

Clinical characteristics and management of coexistent cardiomyopathy in patients with bicuspid aortic valve

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ABSTRACT

BACKGROUND Bicuspid aortic valve (BAV) is the most common congenital heart disease. However, the prevalence, clinical characteristics, and current management of BAV associated with inherited cardiomyopathy, including hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and left ventricular noncompaction (LVNC) have not been well described.

METHODS Consecutive patients diagnosed with BAV at a large tertiary cardiovascular referral center between 2009 and 2018 were retrospectively assessed for HCM, DCM, and LVNC based on clinical and echocardiographic criteria. Patients with coexistent conditions were investigated further.

RESULTS Of 3533 patients with BAV screened, 57 (1.6%) had concomitant cardiomyopathy. BAV was combined with HCM in 30 of these patients, with DCM in 19, and with LVNC in eight. Forty-six patients (80.7%) were male, and the mean age at first diagnosis was 47 years for BAV with HCM, 49 years for BAV with DCM, and 35 years for BAV with LVNC. Heart failure and aortic valve dysfunction were common in these patients, and the prevalence of coexisting aortopathy was 43.3%, 26.3% and 25.0%, respectively, for BAV with HCM, DCM and LVNC. During the index hospitalization, 24 of the 57 patients (42.1%) underwent surgery, 16 (28%) underwent aortic valve and/or aortic surgery, and 16 of the 30 patients with HCM had a Morrow procedure. There were no deaths or other major adverse cardiovascular events.

CONCLUSIONS The prevalence of inherited cardiomyopathy was higher in our patients with BAV than in the general population. Aortopathy and heart failure were common, with almost half of patients requiring surgery at diagnosis.

Bicuspid aortic valve (BAV) is the most common congenital heart disease, with a prevalence of approximately 1%–2% in the general population.^[1] Patients with BAV often present with other congenital heart defects, such as patent ductus arteriosus, ventricular septal defect, and BAV-associated aortopathy, including aortic dilation, aneurysm, and dissection. BAV is a highly heritable trait for which the underlying genetic basis remains largely unknown. However, BAV concomitant with other congenital heart defects indicate a shared underlying genetic basis and has more complex morphology and pathophysiology,^[2–5]

resulting in premature valve dysfunction and heart failure.

Inherited cardiomyopathies, which include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), left ventricular noncompaction cardiomyopathy (LVNC), and arrhythmogenic right ventricular cardiomyopathy (ARVC),^[6] are a heterogeneous group of pathologies characterized by structural and functional alterations of the heart. The importance of these cardiomyopathies as causes of morbidity and mortality, particularly heart failure and sudden cardiac death, has become well understood during the past 30 years.^[7] Although a few

case reports have suggested a possible association between BAV and specific types of cardiomyopathy,^[8–12] data on the prevalence, clinical characteristics, and current management of cardiomyopathy in the BAV population are limited. This study aimed to determine the prevalence of coexisting cardiomyopathy in a large referral BAV population, describe the clinical characteristics of this unique patient cohort, and discuss management.

METHODS

Study Population

Consecutive hospitalized patients diagnosed with BAV by echocardiography or surgical specimens at Fuwai Hospital between January 2009 and December 2018 were considered for analysis. Detailed clinical and imaging characteristics and the discharge summaries of patients with BAV were reviewed by two independent cardiologists (DZ, YL) to identify associated cardiomyopathy according to the criteria proposed by the guidelines. Any disagreements were resolved by discussion between the two reviewing cardiologists. Patients were excluded if they had previously undergone cardiac surgery (valve surgery or transcatheter aortic valve replacement, cardiomyopathy-related surgery, or coronary artery bypass graft surgery), been diagnosed as having cardiomyