortality or heart failure hospitalizations and blacks also faced less improvement in functional status. Mitral regurgitation severity and left ventricular hypertrophy equally regressed in all groups. BNP, B-type natriuretic peptide; CSMC, Cedars-Sinai Medical Center; EF, ejection fraction; HF, heart failure; LV, left ventricular; MR, mitral regurgitation; NYHA, New York Heart Association; PASP, pulmonary arterial systolic pressure; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

measures over the course of follow-up could have interfered with the interpretation of the results. However, these were similarly distributed among the various racial groups, making survival bias unlikely. Moreover, baseline characteristics and procedural details, as well as deaths and hospitalizations, were all documented for the entire cohort. Third, our matched cohorts were relatively small and may not fully control for all unmeasured confounders. Therefore, all multivariable analyses based on these matched populations should be considered exploratory. Fourth, although consistent with a real-world setting (32), medical therapy was suboptimal in present-day standards, making it difficult to extrapolate our observations to medically optimized patients. Fifth, our registry did not include direct information on socioeconomic variables other than insurance, neither did it include data on specific causes of death, thus preventing the appreciation of possible interactions with race. Sixth, we assigned only one race to each patient and based this categorization on self-reporting, not taking into consideration the possibility of mixed racial backgrounds. Lastly, our results may not apply to non-MitraClip systems as those were not employed in our center.

Conclusion

In our single-center experience, major differences in pre-, intra-, and post-procedural features were observed between various racial groups undergoing mitral TEER. The 1-year composite outcome of all-cause mortality or HF hospitalizations occurred more frequently among non-whites (vs. whites) and blacks (vs. non-blacks or whites) and was independently associated with non-white and black races. Functional status improved to a lesser extent in blacks. The prognostic implication of race was restricted to the functional MR subgroup.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Cedars-Sinai Medical Center Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

AS has conceptualized the project, gathered data, performed analyses, and written the first draft of the manuscript. Other co-authors have assisted in revision of the text, as well as in the formulation of the statistical methodology. All authors contributed to the article and approved the submitted version.

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Conflict of interest

RM received grant support from Edwards Lifesciences Corporation, is a consultant for Abbott Vascular, Cordis, and Medtronic, and holds equity in Entourage Medical. TC is a consultant, proctor, and speaker for Edwards Lifesciences and Medtronic, is a consultant for Abbott Lifesciences, and is a consultant and speaker for Boston Scientific.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1111714/full#supplementary-material

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Flow dynamic assessment of native mitral valve, mitral valve repair and mitral valve replacement using vector flow mapping intracardiac flow dynamic in mitral valve regurgitation

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Objectives: The present study aims to assess and describe the intracardiac blood flow dynamic in patients with mitral regurgitation (MR), repaired mitral valves (MV) and mitral valve prostheses using vector flow mapping (VFM).
Methods: Patients with different MV pathologies and MV disease treatments were analysed. All patients underwent 2D transthoracic echocardiography, and images for flow visualization were acquired in VFM mode in an apical three-chamber view and four-chamber view. Vectors and vortices were qualitatively analyzed.
Results: thirty-two (32) patients underwent 2D transthoracic echocardiography (TTE) with VFM analysis. We evaluated intracardiac flow dynamics in 3 healthy subjects, 10 patients with MR (5 degenerative, 5 functional), 4 patients who underwent MV repair, 5 who underwent MV replacement (3 biological, 2 mechanical), 2 surgically implanted transcatheter heart valve (THV), 2 transcatheter edge-to-edge MV repair with MitraClip (TEER), 3 transcatheter MV replacement (TMVR) and 3 transapical off-pump MV repair with NeoChord implantation. Blood flow patterns are significantly altered in patients with MV disease and MV repair compared to control patients. MV repair is superior to replacement in restoring more physiologicalpatterns, while TMVR reproducesan intraventricular flowcloser to normal than surgical MVR and TEER.
Conclusions: Intracardiac flow patterns can be clearly defined using VFM. Restoration of a physiological blood flow pattern inside the LV directly depends on the procedure used to address MV disease.

KEYWORDS

intracardiac flow dynamic, mitral valve disease (MV disease), vector flow mapping (VFM), TMVR, TEER

Abbreviations
AML, anterior mitral leaflet; DMR, degenerative mitral regurgitation; EL, energy loss; FMR, functional mitral regurgitation; LV, leftventricle; LVOT, left ventricle outflow tract; MV, mitral valve; MVR, mitral valve replacement; MVRe, mitral valve repair; PML, posterior mitral leaflet; TEER, transcatheter edge-to-edge repair; THV, transcatheter heart valve; TMVR, transcatheter mitral valve replacement; VFM, vector flow mapping.

Introduction

The study of intracardiac flow patterns has been initially performed using cardiac magnetic resonance (1–4). More recently, vector flow mapping (VFM), which is based on colour Doppler blood flow mapping and wall speckle tracking, has been used to describe the dynamic of blood flow patterns in mitral valve (MV) disease (5–7). Blood flows in the cardiac chambers create vortices that maintain the potential energy and optimize the cardiac workload and efficiency (8). Turbulent and not organized flow patterns are not efficient and increment the dissipation of potential energy deteriorating the ventricular function (9–12). Several studies demonstrated that surgical mitral valve repair (MVRe) is associated with better survival and left ventricular (LV) function improvement when compared to other treatments (surgical valve replacement, transcatheter valve repair or replacement) (13). This difference might be explained by a more physiological restoration of the intracardiac blood flow patterns after surgical repair, which translates into a reduced LV workload. Previously, Nakashima and Akiyama used VFM to flow patterns and energy dynamics of the intraventricular vortices in patients who underwent mitral valve surgery (6, 7). These studies show that flow dynamic is usually altered compared to healthy individuals independently from the type of treatment used to address the mitral valve disease; however mitral repair provided the most similar pattern to healthy individuals. Previous studies compared the intracardiac flow patterns and LV efficiency after surgical MVRe and MV replacement (MVR), confirming that repair usually preserves the normal LV vortices better than replacement (6, 9). However, no descriptive data are available regarding new techniques,such as transcatheter procedures, which are now taking over the scene of MV procedures, particularly in patients who might benefit the most from restoring the most physiologic flow pattern.

The present article aims to systematically describe the intracardiac blood flow patterns of the entire spectrum of MV regurgitation disease and the possible alternative techniques to address it.

Methods

Between June 1st, 2021 and January 31st, 2022, healthy subjects, patients with functional and degenerative MV disease and patients who underwent MV treatments at our Centre, either surgical or transcatheter, were included in the study. The reason for MV surgical or transcatheter MV treatment was isolated MR, either degenerative or functional. All patients who underwent MVRe or MVR presented with degenerative disease, while patients undergoing transcatheter procedures presented variably with degenerative or functional disease. No other procedures were performed. Patients with inadequate acoustic window and/or atrial fibrillation at the time of image acquisition were excluded from the study. All patients signed a dedicated informed consent before being included in the present study that was approved by the local Ethical Committee. At 1 month after surgery all patients underwent dedicated 2D transthoracic echocardiography. None of the patients had TTE both before and after surgery. Intracardiac flow images were recorded using a 5-MHz matrix array single crystal technology ultrasound transducer (Hitachi Medical Systems, Tokyo, Japan). Images for flow visualisation were acquired in VFM mode in an apical three-chamber view and four-chamber view. All images were acquired in three consecutive cardiac cycles with a target frame rate set inthe range of 20–25 frames/s. The color Nyquist limit was set sufficiently high to mitigate aliasing phenomena, and automatic self-aliasing was used as well. The Doppler signal provided the axial component of the blood velocity, while the time-varying position of the boundaries (LV walls) was obtained from 2D STE. The offline analysis was computed with dedicated software (DAS-RS1 5.0; Hitachi Medical Systems, Tokyo, Japan). The cardiac cycles were determined according to the valve openings and closings with the synchronous ECG: T wave defined the end of the contraction, while the R peak of the QRS complex set the end of the diastolic phase. The LV endocardial border was traced in the first frame image, and the software automatically tracked the endocardial border throughout the cardiac cycle. After determining the ROI, qualitative images (velocity vectors and streamlines) were displayed in 2D for each frame of the cine loop image.Energy loss expresses the amount of energy dissipated as heat in the LV by viscous friction in turbulent blood during the process of relaxation (diastole) and contraction (systole). Since turbulent flow results in an irreversible loss of the total fluid energy, the higher the EL, the greater the LV inefficiency. After tracing the ROI of the LV cavity, a sample line was placed at the level of the mitral annulus (in the apical four-chamber and long-axis view) and in the LV outflow tract(in the apical long-axis view) to acquire the time-flow curves of the diastolic and systolic period, respectively. Therefore, EL is quantified as the sum of the square of the difference between adjacent velocity vectors:

$$\begin{aligned} EL &= \sum i, j \int 12\mu(\partial ui \partial xj + \partial uj \partial xi) 2 \partial v EL \\ &= \sum i, j \int 12\mu \partial ui \partial xj + \partial uj \partial xi 2 \partial v \end{aligned}$$

where μ is the coefficient of blood viscosity (μ blood = 4.0×10^{-3} Newton·s·m $^{-2}$), u and x are the velocity vector components, i and j are the coordinates of the Cartesian system built on a 2D vector field, and v is the vector velocity. EL represents the rate at which energy is expended in a 2D system; hence, it is measured in watts/m: W/m = Joule/(m·s). According to the formula, EL increases at points where the size and direction of velocity vectors change. EL measurements were estimated from an apical three-chamber view.

Results

Thirty-two (32) patients were evaluated. We included 3 healthy individuals to describe the normal intracardiac flow patterns. Ten

(10) patients presented severe mitral regurgitation (MR) (5 degenerative-DMR, 5 functional-FMR), 4 patients underwent MVRe (3 with annuloplasty ring and posterior leaflet resection and 1 with ring and artificial polytetrafluoroethylene chordae), 5 patients had a surgical mitral prosthesis (3 biological, 2 mechanical all in antianatomic orientation), 2 patients had a Sapien 3 transcatheter heart valve (Edwards Lifesciences, Irvine, CA, USA) surgically implanted through the left atrium with anterior mitral leaflet resection, 2 patients underwent transcatheter edge-to-edge mitral valve repair (TEER) with a MitraClip (Abbott Vascular, Plymouth, MN, USA), 3 patients had a transcatheter mitral valve replacement (TMVR) with a Tendyne prosthesis (Abbott Vascular, Plymouth, MN, USA) and 3 patients underwent transapical off-pump mitral valve repair with NeoChord implantation (NeoChord, Inc., St. Louis Park, MN, USA).

Out of the 5 patients with DMR 2 had an extensive posterior multi-scallop disease (Barlow-type), while the other 3 presented with fibroelastic deficiency and less extensive leaflet involvement (prolapse or flail of one scallop). Patients with FMR had underlying ischemic cardiomyopathy in 2 cases while primitive dilative cardiomyopathy in 3 cases.

All mechanical valves were bileaflet Regent prostheses (Abbott Vascular, Plymouth, MN, USA), while all implanted biological valves were Mosaic porcine prostheses (Medtronic, Minneapolis, MN, USA). All patients had their subvalvular apparatus preserved, and in case of mechanical replacement, the prosthesis had an antianatomical orientation.

In all cases of MVRe, a semi-rigid Simulus annuloplasty ring was used (Medtronic, Minneapolis, MN, USA).

Both patients who underwent TEER primarily presented with ischemic cardiomyopathy and showeda residual mild-to-moderate MR after the procedure. TMVR with low-profile Tendyne prosthesis was performed in patients with FMR due to dilative or ischemic cardiomyopathy. All patients treated with Sapien 3 prosthesis presented severe mitral annular calcification (MAC) and underwent concomitant anterior mitral leaflet resection (AML) to prevent the occurrence of potential left ventricular outflow tract (LVOT) obstruction.

The three patients who underwent Neochord procedure presented degenerative MR involving the posterior mitral leaflet (PML) with preserved LV function. One of them previously underwent mitral valve repair receiving isolated annular ring implantation.

Complete transthoracic echocardiography data and procedural details of the patients which were selcted as images and video examples for each condition are reported in **Table 1**.

Flow analysis

In the healthy controls (**Figure 1**, panel A1,A2,A3, **Supplementary Video S1**), blood enters the LV cavity through the MV smoothly, creating two vortices that move in opposite directions, a main clockwise vortex beneath the AML and a smaller counterclockwise vortex beneath the PML. While the posterior vortex dissipates quickly, the anterior vortex keeps getting bigger during diastole moving downstream and pushing the blood flow towards the posterior wall of the LV and then redirecting the flow towards the LVOT during systole. In systole, hemodynamic forces are directed mainly along the left ventricle longitudinal axis, from the apex to the LVOT, without significant vortices (i.e., vortices that persist for at least two consecutive frames).

In patients with DMR (**Figure 1**, panel B1,B2,B3, **Supplementary Video S2**),the diastolic flow pattern composed ofthe two LV vortices is preserved. However, during late diastole and early systole, the anterior vortex does not direct the flow toward the LVOT because the hemodynamic forces are directed from the apex to both the LVOT and the left atrium due to the posterior leaflet prolapse, leading to the formation of multiple vortices proximal to the MV (mainly with a clockwise rotation). In FMR (**Figure 1** panel C1,C2,C3, **Supplementary Video S3**), we observed only one clockwise vortex distal to the AML during early filling. In systole, because of PML tethering causing MV malcoaptation, hemodynamic forces are directed from the apex both to the LVOT and to the left atrium leading to the formation of a counterclockwise vortex proximal to the MV.

After MVRe, the intracavitary blood flow pattern is mostly restored (**Figure 2**, **Supplementary Video S4**). Whether a triangular resection alone or neochords implantation was combined with the annuloplasty ring the formation of two vortices with the movement of the blood flow toward the posterior wall of the LV could be observed, optimizing LV forces and minimizing the turbulence in the LVOT during systole. The only difference with healthy control was the slightly longer persistence of the posterior vortex during diastole.

After MVR with bioprostehsis (**Figure 3**, panel A1,A2,A3, **Supplementary Video S5**), we can observe in diastole only one vortex distal to the bioprosthetic valve with a counterclockwise rotation (opposite to the healthy control). The vortex occupies the center of the LV cavity to redirect blood toward the LVOT. In systole, we observed intraventricular vortices probably related to the LV systolic dysfunction. Moreover, it is possible to notice a vortex rotating clockwise within the struts of the bioprosthesis. Similarly, in patients with a mechanical prosthesis in antianatomical orientation (**Figure 3**, panel B1,B2,B3, **Supplementary Video S6**), during diastole, there is a major counterclockwise vortex in the LV mid cavity and a smaller clockwise one that disappears quickly. The main vortex redirects the flow towards the LVOT. In this group, turbulence during systole is less evident.

After TEER (**Figure 4**, **Supplementary Video S7**), during diastole, we observe multiple vortices without forming the typical main clockwise vortex occupying the center of the cavity. In systole, hemodynamic forces are partially restored along the LV longitudinal axis, from the apex to the LVOT, with an incomplete pair of counterrotating vortices in the left atrium due to the residual MR.

The three patients who underwent TMVR presented a nearly normal flow pattern (**Figure 5**, **Supplementary Video S8**). During early filling, we observed the formation of the typical two

TABLE 1 Ultrasound evaluation.

Variable	Normal MV	Degenerative MR	Functional MR	MV repair	TEER	MV replacement	MV replacement	TMVR	Sapien 3 in MAC	NeoChord TM Device
Gender	Female	Male	Female	Male	Male	Male	Female	Female	Female	Male
Age, years	54	75	73	60	79	44	71	72	70	49
Technical procedure	–	–	–	1 pair of artificial chord for P2 + Medtronic Simulus 36 annuloplasty ring	Transcatheter mitral edge-to-edge with 2 MitraClips	Medtronic Mosaic 33	Corcym Carbomedics 29	Transcatheter Tendyne LP 33S	Surgical Sapien 3 29	Transapical off-pump implantation of 3 pairs of Neochords for P2
Conventional echocardiography										
LVMi, g/m^2	75	110	122	100	159	136	90	120	113	150
LVEDV, mL	80	145	149	148	198	185	110	138	124	181
LV Ejection fraction, %	60	60	45	60	42	43	59	45	67	60
Mitral E wave, cm/s	80	110*	150	87	105	110	135	100	125	84
Average e', cm/s	11	16	6	9	7	8	7	7	6	10
Average E/e'	7	7	25	10	15	14	19	14	21	11
LAVi, mL/m^2	19	38	49	42	52	41	40	42	47	32
TAPSE, mm	21	20	18	16	19	15	17	17	17	17
Systolic PAP, mmHg	20	35	59	35	38	40	35	38	40	22
Vector Flow Mapping										
Energy loss, J/m·s*	0.36	0.51	0.65	0.39	0.67	0.48	0.55	0.47	0.74	0.41

EDV, end-diastolic volume; LAVi, left atrial volume index; LV, left ventricle; LVMi, left ventricle mass index; PAP, pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; MV, mitral valve; MR, mitral regurgitation; TEER, transcatheter edge-to-edge repair; TMVR, transcatheter mitral valve replacement; MAC, mitral annulus calcification.

*Expressed as the mean energy loss of three complete cardiac cycles.

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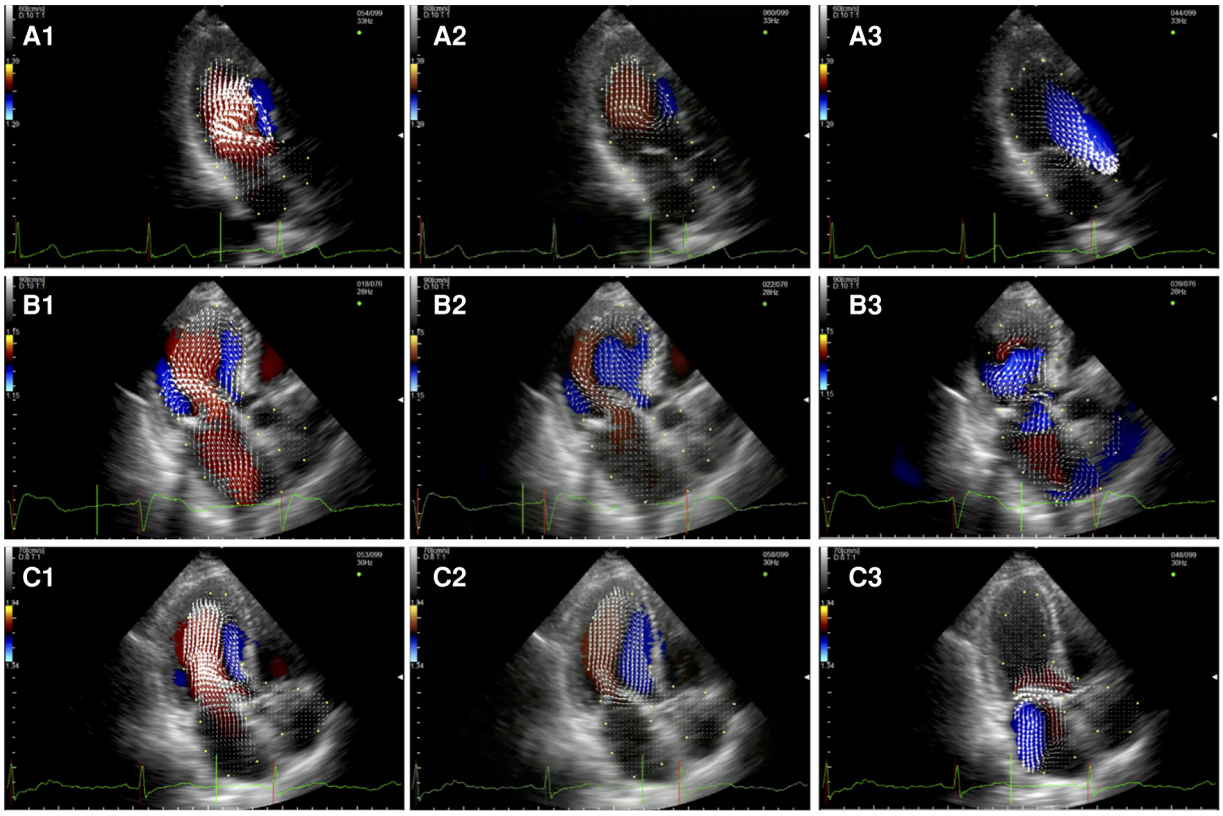

FIGURE 1
Apical long-axis view. Intracardiac flow vectors in early diastole (A1–C1) and late diastole (A2–C2) for control patient, patient with DMR and patient with FMR respectively; intracardiac flow vectors in mid-systole for control patient (A3), patient with DMR (B3) and patient with FMR (C3).

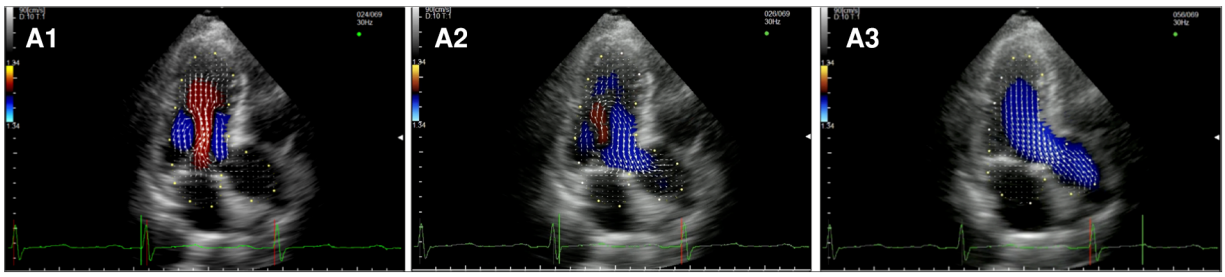

FIGURE 2
Apical long-axis view. Intracardiac flow vectors in mid-to-late diastole (A1,A2) and mid-systole (A3) after surgical mitral valve repair neochords and annuloplasty ring.

counterrotating vortices, with the major one below the AML pushing back the blood flow and redirecting it towards the LVOT during mid-systole.

In the two subjects who underwent surgical implantation of a Sapien 3 THV (Figure 6, Supplementary Video S9), there was a pair of counterrotating vortices during diastole. Still, the main vortex had a counterclockwise rotation (opposite to the healthy control). In systole, hemodynamic forces were directed mainly along the left ventricle longitudinal axis, from the apex to the LVOT. Multiple secondary vortices occur throughout the cardiac cycle distal and proximal to the bioprosthesis.

After Neochord Procedure (Figure 7, Supplementary Video S10), we observed a flow pattern that was similar to healthy subjects and patients who underwent surgical repair with a larger clockwise vortex below the anterior leaflet and the smaller counterclockwise one under the posterior leaflet during early diastole. Again we observed the displacement of the flow vectors towards the apical region during the later phases of the diastole and only mildly turbulent systolic flow in the LVOT.

Graphical representation of our findings is also shown in Figure 8.

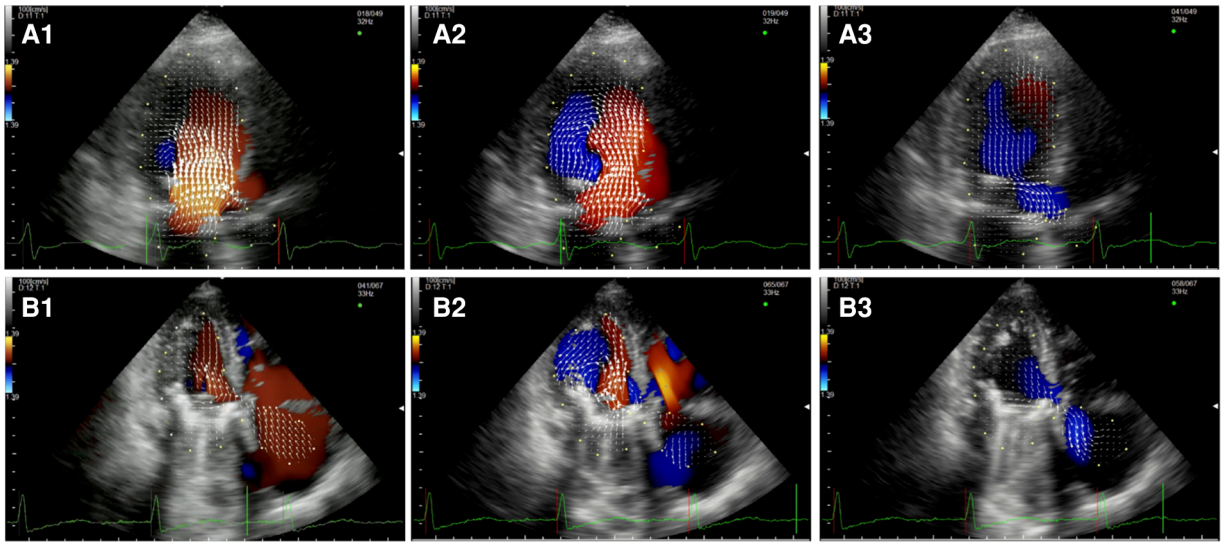

FIGURE 3
Apical long-axis view. Intracardiac flow vectors in early diastole (A1,B1) and late diastole (A2,B2) after mitral valve replacement with bioprosthesis and mechanical prosthesis (antianatomicalorientation) respectively; intracardiac flow vectors in mid-systole (A3,B3) after mitral valve replacement with bioprosthesis and mechanical prosthesis (antianatomicalorientation) respectively.

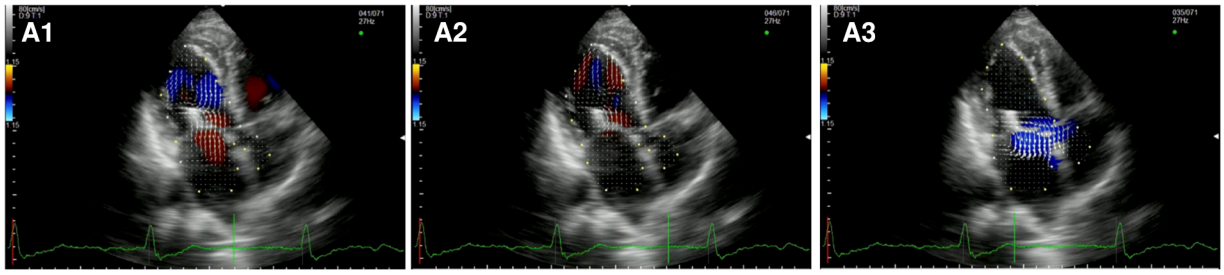

FIGURE 4
Apical long-axis view. Intracardiac flow vectors in early and late diastole (A1,A2) and mid-systole (A3) after transcatheter mitral valve repair with MitraClip (residual mild-moderate MR).

More images and videos depicting the intracavitary vortices and the enery loss loops are available as **Supplemenary Material**.

Discussion

There is increasing interest in studying intracardiac blood flow patterns to clarify the physiopathological mechanisms at the base of different cardiac conditions, and various imaging techniques have been developed over the last few years (8, 14). Apart from 4D flow MRI, which enables an extremely accurate 3D evaluation of vortex flow patterns and LV workload through EL quantification on the base of a single cardiac cycle (1, 15), echocardiography has been reliable in visualizing intracardiac flows (16, 17). In particular, echocardiography VFM, based on color-Doppler and speckle-tracking techniques, was developed (18, 19) and has already been used to analyseflows after cardiac surgery (6, 7) in particular in the field of mitral valve surgery. Since the late 1980s,MVRe has been superior to MVR in preserving LV function (13). One possible explanation of this phenomenon is the preservation of the subvalvular apparatus that causes a reduction of the LV radius and, therefore, the LV wall stress (20, 21). However, this explanation does not entirely justify the dramatic difference in LV function preservation. Restoring normal intracardiac LV flow patterns observed mainly after MVRe may helppreservethe kinetic energy momentum reducing LV workload and shear stress as previously demonstrated (8).

This is the first comprehensive description of LV flow patterns in MV disease using VFM. The main findings of our descriptive analysis are that intracardiac blood flow patterns are restored after MVRe independently from the repair technique, MVR (both with biological and mechanical prostheses in antianatomical orientation) is affected by the persistence of altered blood flows, TEER completely alters LV vortices and

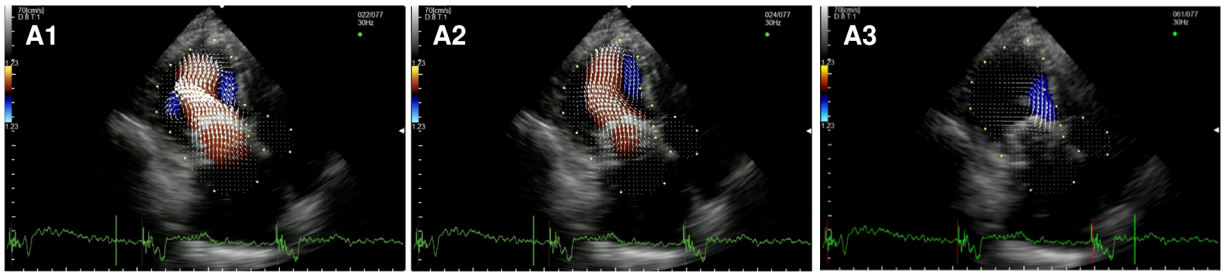

FIGURE 5
Apical long-axis view. Intracardiac flow vectors in early and late diastole (A1,A2) and mid-systole (A3) after transcatheter mitral valve replacement with Tendyne system.

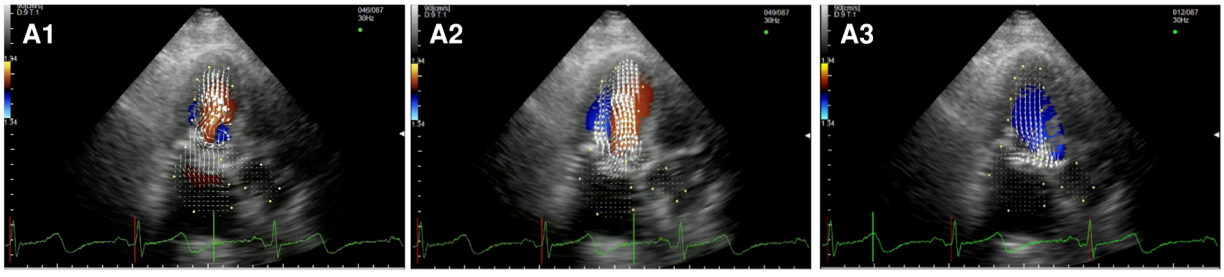

FIGURE 6
Apical long-axis view. Intracardiac flow vectors in early and late diastole (A1,A2) and mid-systole (A3) after surgical implantation of a Sapien 3 valve in mitral annular calcification (MAC).

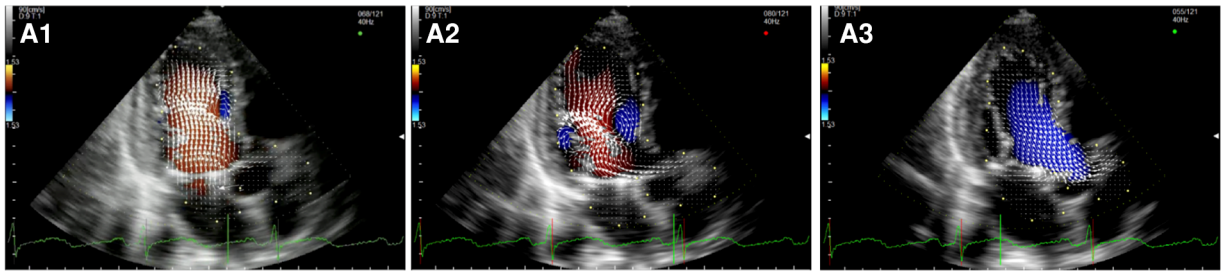

FIGURE 7
Apical long-axis view. Intracardiac flow vectors in early and late diastole (A1,A2) and mid-systole (A3) after transapical off-pump mitral valve repair with NeoChord TM device.

TMVR with Tendyne valve has a similar effect to MVRe on flow patterns restoration (**Figure 8**).

Our findings in healthy subjects are largely comparable to those reported in the literature. The physiological flow pattern was also confirmed in our healthy subjects. However, we did not observe prolonged persistence of vortices during early systole as elsewhere described (22, 23). This difference might be explained because we considered as relevant only vortices persisting longer than two consecutive frames. However, based on the small study population, it is possible that more significant vortices were not observed because they were not included in the imaging plane. A larger study could solve this issue, albeit the diastolic pattern was largely comparable with that reported by other authors. In the presence of FMR, flow patterns were altered and presented some similarities with those described by other authors. Indeed we observed only one large vortex that moved from the MV to the mid cavity with an initial clockwise rotation and a late counterclockwise movement. Pilla et al. (24) found the presence of two vortices below the MV leaflets, with the anterior one bigger than the posterior one and a later single mid-cavity vortex. Differently from Pilla, who analysed suine models in which a posterolateral infarction was induced, all our patients did

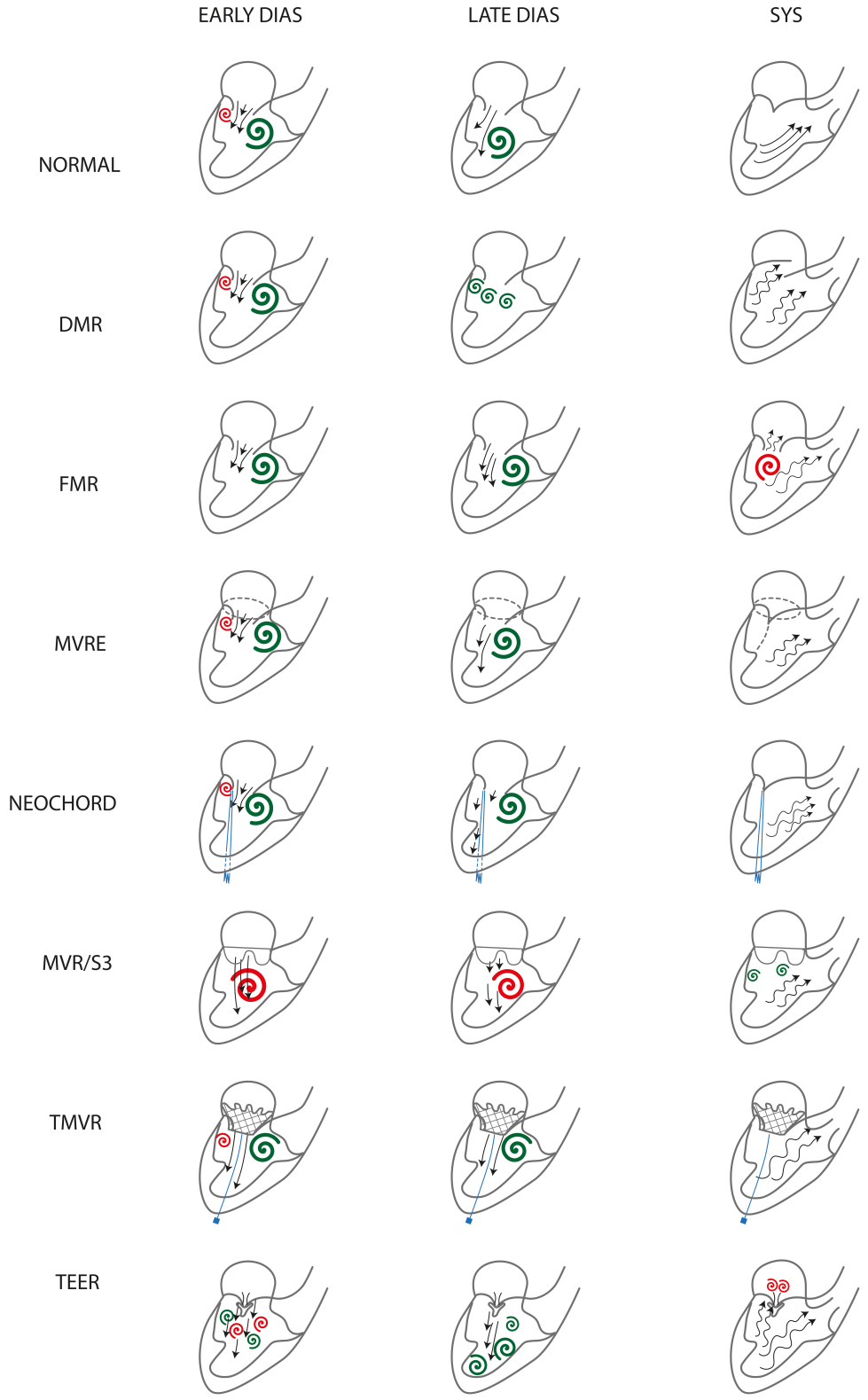

FIGURE 8
Flow patterns graphical representation. Clockwise vortices are green, counterclockwiseones are red. DMR, degenerative mitral regurgitation; FMR, functional mitral valve regurgitation; MVRe, mitral valve repair; Neochord, transapical off-pump mitral valve repair withrhNeoChord implantation; MVR, mitral valve replacement; S3, Valve in MAC with Edwards Sapien 3; TMVR, transcatheter mitral valve replacement; TEER, transcatheter edge-to-edge mitral valve repair.

not have specific regional wall abnormalities, which could explain these small differences in intraventricular flows.

The conservation of the kinetic energy is enabled by the presence of vortices, particularly the anterior clockwise vortex, which appears beneath the AML. The formation of this vortex is guaranteed by the higher length of the AML comparedto the PML and the apical direction of the flow through the MV, as previously described by Pedrizzetti et al. (25).

MVRe preserves this difference in length since surgeons usually try to maintain the physiological 2/3:1/3 ratio between AML and PML surface mostly reducing the PML height to prevent an anteriorly displaced coaptation line that would increase the risk of AML systolic anterior motion. Our observations were consistent with these findings since in all patients who underwent MVRe we could appreciate the formation of a large anterior vortex that pushed the blood flow towards the posterior LV wall helping the flow entering the LVOT. In our experience, similarly to what was reported by other groups (2, 7), the type of repair did not affect physiological vortex formation; we only observed a slightly prolonged persistence of the posterior counterclockwise vortex in patients who received chordal implantation. However, this observation did not determine any significant increase of EL during the cardiac cycle or the formation of turbulent patterns in the LVOT. Morichi et al. (2), using 4D flow MRI, studied the effect of different types of annuloplasty rings and bands on intracardiac flow patterns. They observed a more preserved pattern when a flexible band or ring was used compared to semi-rigid bands or rings. In our series, only semi-rigid rings were implanted. In all these patients, the flow pattern was similar to healthy controls. The absence in our series of the flow alteration observed by Morichi et al. in semi-rigid rings might be explained by the large size of the rings we implanted. A smaller orifice area is associated with a larger posterior vortex which pushes the flow toward the anterior wall opposite to the healthy control. The desired effect of ring annuloplasty is to reduce the AP diameter without excessive reduction of the MV orifice area. For this reason, the implanted ring should be onesize greater than the actual measured AML area. Moreover, Morichi's group supposed that the increased EL observed for semi-rigid rings was also determined by the restrictive effect of the ring on the LVOT. This condition does not apply to the Simulus ring,whichhas a very soft and adaptable anterior section. Interestingly Neochord Procedure was associated with similar findings to standard surgical repair, confirming the restoration of pseudonormal flow patterns independently from the presence of the annuloplasty ring and supporting the hypothesis of future positive remodelling of the LV also when the MV ring is not addressed.

Also, our observations confirm that MVR does not restore physiological flow patterns (6, 9). Other groups found a difference between biological prostheses and anatomically oriented mechanical prostheses; only the latter provided two counterrotating vortices, while the former determined the creation of a single counterclockwise vortex that pushed the blood flow towards the anterospetal wall, then to the apex and finally to the posterior wall. In our experience, we could only examine biological prostheses and antianatomically oriented mechanical valves, and in both cases, a single large counterclockwise vortex was observed. Other groups had similar findings regarding mechanical valves in antianatomical orientation. This difference might be explained by how the blood enters the LV cavity. The sutures used to implant a MV prosthesis follow the saddle shape of the MV annulus orienting the valve oblique with respect to the posterior annulus level. Indeed the anterior portion of the sewing ring tends to be positioned higher thanthe posterior aspect on the mitral annulus plane; this anteriorly tilted angle creates an altered entrance angle for the blood, which is naturally directed towards the anteroseptal wall creating the large counterclockwise vortex. A similar condition is observed for the surgically implanted THV Sapien 3 valve. When deployed within the MV annulus, the THV slides posteriorly, remaining higher on the anterior aspect of the annulus anddirecting the flow anteriorly inside the LV chamber. To prevent paravalvular leaks, the surgeon manually sutures an adjunctive Teflon skirt on the atrial portion of the THV stent to seal the stent to the periannular area (26, 27). It is possible that trimming this skirt to slide the THV higher on the posterior annulus might prevent the anterior tilting providing a more apical-directed LV flow and enabling the formation of the physiological double vortices. Our observations on TMVR support this theory. Because of the apical pad that anchors the THV to the LV wall and the particular shape of the valve stent and atrial skirt, the prosthesis is forced to a more coplanar position to the MV annulus. Indeed the flow pattern observed for Tendyne is very close to a normal subject.

Finally, TEER completely disrupts the LV physiological vortices creating turbulent flow during diastole and systole. There are no reports about intracardiac patterns after TEER, and ours are the first descriptive findings. We hypothesize that this flow disarray is due to the combination of two elements. First, the creation of a double orifice valve with the major axis oriented at 90° with respect to the LV major axis as it is observed for mechanical valves in antianatomic orientation; second, the presence of a rigid element (the clip) attached to the leaflets that prevents the normal swirling of the blood flow around the tips of the leaflets. This finding should be carefully evaluated since TEER is frequently indicated in patients with reduced LV function, who might be the ones that might benefit the most from the restoration of normal LV flow patterns reducing LV workload and enhancing LV function recovery.

Three subjects of the study population presented HFrEF, one of them underwent TEER, another received a surgical bioprosthesis, and the third one had TMVR. In all cases, LV impairment was due to global hypokinesia with no regional wall motion abnormalities and with PML tethering. HFrEF was associated with altered intracardiac flow patterns (28) in the presence of apically displaced vortices. This is consistent with our findings in the HFrEFpatients who underwent MVR with a bioprosthesis; however, no such observations were made after TEER and TMVR. Unfortunately,TEER completely disrupts intracardiac flow patterns making it impossible to evaluate any possible effect of LV function of vortex formation. Interestingly

the patient who had TMVR seemed not to be affected by HFrEF-related abnormalities and presented an almost complete restoration of a normal flow. This might be explained by a fully reversible myocardial impairment that responded well to volume and pressure overload resolution. Such inferences should be confirmed by advanced myocardial function analysis, as LV wall strain.

The main limitation of the present research is the small, heterogeneous sample size. However, this is a pivotal study analyzing all currently available MV treatments. It couldopen up the field of VFM analysis of MV surgery to define the optimal strategy to address MV disease.

Moreover, VFM evaluation is based on echocardiography which is operator dependent. All studies and post-processing analyses were performed by the same operator. More reproducible imaging techniques exist, such as cardiac MR, butthey are more expensive, present several limitationsand are less tolerated by the patient.

Finally, this is a 2D-TTE study. As demonstrated by the wide flow disruption after TEER in all 3 dimensions of the space, it is plausible that some of the vortices might have been missed because out of the imaging plane. 3D-TTEmight overcome this problem and shed new light on intracardiac flow mapping.

In conclusion, our findings confirm that intracardiac flow patterns are altered in patients with mitral disease and that MVRe is superior to MVR in restoring normal patterns. Based on our observations, TMVR might represent a better strategy than TEER to optimize LV function in the mid and long-term, thanks to its nearly normal flow patterns. Finally, better angulation of prosthetic valves and anatomical orientation can lead to more physiological intracardiac flow dynamics.

Our findings, even if qualitative and limited to a small study population, suggest that the treatment used to correct MR have an impact on postoperative intracardiac flow patterns. In the surgical community is a shared knowledge that MVRe is preferable over MVR because of better long-term outcomes. Similarly, TEER is associated with improved survival and symptoms only in selected patients. We believe that further studies of postprocedural intracardiac flow patterns can explain these differences supporting one therapy over another because more efficient in preserving or restoring physiological flow patterns.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by University of Pisa Ethic Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

NRP and GF: acquired and processed echo images; NRP: contributed to manuscript writing; LB: developed the study and wrote the manuscript; CP: was responsible of figure and video editing; other authors critically revised the manuscript. All authors contributed to the article and approved the submitted version

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1047244/full#supplementary-material.

Supplementary Figure S1
Apical long-axis view. Intracardiac vortices in early diastole (A) and mid systole (B) for control patient.

Supplementary Figure S2
Apical long-axis view. Intracardiac vortices in early diastole (A) and mid systole (B) for patient with DMR.

Supplementary Figure S3
Apical long-axis view. Intracardiac vortices in early diastole (A) and mid systole (B) for patient with FMR.

Supplementary Figure S4
Apical long-axis view. Intracardiac vortices in early diastole (A) and mid-systole (B) after surgical mitral valve repair with neochords and annuloplasty ring.

Supplementary Figure S5
Apical long-axis view. Intracardiac vortices in early diastole (A) and mid-systole (B) after transcatheter mitral valve repair with MitraClip (residual mild-moderate MR).

Supplementary Figure S6
Apical long-axis view. Intracardiac vortices in early diastole (A) and mid systole (B) after mitral valve replacement with bioprosthesis.

Supplementary Figure S7
Apical long-axis view. Intracardiac vortices in early diastole (A) and mid systole (B) after mitral valve replacement with mechanical prosthesis.

Supplementary Figure S8
Apical long-axis view. Intracardiac vortices in early diastole (A) and mid-systole (B) after transcatheter mitral valve replacement with Tendyne system.

Supplementary Figure S9
Apical long-axis view. Intracardiac vortices in early diastole (A) and mid-systole (B) after surgical implantation of a Sapien 3 valve in mitral annular calcification (MAC).

Supplementary Figure S10
Apical long-axis view. Intracardiac vortices in early diastole (A) and mid-systole (B) after transapical off-pump mitral valve repair with NeoChord TM device.

Supplementary Video S1
Energy loss distribution during the cardiac cycle in the left ventricle in control patient.

Supplementary Video S2
Energy loss distribution during the cardiac cycle in the left ventricle in patient with degenerative mitral regurgitation.

Supplementary Video S3
Energy loss distribution during the cardiac cycle in patient with functional mitral regurgitation.

Supplementary Video S4
Energy loss distribution during the cardiac cycle after mitral valve repair with neochords and annuloplasty ring.

Supplementary Video S5
Energy loss distribution during the cardiac cycle after transcatheter mitral valve repair with MitraClip.

Supplementary Video S6
Energy loss distribution during the cardiac cycle after mitral valve replacement with bioprosthesis.

Supplementary Video S7
Energy loss distribution during the cardiac cycle after mitral valve replacement with mechanical prosthesis.

Supplementary Video S8
Energy loss distribution during the cardiac cycle after transcatheter mitral valve replacement with Tendyne system.

Supplementary Video S9
Energy loss distribution during the cardiac cycle after surgical implantation of a Sapien 3 valve in mitral annular calcification (MAC).

Supplementary Video S10
Energy loss distribution during the cardiac cycle after transapical off-pump mitral valve repair with NeoChord TM device.

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Congenital aortic valve stenosis: from pathophysiology to molecular genetics and the need for novel therapeutics

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Congenital aortic valve stenosis (AVS) is one of the most common valve anomalies and accounts for 3%–6% of cardiac malformations. As congenital AVS is often progressive, many patients, both children and adults, require transcatheter or surgical intervention throughout their lives. While the mechanisms of degenerative aortic valve disease in the adult population are partially described, the pathophysiology of adult AVS is different from congenital AVS in children as epigenetic and environmental risk factors play a significant role in manifestations of aortic valve disease in adults. Despite increased understanding of genetic basis of congenital aortic valve disease such as bicuspid aortic valve, the etiology and underlying mechanisms of congenital AVS in infants and children remain unknown. Herein, we review the pathophysiology of congenitally stenotic aortic valves and their natural history and disease course along with current management strategies. With the rapid expansion of knowledge of genetic origins of congenital heart defects, we also summarize the literature on the genetic contributors to congenital AVS. Further, this increased molecular understanding has led to the expansion of animal models with congenital aortic valve anomalies. Finally, we discuss the potential to develop novel therapeutics for congenital AVS that expand on integration of these molecular and genetic advances.

KEYWORDS
congenital aortic valve stenosis, bicuspid aortic valve, human genetics, cardiac development, animal models

Introduction

Congenital heart disease (CHD) is the most frequently occurring birth defect with an incidence of 0.8%–1.2% among live births (1, 2). Congenital aortic valve stenosis (AVS) has an incidence of 3.8–4.9 per 10,000 live births, representing ~3%–6% of all CHD (1–3). Congenital AVS occurs more commonly in males as compared to females, with a reported ratio ranging from 3 to 5:1 (4, 5). It is defined as an obstruction of the aortic valve orifice due to a congenital valve malformation, which could be in the form of a bicuspid aortic valve (BAV), unicuspid aortic valve, or fused or malformed aortic valve cusps (6, 7) Associated CHD is found in approximately 20% of patients with congenital AVS, including ventricular septal defect (VSD), coarctation of the aorta (CoA), and patent ductus arteriosus (8). In this review, we aim to describe our

understanding of aortic valve development with a particular focus on the embryology, anatomy and pathology relevant to congenital AVS. Further, we discuss the clinical characteristics of congenital AVS, including the natural history and current treatment options. Lastly, we highlight the molecular genetics of congenital AVS and discuss the prospects for the development of future potential therapeutics.

Embryology

Heart development occurs during the first trimester of pregnancy in humans from the embryonic gestational ages of 6 to 9 weeks. Here, we focus on semilunar valve development and refer the reader to comprehensive reviews on cardiac morphogenesis for details on this process (9, 10). Development of semilunar valves, which include the aortic valve and pulmonary valve, initiates between 7 and 9 weeks of gestation in the human embryo, and development of mature valve cusps continues after birth (11). This process has been well studied in mouse embryogenesis and is detailed here (12, 13). The primitive linear heart tube consists of an outer layer of myocardium and an inner layer of endocardium at embryonic day (E) 8.0. By E9.5, the heart has undergone rightward looping and is composed of the following 4 segments: the atrium, atrioventricular canal (AVC), ventricle, and outflow tract (OFT). During this time, a subset of endocardial cells forms swellings known as endocardial cushions within the AVC and embryonic cardiac OFT. In response to molecular signals from the adjacent myocardium, endocardial cells covering the cushions undergo endothelial-to-mesenchymal transformation (EMT) between E9.5 and E11.5 (**Figure 1A**). These mesenchymal cells migrate into the cardiac jelly and proliferate to occupy the endocardial cushions in the proximal OFT, while in the distal OFT the cardiac neural crest cells (CNC) are the major contributor. By E11.5, the AVC and OFT cushions have completed cellularization. After E11.5, the AVC and OFT cushions rapidly grow and remodel. This involves both apoptosis of valvular interstitial cells (VICs) as well as dynamic ECM arrangement (**Figure 1B**). Complex molecular networks tightly regulate each step of EMT, including the transforming growth factor-β (TGF-β) (14, 15), bone morphogenetic protein (BMP) (15, 16), WNT (17, 18), Notch (19, 20) and vascular endothelial growth factor A (VEGF) signaling pathways (21, 22). Although EMT is required for pooling mesenchyme valve precursors within the endocardial cushions, other cell lineages also play an essential role, including the CNC and secondary heart field (SHF) cells (23–27). CNC cells occupy the distal outflow tract cushions after migration from the aortic sac. By E12.5, the distal outflow tract is divided into the into the aorta and pulmonary artery by the aortopulmonary septum. On the other hand, the proximal outflow tract cushion contains mostly EMT-derived mesenchymal cells. During cushion development, the two cushions fuse at the distal-proximal boundary, where neural crest- and endothelium-derived mesenchymal cells meet, and the proximal outflow tract is separated into two ventricular outlets. The non-fused cushions then undergo extensive ECM remodeling and morphological sculpting and extend to become the coronary apex of the aortic valve. Mature left and right coronary cusps are derived primarily from endothelium-derived mesenchymal progenitor cells, with little contribution from CNC cells, while non-coronary cusp contains cells of the SHF lineage (28, 29).

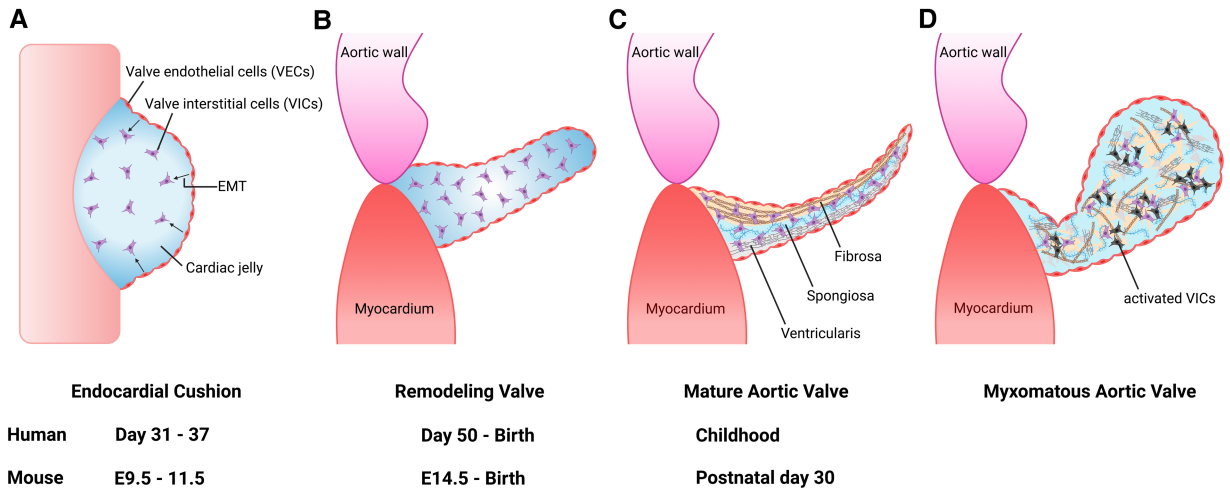

FIGURE 1
Aortic valve development and progression to myxomatous aortic valve. (**A**) Valve development begins with endocardial cushion formation. Valve endothelial cells (VECs) lining the cushion undergo endothelial-to-mesenchymal transformation (EMT) to differentiate into valve interstitial cells (VICs) between 7 and 9 weeks gestation in humans, and embryonic day (**E**) 9.5 and E11.5 in the mouse. (**B**) The outflow tract endocardial cushions undergo remodeling into mature valve leaflet. (**C**) Mature valve layers consist of fibrosa, spongiosa, and ventricularis. (**D**) Myxomatous alterations associated with leaflet thickening, activated VICs (black cells), disorganized extracellular matrix, diffuse accumulation of proteoglycans and fragmentation of collagen and elastin fibers.

Aortic valve anatomy

The aortic valve is located between the left ventricle (LV) and ascending thoracic aorta (6). Like all valves in the heart, it serves to maintain unidirectional flow. The aortic valve is avascular and is connected to the aortic root by the fibrous annulus (30). Each leaflet is named according to the location corresponding to the coronary artery ostia and are accordingly referred to as the right coronary cusp, left coronary cusp and noncoronary cusp (31). Each cusp is composed of three layers of extracellular matrix (ECM) components that are oriented relative to blood flow, including the fibrosa comprised of collagen, the proteoglycan-rich spongiosa, and the elastin fiber-containing ventricularis (32) (**Figure 1C**). In addition, fibronectin and lamin are included in the aortic valve cusps as minor ECM components (33). The cellular composition of the aortic valve is comprised of VICs and valve endothelial cells (VECs). VICs are found within the interior of each cusp and important for ECM synthesis and homeostasis, while VECs form a protective cellular layer that surrounds each cusp. The communication between VICs and VECs *via* paracrine signaling is necessary to preserve ECM homeostasis and prevent disease (34–36).

Aortic valve pathology

The pathologic features of diseased heart valves include myxomatous degeneration, which is characterized histologically by leaflet thickening, diffuse accumulation of proteoglycans and fragmentation of collagen and elastin fibers (**Figure 1D**) (37). Myxomatous valve disease is more commonly found in the mitral valve. It can be caused by congenital valve malformations, genetic abnormalities such as pathogenic variants in ECM genes, or can be acquired due to autoimmune diseases, progressive cardiovascular dysfunction/heart failure and infective endocarditis (38–40). Myxomatous valves also demonstrate an increased recruitment of pro-inflammatory macrophages and immunogenic ECM remodeling consistent with an inflammatory micro-environment (41). These findings suggest that macrophages play a role in the initiation and progression of myxomatous valve disease.

Aortic valves in infants with severe congenital AVS were reported to be described as "greatly thickened" and "nodular" and often had bicuspid morphology (42). Pathological and histological findings of congenital AVS demonstrated the primitive mesenchymal tissue, located between the valve endothelial layers, to be increased as well as containing a loose myxomatous ground substance. Further, the cells within the ground substance were described as spindle-shaped, similar to that seen in myxomatous valve tissue (**Figure 1D**). Interestingly, the valvular tissue resembled that of the endocardial cushions in the developing fetal heart. In normal heart development, loose connective tissue within the endocardial cushions is supposed to thin out and transition into dense, mature tissue. As a result, it is suggested this persistence of this loose embryonic connective tissue and likely its continued growth is a defining feature of congenital AVS.

Inflammation remains unclear as a contributor to congenital AVS. However, inflammation plays a significant role in many of the chronic diseases of adulthood, including cardiovascular disorders (43). Valvular inflammation can result in fibrosis, thickening, and calcification. Calcific aortic valve disease (CAVD) is the most common valvular condition in the developed world and increases in prevalence with age (44). Evidence of chronic inflammatory infiltrates in tissue exhibiting CAVD has been demonstrated along with a positive correlation between rate of progression and density of leukocytes (45). In the case of BAV, chronic inflammation may explain the earlier onset of disease, given that stenosis of a BAV is associated with increased inflammatory cells and vascularity in comparison to AVS in a tricuspid aortic valve (46). Together, these findings demonstrate that congenital AVS and adult-onset AVS may differ in regard to inflammation. There are multiple glycoproteins which regulate the aortic valve structure during development and are associated with progression (47, 48). N-glycosylation was found to be spatially regulated within the normal aortic valve and sialylated N-glycans were increased in pediatric end-stage congenital AVS (49). Collagen deregulation is a distinctive feature of congenital AVS, while the regulation of the collagen fibers in the aortic valve remains largely elusive. A recent study identified the collagen types and hydroxylated prolines (HYP) modifications, which are critical to stabilizing the triple helix of collagen, that are seen during human aortic valve development and at pediatric end-stage congenital AVS (50). Histological and proteomic analysis identified a unique region of high-density collagen present in pediatric end-stage congenital AVS and reported that specific collagen peptides were modified by HYP. In addition, network analysis identified BAMBI (BMP and Activin Membrane Bound Inhibitor) as a prospective regulator of the collagen interactome.

Clinical characteristics, natural history and management of congenital AVS

Clinical presentations of congenital AVS vary widely, ranging from mild to critical, depending on the aortic valve morphology and the severity of AVS, but progress over time. During the fetal period, mild or moderate AVS leads to increased LV pressures and LV hypertrophy. Severe AVS results in severe LV hypertrophy and decreased flow through LV, which may ultimately lead to hypoplastic left heart syndrome (HLHS) (51–53). The fetus usually tolerates severe AVS, but symptoms can develop rapidly after birth. Critical AVS in neonates often presents with heart failure, cardiogenic shock, and other end organ dysfunction and can lead to death within the first weeks of life (54). Older children and adolescents with AVS tend to be asymptomatic with approximately 10% experiencing symptoms and signs of congestive heart failure, including dyspnea, angina, or syncope especially upon exercise (55). A combination of maximum aortic velocity (V_{max}), mean pressure gradient (MPG),

and aortic valve area (AVA) are used to assess the severity of stenosis as published in the most recent American College of Cardiology (ACC) and American Heart Association (AHA) guidelines (56).

The natural history of patients with congenital AVS shows that progressive obstruction is likely to occur by late adulthood. In childhood, significant progression was seen in one third of all medically managed patients in the Natural History Study (57). A follow-up study for 30 years found that the diagnosis of mild AVS before 6 months of age was associated with a significantly increased risk of requiring aortic valvotomy and balloon valvuloplasty with age (58). The likelihood that the stenosis remains mild was reported to be less than 20%, thus supporting the need for long-term follow-up of mild AS into adulthood. Recently, the probability of requiring balloon valvuloplasty is shown to be 20% in patients with catheter-measured peak pressure gradients less than 25 mmHg, and 40% and 70% in patients with gradients 25–49 mmHg and >50 mmHg, respectively (59). Notably, congenital AVS is a progressive disorder as the risk of morbid events such as heart failure, sudden death, and ventricular arrhythmia increase at a rate of 1%–1.5% per year, if left untreated (6, 59). Similarly, the risk of developing AVS in children with isolated BAV increases along with age (6). As with all CHD, bacterial endocarditis remains a potential complication of AVS, with an incidence of 27.1 per 10,000 person years (60). As congenital AVS is a progressive condition, guidelines have been developed which outline the indications for intervention. These interventions are limited to balloon valvuloplasty in the cardiac catheterization laboratory and transcatheter aortic valve replacement or surgical aortic valve replacement. We refer readers to recent clinical management guidelines from the ACC/AHA or European Society of Cardiology (ESC) for timing of intervention and different valve replacement options as these details are beyond the scope of this review (56, 61, 62).

Molecular genetics of congenital aortic valve disease

Recent advances in genetic sequencing technologies, such as massively parallel sequencing, as well as interpretation of the clinical presentation and genetic variants, have made it easier for establishing a diagnosis and discovering new genetic etiologies for congenital aortic valve disease, including *ADAMTS19, SMAD6 and ROBO* gene family members (63, 64). Multiple human genetic abnormalities associated with syndromic and non-syndromic congenital aortic valve disease have been identified, including AVS and BAV (**Tables 1**, **2**). However, compared to BAV, well established genetic contributors to congenital AVS are scarce. Common syndromes associated with congenital AVS are Turner syndrome and Jacobson syndrome. Turner syndrome is caused by chromosomal aneuploidies (Monosomy X) and associated CHD is observed in 30% of cases, including AVS, BAV, CoA and HLHS (65). Jacobsen syndrome is caused by terminal deletion of chromosome 11q and associated CHD is found in 56% of cases, including AVS, HLHS, CoA and VSD (66). In addition to Turner syndrome and Jacobsen syndrome, several common syndromes associated with BAV are known. Congenital heart valve anomalies associated with Trisomy 18 (Edwards syndrome) include BAV, bicuspid pulmonary valve and polyvalvular nodular dysplasia (67, 68). BAV is present in 1p36 deletion syndrome as well as Kabuki syndrome caused primarily by *KMT2D* and *KDM6A* variants (69–71). BAV and thoracic aortic aneurysm (TAA) have been also described in Marfan syndrome associated with *FBN1* variants (72) or Loeys-Dietz syndrome associated with *TGFBR1* and *TGFBR2* variants (73).

For non-syndromic congenital AVS, only a few genes have been implicated. *NOTCH1* pathogenic variants were identified in individuals with left ventricular outflow tract (LVOT) malformations, including congenital AVS, CoA and HLHS (74, 75). *SMAD6* variants were observed in patients with AVS and BAV (83). *ROBO4* variants were also identified in individuals with AVS and atrial septal defect (ASD) (84). Furthermore, variants in *vascular endothelial growth factor-A* (*VEGFA*) were found in a patient with congenital tricuspid AVS and LVOT obstruction (85, 86). Moreover, *ADAMTS19* variants were found to cause a spectrum of congenital heart valve diseases, including AVS, aortic valve insufficiency, subaortic stenosis, pulmonary valve stenosis, pulmonary valve insufficiency and atrioventricular valve insufficiency (87, 88). However, no other genes have been reported as monogenic causes of congenital AVS. Previous studies reported that common variants in genes linked to cardiac development such as *ERBB4*, *BMP4*, and *ISL1*, may bestow risk for LVOT defects, including congenital AVS (103–105).

Taking another approach, genome-wide DNA methylation analysis identified significant alterations in CpG methylation at 59 sites in 52 genes for congenital AVS (106). A significant epigenetic change in the *APOA5* and *PCSK9* genes, which are known to be important in lipid metabolism, was also observed associated with AVS. It remains to be determined if pathogenic variation in the other 50 genes will be implicated in congenital AVS.

As BAV is often found in the setting of congenital AVS, there is likely overlap in the genetic etiologies of BAV and congenital AVS. BAV is widely acknowledged to have genetic contributors with a reported heritability of 89% (107). Insights into the genetic contributors of BAV were first provided from studies of familial BAV, where *NOTCH1* variants were discovered to segregate in familial aortic valve disease through linkage analysis, including BAV, AVS and CAVD (74). Since then, pathogenic variants in *NOTCH1* have been found to cause not only left -sided CHD, including BAV, CoA and HLHS (75, 76–79), but also other types of CHD such as tetralogy of Fallot (TOF) and VSD (80–82). The GATA family of zinc-finger transcription factors, particularly GATA4, GATA5, and GATA6, play essential roles in cardiac development. Pathogenic variation in *GATA5* is well characterized in human BAV (89–91), but *GATA5* variants have also been associated with a spectrum of CHD, including TOF,

TABLE 1 Genetic syndromes associated with congenital aortic valve disease.

Syndrome	Gene	Location	Cardiac defects	Gene MIM	Reference
Turner syndrome	Unknown	45, X (monosomy X)	AVS, CoA, BAV, dilated Ao, HLHS	NA	(65)
Jacobsen syndrome	*ETS*	11q terminal deletion	AVS, HLHS, VSD, CoA, Shone's complex	164720	(66)
	FLI1			193067	
Edwards syndrome	Unknown	Trisomy 18	BAV, Bicuspid pulmonary valve, Polyvalvular nodular dysplasia	NA	(67, 68)
Kabuki syndrome	*KMT2D*	12q13.12	BAV, CoA, VSD, TOF, HLHS, TGA	602113	(69–71)
	KDM6A	Xp11.3		300128	
Marfan syndrome	*FBN1*	15q21.1	BAV, TAA, aortic dissection, mitral valve prolapse	134797	(72)
Loeys-Dietz syndrome	*TGFBR1*	9q22.33	BAV, TAA, aortic dissection, mitral valve prolapse	190181	(73)
	TGFBR2	3p24.1		190182	

AVS, aortic valve stenosis; BAV, bicuspid aortic valve; CoA, coarctation of the aorta; dilated Ao, dilated ascending aorta; HLHS, hypoplastic left heart syndrome; NA, not available; TAA, thoracic aortic aneurysm; TGA, transposition of great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

TABLE 2 Human genes associated with congenital aortic valve disease.

Gene	Location	Cardiac defects	Gene MIM	Reference
NOTCH1	9q34.3	AVS, BAV, CAVD, HLHS, TOF, PS, VSD, CoA, TAA	190198	(74–82)
SMAD6	15q22.31	AVS, BAV, CoA, TAA	602931	(83)
ROBO4	11q24.2	AVS, BAV, ASD, TAA	607528	(84)
VEGFA	6p21.1	AVS, BAV, CoA, VSD, PDA, dilated Ao	192240	(85, 86)
ADAMTS19	5q23.3	AVS, Aortic valve insufficiency, BAV, subaortic stenosis, PVS, pulmonary valve insufficiency, mitral/tricuspid valve insufficiency	607513	(87, 88)
GATA5	20q13.33	BAV, ASD, VSD, DORV, TOF	611496	(89–91)
GATA4	8p23.1	BAV, ASD, VSD, AVSD, PS, TOF	600576	(92, 93)
GATA6	18q11.2	PTA, TOF, BAV	601656	(94–96)
NKX2.5	5q35.1	BAV, ASD, atrioventricular conduction delay, TOF, HLHS	600584	(97)
NOS3	7q36.1	BAV	163729	(98, 99)
TAB2	6q25.1	BAV, Aortic stenosis, subaortic stenosis, ASD, TOF, VSD, myxomatous mitral/tricuspid valves	605101	(100, 101)
MAT2A	2q11.2	BAV, TAA	601468	(102)

ASD, atrial septal defect; AVS, aortic valve stenosis; AVSD, atrioventricular septal defect; BAV, bicuspid aortic valve; CoA, coarctation of the aorta; dilated Ao, dilated ascending aorta; DORV, double-outlet right ventricle; HLHS, hypoplastic left heart syndrome; PDA patent ductus arteriosus; PS, pulmonary stenosis; PTA, persistent truncus arteriosus; PVS, pulmonary valve stenosis; TAA, thoracic aortic aneurysm; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

VSD, ASD and double outlet right ventricle (DORV) (108–110). *GATA4* pathogenic variants were identified in BAV cases (92) and in addition, the burden of rare variants in *GATA4* were shown to be significantly enriched in early-onset BAV (93). Although *GATA6* variants have been mainly implicated in conotruncal heart defects (94, 95), *GATA6* loss-of-function variants were identified in a family with BAV (96). Furthermore, a deleterious variant in *NKX2.5* was identified in a family with BAV (97), while pathogenic variants in *NKX2.5* have been reported in ASD along with atrioventricular conduction abnormalities, VSD, TOF and HLHS (111–113). The contribution of other candidate genes, such as *NOS3, TAB2,* and *MAT2A* has been also suggested in BAV (98–102).

Mouse models of congenital aortic valve disease

Since congenitally stenotic aortic valves have often been manipulated due to current management strategies, there is limited access to diseased human tissues to investigate mechanisms of disease initiation and progression. Accordingly, animal models serve an important role in understanding the genetic etiologies and progression of congenital AVS (114). A summary of reported genetic mouse models found to exhibit congenital aortic valve disease can be found in **Table 3**, including congenital AVS and BAV. Morphological phenotypes in BAV are summarized in **Figure 2** (133). Although *NOTCH1* has been implicated in human aortic valve disease, *Notch1* haploinsufficiency causes CAVD and ascending aortic aneurysms in mice, but not congenital aortic valve abnormalities (134, 135). Interestingly, while mice which are homozygous for a null mutation in endothelial NOS ($Nos3^{-/-}$) display a partially penetrant BAV at an incidence of ~25% (117, 118), *Notch1*; *Nos3* compound mutant mice ($Notch1^{+/-}$; $Nos3^{-/-}$) display congenital aortic valve disease such as BAV and AVS at a penetrance of 64%. These aortic valve abnormalities are accompanied by additional cardiac outflow tract defects resulting in ≈65% lethality by postnatal day 10 (35, 115). Telomere shortening in *Notch1* haploinsufficient mice ($Notch1^{+/-}$ mTR^{G1-3}) elicit age-dependent tricuspid AVS and aortic valve calcification, however, early lethality is observed (116). In addition, cell-specific deletion or inactivation of mediators of Notch signaling pathway, such as *JAG1* or *RBPJ,* in mice demonstrate BAV at a penetrance of 47%–54% with high perinatal lethality (121, 122). Interestingly, no endocardial cushion defects are observed in these murine models of BAV targeting Notch ligands, suggesting that congenital aortic valve disease may result from a disruption in the process that occurs after EMT, potentially during the valve remodeling. Genetic

TABLE 3 Mouse models of congenital aortic valve disease.

Gene	Genotype of mouse model	Valve phenotype	Aortic valve disease penetrance	BAV subtype	Other cardiac defects	Lethality	Reference
NOTCH1	*Notch1*$^{+/-}$; *Nos3*$^{-/-}$	BAV, thickened AoV and PV	≈64%	NA	Ascending aortic dilation, VSD, overriding aorta	≈65%	(35, 115)
	Notch1$^{+/-}$ *mTR*$^{G1-3}$ (mTR$^{-/-}$ generation 1–3)	AVS, Thickened AoV, CAVD, PVS	NA	None	Ascending aortic dilation, ASD, VSD	70%	(116)
NOS3	*Nos3*$^{-/-}$	BAV	27–42%	R/NC	None	None	(117, 118)
GATA5	*Gata5*$^{-/-}$	BAV	25%	R/NC	Mild LV hypertrophy	None	(119)
GATA6	*Gata6*$^{+/-}$	BAV	56% males, 27% females	R/L	None	None	(120)
ROBO4	*Robo4*$^{tm1Lex/tm1Lex}$	BAV, AVS, thickened AoV	18% males, 11% females	NA	Ascending aortic dilation	None	(84)
ADAMTS19	*Adamts19*$^{KO/KO}$	AVS, AR, thickened AoV, BAV	38%	NA	None	None	(87)
JAG1	*Nkx2.5Cre+*; *Jag1*$^{flox/flox}$	BAV	47%	R/NC or R/L	VSD	94%	(121)
RBPJ	*Nkx2.5Cre+*; *Rbpj*$^{flox/flox}$	BAV	54%	75% R/NC, 25% R/L	VSD, DORV	100%	(122)
NKX2.5	*Nkx2.5*$^{+/-}$	BAV, AVS	8.2%	NA	ASD	None	(123)
MATR3	*Matr3*$^{Gt-ex13}$ heterozygotes	BAV	15%	NA	CoA, PDA, VSD, DORV	None	(124)
EGFR	*Egfr*$^{Vel/+}$	Unicuspid AoV, AVS, AR	38%	None	None	None	(125)
BRG1	*Nfatc1Cre+*; *Brg1*$^{flox/flox}$	BAV, thickened AoV and PV	35%	67% L/NC, 33% R/NC	VSD	97%	(126)
HOXA1	*Hoxa1*$^{-/-}$	BAV	24%	NA	VSD, TOF, IAA	NA	(127)
ADAMTS5	*Adamts5*$^{-/-}$; *Smad2*$^{+/-}$	BAV	41%	NA	Ascending aortic anomalies	None	(128)
EXOC5	*Nfatc1Cre+*; *Exoc5*$^{flox/+}$	BAV, AVS, dysmorphic AoV	45%	80% R/NC, 20% L/N	VSD	None	(129)
ALK2	*Gata5Cre+*; *Alk2*^{FXKO}	BAV	78%	NA	VSD	55%	(130)
NPR2	*Npr2*$^{+/-}$	BAV, AVS, CAVD	9.4%	R/NC	Ascending aortic dilation, LV dysfunction	None	(131)
	Npr2$^{+/-}$; *Ldlr*$^{-/-}$						
VGLL4	*Vgll4*$^{-/-}$	Thickened AoV and PV	NA	NA	LV hypertrophy	89%	(132)
	Tie2Cre+; *Vgll4*$^{-/-}$						

AoV, aortic valve; AR, aortic regurgitation; ASD, atrial septal defect; AVS, aortic valve stenosis; BAV, bicuspid aortic valve; CAVD, calcific aortic valve disease; CoA, coarctation of the aorta; DORV, double-outlet right ventricle; IAA, interrupted aortic arch; L/NC, left/noncoronary fusion; LV, left ventricular; NA, not available; NS, non-syndromic; PDA patent ductus arteriosus; PV, pulmonary valve; PVS, pulmonary valve stenosis; R/L, right/left fusion; R/NC, right/noncoronary fusion; SVAS, supravalvular aortic stenosis; TGA, transposition of great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

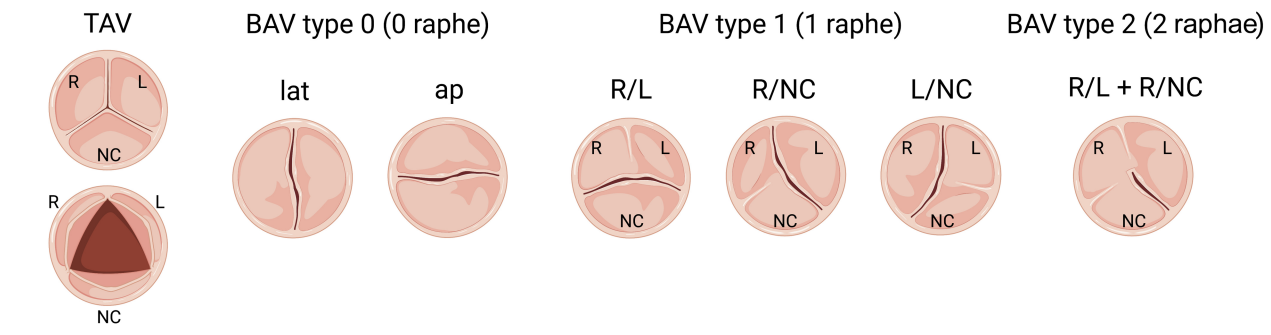

FIGURE 2
Schematic of morphologic phenotypes in bicuspid aortic valve (BAV). Schematic depiction of a normal tricuspid aortic valve (TAV) and three subtypes of BAV based on the raphe position relative to coronary artery origins: Type 0 (no raphe), Type 1 (one fibrous raphe) and Type 2 (two raphae). Type 1 is the most common, including BAV R/L (right-left fusion), R/NC (right-noncoronary fusion) and L/NC (left-noncoronary fusion), followed by Type 0, including lat (lateral arrangement of the free edge of the cusps) and ap (anterior-posterior arrangement of the free edge of the cusps), and the most infrequent is Type 2.

deletion of *Gata5* in mice (*Gata5*$^{-/-}$) lead to R/NC subtype BAV at a partially penetrance of 25% (119). *Gata6* haploinsufficient mice (*Gata6*$^{+/-}$) develop R/L subtype BAV with incidence of 56% in males and 27% in females (120). Furthermore, SHF-specific deletion of *Gata6* within the *Isl1*-lineage recapitulated the BAV phenotype, suggesting the role of Gata6 in SHF during valve development. Heterozygous *Nkx2.5* knockout mice display a variety of cardiac phenotypes, depending on the genetic background, including BAV with AVS at a low penetrance of 8.2% (123). In addition to these mice, other genetic mouse models of congenital aortic valve disease have been described, whereas the majority have limitations with regards to a low

penetrance or high lethality (84, 87, 124–132). Further studies are needed to generate murine models with a high penetrance that survive to adulthood, allowing us to validate the role of cardiac developmental genes in the etiology of aortic valve disease as well as investigate their role in disease progression and to serve as models to test novel therapies.

Clinical implications and future directions

Given the limited translation of molecular mechanisms found in animal models to human patients, effective pharmacologic therapies for congenital AVS remain elusive. The current standard treatment is transcatheter/surgical repair or replacement of the diseased valve. Recently, fetal aortic valvuloplasty has been performed in fetuses with AVS and evolving HLHS. However, outcomes for achieving biventricular circulation remain controversial and this has not been applied to isolated congenital AVS (136, 137). Thus, development of novel medical treatment for congenital AVS is essential, while pharmacological therapies are limited. One limited treatment option is statin therapy to treat elevated cholesterol levels. Statins have been demonstrated to reduce cardiovascular risk and prevent cardiovascular disease such as coronary artery disease (138, 139). Although some attempts have been made to utilize pharmacologic treatments such as statins to treat CAVD with associated AVS in adults, these studies did not show consistent beneficial effects for progression of AVS (140, 141). The pathophysiology of degenerative AVS in adults is similar to coronary artery disease, whereas atherosclerosis pathway may not play a significant role in the development of congenital aortic valve disease, including BAV. Therefore, statins have not been tested in children with aortic valve disease and the clinical impact on congenital AVS in children remains unknown. Increased understanding the molecular pathways regulating aortic valve development along with advances in genetic sequencing technologies have allowed for the discovery of new candidate genes for congenital aortic valve disease. In addition, genetic murine models of aortic valve disease have been generated and uncovered molecular pathways as potential therapeutic targets. Specifically, TGF-β signaling is activated in degenerative valves with ECM abnormalities and may be a potential therapeutic target, as TGF-β antagonists such as the angiotensin II type 1 receptor blocker, losartan, could prevent abnormal aortic root growth in a mouse model of Marfan syndrome (142). In addition, targeting monocyte-derived macrophages has emerged as a potential therapeutic approach to prevent myxomatous valve disease in Marfan syndrome mice (41). Recent studies by using single-cell RNA-sequencing, human induced pluripotent stem cell (iPSC) technology and machine learning, identified new pathogenic pathways and a new therapeutic candidate to prevent aortic valve disease in mouse models of CAVD, although the implications for congenital AVS are unknown (36, 143). Further, the molecular and genetic links between congenital aortic valve disease and adult CAVD need to be defined. Improved identification of human aortic valve disease genes, generation of murine models for clinically relevant congenital AVS, and new technologies such as single cell genomics, iPSC modeling and machine learning may reveal novel therapeutic targets to develop effective treatments for early intervention.

Conclusions

Congenital AVS is a complex and progressive disease that affects children and adults throughout their lives. Although advances in transcatheter aortic valvuloplasty and transcatheter or surgical aortic valve implantation have improved morbidity and mortality in this patient population, pharmacologic therapies for congenital AVS remain elusive. Several potential therapeutic targets have been proposed in animal models to prevent the myxomatous valve disease by using next-generation sequencing, single-cell genomics, machine learning, cardiac organoid and bioengineering technologies. A continued escalation of our understanding in molecular genetics of congenital AVS has clinical implications as it will facilitate the development of new treatment options to prevent the progression or treat congenital AVS.

Author contributions

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Treatment of pure aortic regurgitation using surgical or transcatheter aortic valve replacement between 2018 and 2020 in Germany

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Background: In pure aortic regurgitation, transcatheter aortic valve replacement (TAVR) is not yet used on a regular base. Due to constant development of TAVR, it is necessary to analyze current data.
Methods: By use of health records, we analyzed all isolated TAVR or surgical aortic valve replacements (SAVR) for pure aortic regurgitation between 2018 and 2020 in Germany.
Results: 4,861 procedures—4,025 SAVR and 836 TAVR—for aortic regurgitation were identified. Patients treated with TAVR were older, showed a higher logistic EuroSCORE, and had more pre-existing diseases. While results indicate a slightly higher unadjusted in-hospital mortality for transapical TAVR (6.00%) vs. SAVR (5.71%), transfemoral TAVR showed better outcomes, with self-expanding compared to balloon-expandable transfemoral TAVR having significantly lower in-hospital mortality (2.41% vs. 5.17%; $p = 0.039$). After risk adjustment, balloon-expandable as well as self-expanding transfemoral TAVR were associated with a significantly lower mortality vs. SAVR (balloon-expandable: risk adjusted OR = 0.50 [95% CI 0.27; 0.94], $p = 0.031$; self-expanding: OR = 0.20 [0.10; 0.41], $p < 0.001$). Furthermore, the observed in-hospital outcomes of stroke, major bleeding, delirium, and mechanical ventilation >48 h were significantly in favor of TAVR. In addition, TAVR showed a significantly shorter length of hospital stay compared to SAVR (transapical: risk adjusted Coefficient = –4.75d [–7.05d; –2.46d], $p < 0.001$; balloon-expandable: Coefficient = –6.88d [–9.06d; –4.69d], $p < 0.001$; self-expanding: Coefficient = –7.22 [–8.95; –5.49], $p < 0.001$).
Conclusions: TAVR is a viable alternative to SAVR in the treatment of pure aortic regurgitation for selected patients, showing overall low in-hospital mortality and complication rates, especially with regard to self-expanding transfemoral TAVR.

KEYWORDS

aortic regurgitation, transcatheter aortic valve replacement, transcatheter aortic valve implantation, surgical aortic valve replacement, in-hospital outcomes, national electronic health records

Introduction

Transcatheter aortic valve replacement (TAVR) has shown rapid developments (1–3). Its use was initially limited to patients with aortic valve stenosis (4–6). For this indication, TAVR is now a common therapy in the United States (7) and Germany (2, 6). However, in pure aortic regurgitation, TAVR is not yet used on a regular base. According to the current European (8) and American (9) guidelines for the management of valvular heart disease, surgery is the standard when valve replacement is required for aortic regurgitation; TAVR might be taken into account in selected patients with an aortic regurgitation who are not eligible for surgical aortic valve replacement (SAVR).

We previously analyzed TAVR in aortic regurgitation in Germany from 2008 to 2015, and concluded that TAVR may be a safe option for treating aortic regurgitation (5). However, in the early years of TAVR, its use in the context of aortic regurgitation was even rarer than it is today. In addition, due to the constant development of TAVR, it is necessary to analyze current data to gain further insights.

We have now compared all patients who were treated with SAVR or TAVR for pure aortic regurgitation between 2018 and 2020 in Germany. Our analysis thus represents the current state of research in this area. Furthermore, we distinguish between the different access routes of TAVR (i.e., transfemoral (TF) or transapical (TA)), and valve types (balloon-expandable (BE) or self-expanding (SE)).

Material and methods

Since 2005, the data of all hospital stays in Germany can be used for scientific purposes via Diagnosis Related Groups (DRG) statistics, which are collected by the Research Data Center of the Federal Bureau of Statistics (DESTATIS). These data on hospital stays, including diagnoses and procedures, are a valuable nationwide data source on in-hospital patient treatment and represent a virtually complete collection of all hospital stays in German centers that are reimbursed in accordance with the DRG system. From this database, data on all isolated SAVR and TAVR procedures conducted between 2018 and 2020 were extracted (2, 10, 11). We defined the isolated procedures using OPS codes, including all aortic valve procedures and excluding concomitant procedures at the mitral valve, tricuspid valve procedures, coronary artery bypass graft procedures and Maze procedures. We included data on patients with pure aortic regurgitation only (main or secondary diagnosis: I35.1, I35.8, I35.9, I06.1, I06.8 or I06.9). Thus, patients with a documented aortic valve stenosis (main or secondary diagnosis: I35.0, I35.2, I06.0, I06.2) were excluded. Since our focus was on isolated SAVR and TAVR procedures, we also excluded those patients with a concomitant cardiac surgery or a percutaneous coronary intervention (5).

Furthermore, we used a set of baseline characteristics to describe the underlying diseases and the risk factors of the patients studied. ICD codes have been previously discussed in more detail (2). Using the European System for Cardiac Operative Risk Evaluation (EuroSCORE) (12), a "best-case scenario" risk score was estimated. In addition to age and sex, we utilized the ICD codes for a chronic pulmonary disease (J43*, J44*), a neurological dysfunction (I69*, G81*, R48*), a previous cardiac surgery (Z95.1–Z95.4), a serum creatinine >200 µmol/L (N18.0, N18.84, N18.5), an active endocarditis (I33*), unstable angina (I20.0), a recent myocardial infarction (I25.20), and a pulmonary hypertension (I27*). An inconspicuous state was supposed for the "preoperative state" and "left ventricular function" due to the lack of data (the "best-case", i.e., no emergency, preserved left ventricular function). To allow comparison of baseline risk factors in patients treated with transcatheter or surgical aortic valve replacement, the logistic EuroSCORE was evaluated assuming isolated aortic valve replacement.

In-hospital outcomes are in-hospital mortality, major bleeding with more than five units of red blood cells needed during the in-hospital stay (OPS: 8-800.c1 et seqq.), stroke (ICD: I63* and I64), and postoperative delirium (ICD: F05). Furthermore, health economic outcomes comprise the length of hospital stay, reimbursement, and mechanical ventilation >48 h, which are provided by DESTATIS' own variable pool.

Due to the lack of codes indicating missing data, an attribution of missing values could not be performed. If a clinical characteristic was not included in the patient's electronic health record, it was presumed not to be present.

To calculate differences in outcomes between groups, Student's t-test and chi-square test were applied for continuous and categorical variables, respectively. In addition, we used multivariable logistic or linear regression models and included 21 baseline characteristics as potential confounders, as listed in **Table 1**. We included a random intercept at the hospital level to account for the correlation of error terms of patients treated at the same hospital. Based on these confounder-adjusted regression analyzes, predicted rates and means were calculated using marginal standardization (13). The results of the regression analyzes are presented in the **Supplementary Appendix S1**.

No adjustment for multiple testing took place. Therefore, the *p*-values may not be interpreted as confirmatory but as descriptive. All analyses were carried out using Stata 17 (Stata Corp, College Station, Texas).

Results

Baseline characteristics

Between 2018 and 2020, a total of 4,861 patients were treated for a pure aortic regurgitation with either TAVR or SAVR (**Table 1**). Of these, 4,025 received SAVR, 50 TA-TAVR, 329 BE TF-TAVR, and 457 SE TF-TAVR. While the number of SAVR procedures decreased from 1,389 to 1,277 between 2018 and 2020, the number of TAVR increased from 268 to 302 (**Figure 1**).

Age was noticeably higher in TAVR than SAVR (SAVR vs. TA vs. BE vs. SE: 62.75a, 76.00a, 76.27a, 77.25a). The same applied to the logistic EuroSCORE, which was higher in TAVR (4.93, 19.08, 18.23, 17.66). Likewise, patients in the TAVR groups had more pre-existing diseases, e.g., more higher grade heart failure NYHA III/IV (33.81%,

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TABLE 1 Baseline characteristics of patients with pure aortic regurgitation between 2018 and 2020 in Germany.

	SAVR		TA-TAVR		TF-TAVR BE		TF-TAVR SE	
N	4,025		50		329		457	
2018	34.51%		34.00%		30.70%		32.82%	
2019	33.76%		26.00%		32.52%		31.95%	
2020	31.73%		40.00%		36.78%		35.23%	
Female	25.42%		38.00%		25.84%		40.26%	
Age in years, mean / SD	62.75	13.58	76.00	9.15	76.27	9.54	77.25	8.11
Logistic EuroSCORE, mean / SD	4.93	5.69	19.08	14.68	18.23	13.45	17.66	12.54
NYHA II	15.65%		xxx		14.59%		xxx	
NYHA III or IV	33.81%		56.00%		52.58%		56.02%	
CAD	14.61%		56.00%		49.24%		42.89%	
Arterial hypertension	58.04%		70.00%		69.30%		67.40%	
Previous MI within 4 months	0.57%		0.00%		0.91%		1.09%	
Previous MI within 1 year	0.52%		xxx		1.22%		xxx	
Previous MI after 1 year	1.57%		xxx		5.47%		xxx	
Previous CABG	1.52%		24.00%		25.53%		20.13%	
Previous cardiac surgery	7.68%		68.00%		71.12%		62.80%	
Peripheral vascular disease	2.83%		24.00%		6.69%		7.66%	
Carotid disease	2.24%		14.00%		4.56%		3.50%	
COPD	7.16%		16.00%		9.73%		11.82%	
Pulmonary hypertension	8.62%		18.00%		24.01%		25.60%	
Renal disease, GFR <15 ml/min	1.71%		xxx		xxx		2.19%	
Renal disease, GFR <30 ml/min	1.81%		xxx		xxx		7.00%	
Atrial fibrillation	44.47%		40.00%		44.07%		50.11%	
Diabetes mellitus	12.20%		18.00%		18.24%		19.04%	
Emergency	14.04%		12.00%		19.15%		17.07%	

BE, balloon-expandable; CABG, coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; GFR, glomerular filtration rate; MI, myocardial infarction; N, number of procedures; NYHA, New York Heart Association; SAVR, surgical aortic valve replacement; SD, standard deviation; SE, self-expanding; TA, transapical; TAVR, transcatheter aortic valve replacement; TF, transfemoral.
xxx: The Research Data Center of the Federal Bureau of Statistics censored all values that could allow conclusions to be drawn about a single patient or a specific hospital. Using the logistic EuroSCORE, a "best-case scenario" risk score was estimated. An inconspicuous state was supposed for the "preoperative state" and "left ventricular function" due to the lack of data (the "best-case", i.e. no emergency, preserved left ventricular function).

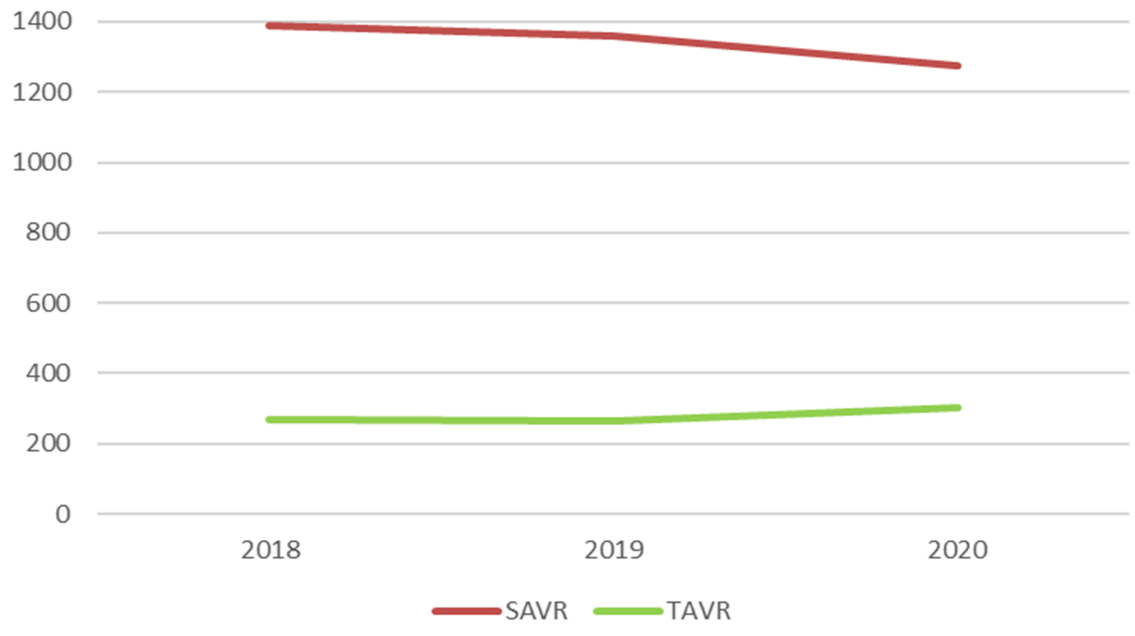

FIGURE 1
Numbers of SAVR and TAVR for pure aortic regurgitation between 2018 and 2020 in Germany. SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

56.00%, 52.58%, 56.02%), coronary artery disease (14.61%, 56.00%, 49.24%, 42.89%), previous coronary artery bypass graft (CABG; 1.52%, 24.00%, 25.53%, 20.13%) or previous cardiac surgery (7.68%, 68.00%, 71.12%, 62.80%). The rate of peripheral vascular disease was highest in TA-TAVR (2.83%, 24.00%, 6.69%, 7.66%).

Unadjusted in-hospital outcomes of patients treated for aortic regurgitation

When comparing the unadjusted in-hospital mortality between SAVR and the analyzed different access routes of TAVR, results indicate a slightly higher mortality rate for TA-TAVR with 6.00% vs. SAVR with 5.71% (Table 2). However, TF-TAVR shows better outcomes than SAVR, with lowest rate of in-hospital mortality in self-expanding TF-TAVR. In addition, self-expanding TF-TAVR is associated with a significantly lower mortality rate in a direct comparison to balloon-expandable TF-TAVR (BE 5.17%, SE 2.41%; $p = 0.039$).

Regarding the unadjusted in-hospital outcomes of stroke, major bleeding, delirium, and mechanical ventilation >48 h, results are in favor of TAVR (Figure 2). Rates of stroke, major bleeding, delirium, and mechanical ventilation >48 h did not differ significantly between balloon-expandable and self-expanding TF-TAVR. Complication rates of TA-TAVR are higher than TF-TAVR for major bleeding, delirium, and mechanical ventilation >48 h. Only the rate of stroke was 0.00% in TA-TAVR, which should be seen in the context of the small number of only 50 patients in TA-TAVR.

TAVR also showed a shorter length of hospital stay, with lowest rates in TF-TAVR (SAVR 17.80d; TA 15.82d; BE 13.75d; SE

TABLE 2: Unadjusted in-hospital outcomes of patients treated for aortic regurgitation between 2018 and 2020.

	SAVR		TA-TAVR		TF-TAVR BE		TF-TAVR SE		*p*-value BE vs SE TF-TAVR
N	4,025		50		329		457		
In-hospital mortality	5.71%		6.00%		5.17%		2.41%		0.039
Stroke	5.66%		0.00%		2.43%		2.19%		0.822
Major bleeding >5 units	21.64%		8.00%		3.04%		2.19%		0.455
Delirium	15.93%		12.00%		6.38%		6.13%		0.884
Mechanical ventilation >48 h	17.61%		6.00%		4.26%		2.84%		0.284
Length of hospital stay (mean, SD)	17.80d	14.91d	15.82d	10.35d	13.75d	9.94d	13.69d	9.75d	0.933
Reimbursement (mean, SD)	24,906€	20,037€	31,005€	7,181€	27,777€	7,289€	27,213€	5,389€	0.213

BE, balloon-expandable; N, number of procedures; SAVR, surgical aortic valve replacement; SD, standard deviation; SE, self-expanding; TA, transapical; TAVR, transcatheter aortic valve replacement; TF, transfemoral.
p-values based on chi-square test or t-test as appropriate.

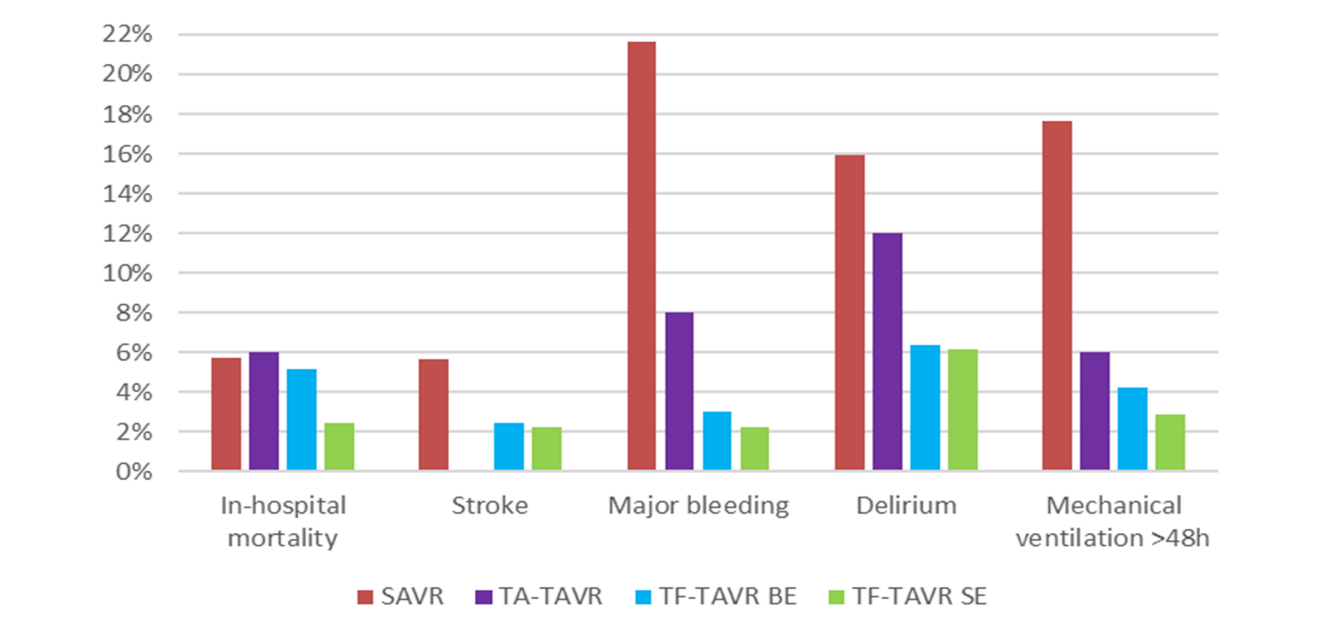

FIGURE 2
Unadjusted in-hospital outcomes of patients treated for aortic regurgitation between 2018 and 2020 in Germany. BE, balloon-expandable; SAVR, surgical aortic valve replacement; SE, self-expanding; TA, transapical; TAVR, transcatheter aortic valve replacement; TF, transfemoral.

13.69d). Reimbursement was highest in TA-TAVR at 31,005€ and lowest in SAVR at 24,906€.

Risk-adjusted in-hospital outcomes of patients treated for aortic regurgitation

After risk adjustment, balloon-expandable as well as self-expanding TF-TAVR were associated with a significantly lower mortality rate vs. SAVR as reference (TA: risk adjusted OR = 0.63 [95% CI 0.18; 2.23], $p = 0.476$; BE: OR = 0.50 [0.27; 0.94], $p = 0.031$; SE: OR = 0.20 [0.10; 0.41], $p < 0.001$; **Table 3**). Accordingly, balloon-expandable as well as self-expanding TF-TAVR showed significantly better standardized rates of in-hospital mortality vs. SAVR (SAVR: 6.58% [5.51%; 7.64%]; TA: 4.39% [−0.52%; 9.29%]; BE: 3.57% [1.68%; 5.45%]; SE: 1.52% [0.57%; 2.47%]; **Figure 3**).

With regard to the risk-adjusted in-hospital outcomes of stroke, major bleeding, delirium, and mechanical ventilation >48 h, ORs were continuously in favor of TAVR. Values for stroke in TA-TAVR could not be calculated because no stroke was reported in any of the 50 patients. Besides that, the best results again were seen in TF-TAVR for major bleeding, delirium, and mechanical ventilation >48 h. The same was reflected in the corresponding standardized rates.

In relation to resource utilization parameters, TAVR showed a significantly shorter length of hospital stay compared to SAVR and the length of stay was shortest in SE TF-TAVR (TA: risk adjusted

TABLE 3: Regression results of in-hospital outcomes of patients treated for aortic regurgitation between 2018 and 2020.

	Odds ratios/Coefficients				Standardized rates/mean		
	OR	*p*-value	95% CI		Standardized rate	95% CI	
In-hospital mortality							
SAVR	1 (reference)				6.58%	5.51%	7.64%
TA-TAVR	0.63	0.476	0.18	2.23	4.39%	−0.52%	9.29%
TF-TAVR BE	0.50	0.031	0.27	0.94	3.57%	1.68%	5.45%
TF-TAVR SE	0.20	0.000	0.10	0.41	1.52%	0.57%	2.47%
Stroke							
SAVR	1 (reference)				6.40%	5.32%	7.47%
TA-TAVR	xx	xx	xx	xx	xx	xx	xx
TF-TAVR BE	0.17	0.000	0.07	0.42	1.31%	0.29%	2.33%
TF-TAVR SE	0.17	0.000	0.08	0.39	1.33%	0.42%	2.25%
Major bleeding							
SAVR	1 (reference)				24.24%	22.03%	26.45%
TA-TAVR	0.12	0.000	0.04	0.37	4.66%	0.11%	9.21%
TF-TAVR BE	0.04	0.000	0.02	0.09	1.81%	0.64%	2.99%
TF-TAVR SE	0.03	0.000	0.02	0.06	1.29%	0.47%	2.12%
Delirium							
SAVR	1 (reference)				18.20%	15.83%	20.57%
TA-TAVR	0.37	0.039	0.14	0.95	8.35%	1.72%	14.99%
TF-TAVR BE	0.19	0.000	0.11	0.32	4.65%	2.46%	6.84%
TF-TAVR SE	0.16	0.000	0.10	0.25	4.00%	2.35%	5.65%
Mechanical ventilation >48 h							
SAVR	1 (reference)				19.72%	17.51%	21.93%
TA-TAVR	0.14	0.002	0.04	0.49	4.01%	−0.51%	8.54%
TF-TAVR BE	0.09	0.000	0.05	0.17	2.72%	1.19%	4.25%
TF-TAVR SE	0.06	0.000	0.03	0.11	1.83%	0.78%	2.87%
	Coefficient	*p*-value	95% CI		Standardized mean	95% CI	
Length of hospital stay							
SAVR	(reference)				18.94d	17.99d	19.90d
TA-TAVR	−4.75d	0.000	−7.05d	−2.46d	14.19d	11.92d	16.45d
TF-TAVR BE	−6.88d	0.000	−9.06d	−4.69d	12.06d	10.14d	13.99d
TF-TAVR SE	−7.22d	0.000	−8.95d	−5.49d	11.72d	10.17d	13.27d
Reimbursement							
SAVR	(reference)				25,841.58€	24,850.03€	26,833.14€
TA-TAVR	2,708.97€	0.038	152.25€	5,265.69€	28,550.55€	26,309.01€	30,792.10€
TF-TAVR BE	−799.40€	0.486	−3,049.58€	1,450.79€	25,042.19€	23,157.85€	26,926.53€
TF-TAVR SE	−1,666.56€	0.047	−3,307.30€	−25.82€	24,175.02€	22,964.89€	25,385.16€

BE, balloon-expandable; CI, confidence interval; N, number of procedures; OR, odds ratio; SAVR, surgical aortic valve replacement; SD, standard deviation; SE, self-expanding; TA, transapical; TAVR, transcatheter aortic valve replacement; TF, transfemoral.
xx: Values of stroke in TA-TAVR could not be calculated due to a stroke rate of 0.00% in TA-TAVR.

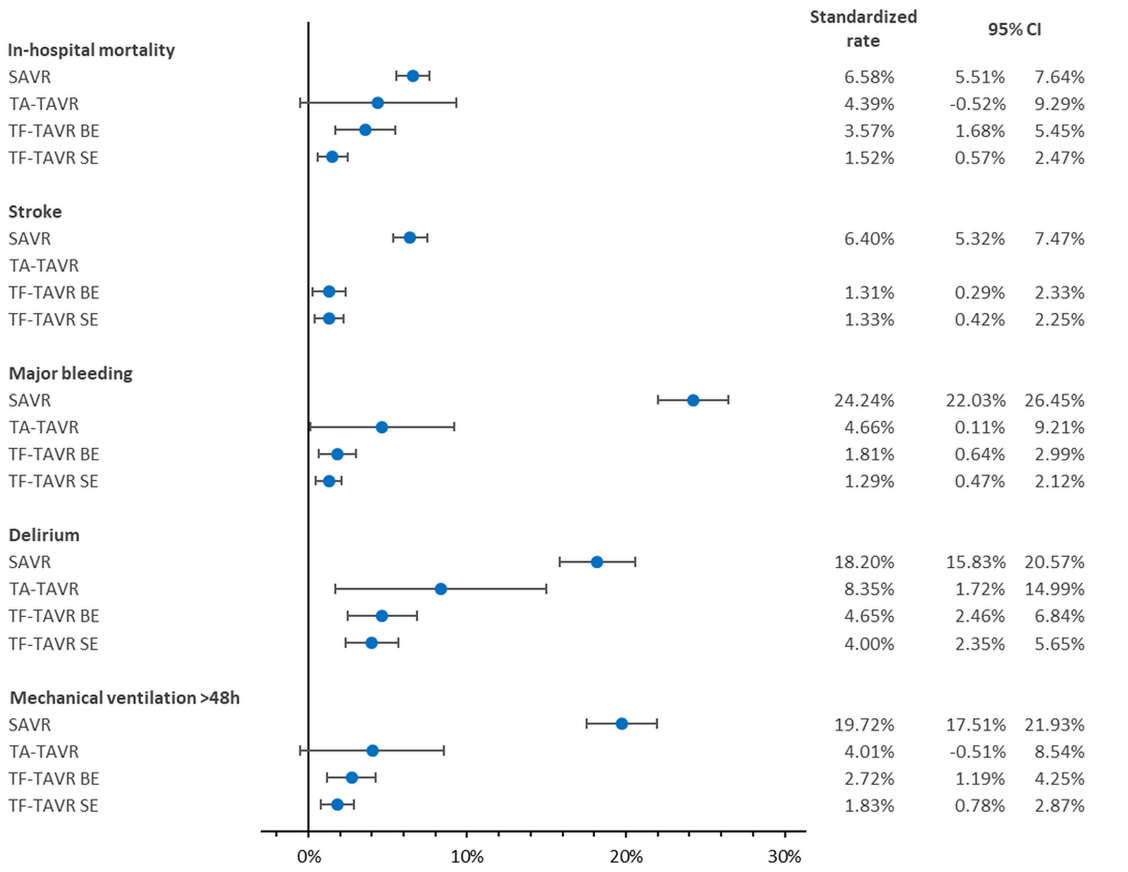

FIGURE 3
Standardized rates of in-hospital outcomes of patients treated for aortic regurgitation between 2018 and 2020 in Germany. BE, balloon-expandable; CI, confidence interval; SAVR, surgical aortic valve replacement; SE, self-expanding; TA, transapical; TAVR, transcatheter aortic valve replacement; TF, transfemoral. Values of stroke in TA-TAVR could not be calculated due to a stroke rate of 0.00% in TA-TAVR.

Coefficient = −4.75d [−7.05d; −2.46d], $p < 0.001$; BE: Coefficient = −6.88d [−9.06d; −4.69d], $p < 0.001$; SE: Coefficient = −7.22 [−8.95; −5.49], $p < 0.001$). This was also reflected in the standardized means (SAVR: 18.94d [17.99d; 19.90d]; TA: 14.19d [11.92d; 16.45d]; BE: 12.06d [10.14d; 13.99d]; SE: 11.72d [10.17d; 13.27d]). For reimbursement, the results were mixed: It was significantly higher in TA-TAVR than SAVR [Coefficient = 2,708.97€ (152.25€; 5,265.69 €), $p = 0.038$] and significantly lower in SE TF-TAVR [Coefficient = −1,666.56€ (−3,307.30€; −25.82€), $p = 0.047$].

Discussion

In this study, we examined 4,861 SAVR and TAVR for pure aortic regurgitation between 2018 and 2020 in Germany. Despite a higher age and logistic EuroSCORE as well as overall more pre-existing diseases in patients with TAVR compared to SAVR, we observed convincing results of TAVR in the analyzed patient collective. Especially self-expanding TF-TAVR achieves a significantly lower in-hospital mortality as well as noticeably lower complication rates.

For aortic valve stenosis, TAVR is a common therapy in the United States (7) and Germany (2, 6). However, TAVR is not yet routinely used in pure aortic regurgitation, where a surgical approach is the standard when valve replacement is required. It should be noted that TAVR was used off-label in the treatment of aortic regurgitation in Germany between 2018 and 2020. According to the current European (8) and American (9) guidelines for the management of valvular heart disease, TAVR might be taken into account in selected patients with an aortic regurgitation who are not eligible for SAVR. However, with reference to the recommendations for aortic valve stenosis, TAVR is not recommended for patients with, for example, endocarditis or unsuitable anatomical conditions such as unfavorable aortic annular dimensions or a significant dilatation of the aortic root respectively ascending aorta (8). Another difficulty is a potentially insufficient amount of calcification, which may make TAVR more challenging (5).

We observe that the number of TAVR cases in aortic regurgitation is still small compared to SAVR. Nevertheless, compared to a previous analysis of TAVR in aortic regurgitation in Germany from 2008 to 2015 (5), we see a further growth of TAVR procedures. The increased TAVR numbers in 2020 are particularly surprising: Due to the COVID-19 pandemic with lockdown restrictions in 2020 in Germany, including postponing elective procedures to provide hospital resources for COVID-19

patients (14), lower numbers could have been expected, as this also was observed in acute ST-elevation myocardial infarction (15).

Furthermore, in contrast to a previously stated rise of TA-TAVR procedures (5), we now observe noticeably fewer cases compared to the steadily increasing TF-TAVR numbers. The same trend could be seen in TAVR for aortic valve stenosis in Germany some years ago (5). Several analyses saw favorable outcomes for TF-TAVR vs. TA-TAVR (16–18) in aortic valve stenosis and most centers prefer a transfemoral access (19). This parallels our results in aortic regurgitation. Also the European (8) and American (9) guidelines recommend TF-TAVR in aortic valve stenosis. Alternative access routes such as TA-TAVR are generally only performed if transfemoral is not possible (20, 21). This also explains the highest rate of peripheral vascular disease in TA-TAVR in our analysis when TF-TAVR cannot be used e.g., due to calcification.

Furthermore, we see better results especially with TF-TAVR vs. SAVR in aortic regurgitation, despite a higher age and logistic EuroSCORE as well as overall more pre-existing diseases in TAVR. Thus, TAVR has continued to be used mainly in patients suffering from aortic regurgitation with a comparatively high surgical risk in recent years, but has shown good results even in these patients.

A reason for the still high mortality of SAVR in aortic regurgitation could be its use in acute aortic regurgitation due to endocarditis or aortic dissection (5, 8, 22, 23). Again, it is important to mention that TAVR is not recommended for patients with, for example, endocarditis (8). Therefore, it must be taken into account that the observed patient groups are presumably preselected to a certain extent and may not be fully comparable.

Previously (5), we reported a markedly varying in-hospital mortality for TF-TAVR in aortic regurgitation between 2008 and 2015 (15.2% in 2011, 2.8% in 2015) as well as TA-TAVR (17.7% in 2012, 0% in 2014), which could be due to the low TAVR numbers in aortic regurgitation. Compared to the mean in-hospital mortality of 8.61% in TF-TAVR and 7.66% in TA-TAVR in that study, we now see a further decrease in in-hospital mortality. Regarding TF-TAVR in particular, the same applied for most in-hospital complications as well as length of hospital stay.

Arora et al. (24) as well as Isogai et al. (25) analyzed TAVR for aortic regurgitation in the United States in 2016-2017. They observed an in-hospital or 30-day mortality rate of between 2.4 and 3.3%, which is lower than our results for balloon-expandable TF-TAVR but consistent with or slightly higher than those for self-expanding TF-TAVR. The stroke rate was between 0.6 and 1.8%. Furthermore, Arora et al. (24) report a rate of major bleeding requiring blood transfusion of 2.2% in-hospital and 7.7% at 30 days, while Isogai et al. (25) saw bleeding complications in 17.4% with a blood transfusion rate of 8.0%. Mean length of hospital stay was between 3 and 4 days, which is noticeably shorter than ours. In addition, Isogai et al. (25) found that TAVR for aortic regurgitation vs. aortic valve stenosis was significantly associated with a higher risk of acute kidney injury (OR = 1.64, $p < 0.001$), cardiac tamponade (OR = 1.98, $p = 0.0498$), and prolonged hospital stay (OR = 1.59, $p < 0.001$), but not with in-hospital mortality (OR = 1.55, $p = 0.058$).

Comparing the current results with an analysis of ours on TF-TAVR for aortic valve stenosis in Germany in 2018 (26), the rates of in-hospital mortality and complications in aortic regurgitation have approached those of aortic valve stenosis. In addition, we observe advantages in favor of self-expanding vs. balloon-expandable TF-TAVR in aortic regurgitation. This is in contrast to findings in aortic valve stenosis, where broadly equivalent outcomes have been seen (26–28). The reasons for the advantages of self-expanding TF-TAVR in aortic regurgitation remain speculative. One hypothesis could be that our analysis might contain valve-in-valve TAVR with possibly better hemodynamic characteristics in SE TF-TAVR, resulting in less patient-prosthesis mismatch as well as lower transvalvular gradients after TAVR. This hypothesis may be of particular interest for long-term outcomes. However, the CENTER-study (29) also analyzed results of valve-in-valve TAVR in aortic valve stenosis and showed a lower rate of major bleeding after 30 days in SE valve-in-valve TAVR, but mortality did not differ significantly for in-hospital outcomes, after 30 days, and after one year.

Our analysis shows promising results, despite the off-label use of TAVR so far, and it is conceivable that TAVR will be used more frequently in aortic regurgitation in the future, even in selected patients with a lower surgical risk. This will require further research, particularly with new approved prostheses.

Our analysis has several strengths and limitations, as mentioned in previous studies (26, 30–34). First, a strength is the availability of complete national data of all TAVR and SAVR in pure aortic regurgitation. A limitation is the use of administrative data. Hence, coding errors can exist. Our model is missing some interesting parameters, for example information on the exact type of valve used in each procedure, the presence of a valve-in-valve procedure, the specific previous cardiac surgeries coded as well as echocardiographic parameters. The use of administrative data is limited in granularity. Furthermore, based on these codes in Germany, we used >5 units of red blood cells as definition of bleeding. This corresponds approximately to the bleeding classification Type 3 (life-threatening bleeding) according to the Valve Academic Research Consortium 3 (VARC-3) definition (35). In addition, since a long-term follow-up is not available due to the characteristics of our data source, we present an analysis of in-hospital outcomes.

Conclusions

4,861 SAVR or TAVR for pure aortic regurgitation between 2018 and 2020 in Germany were examined. Taking into account the different selection criteria for TAVR or SAVR in aortic regurgitation, the data demonstrate that TAVR is a viable alternative to SAVR in the treatment of pure aortic regurgitation for selected patients, showing overall low in-hospital mortality and complication rates, especially with regard to self-expanding TF-TAVR.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

VO—conception and design as well as analysis and interpretation of the data, first draft, critical revision for important intellectual content. IH—analysis and interpretation of data, critical revision for important intellectual content. DWo—analysis and interpretation of data, critical revision for important intellectual content. PS—analysis and interpretation of data, critical revision for important intellectual content. AH—analysis and interpretation of data, critical revision for important intellectual content. MZ—analysis and interpretation of data, critical revision for important intellectual content. DWe—analysis and interpretation of data, critical revision for important intellectual content. KK—conception and design as well as acquisition and analysis and interpretation of the data, first draft, critical revision for important intellectual content. CvzM—conception and design as well as analysis and interpretation of the data, first draft, critical revision for important intellectual content. All authors have approved the submitted version to be published and have agreed to be 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. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1091983/full#supplementary-material.

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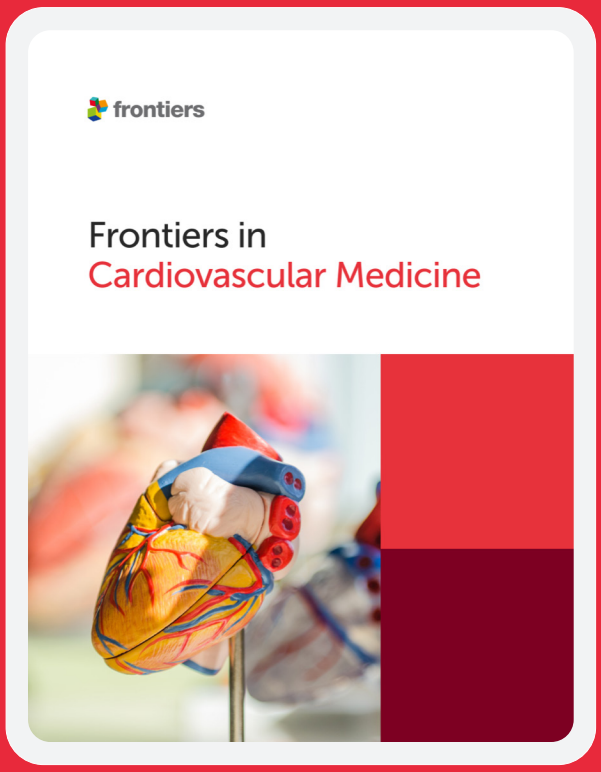

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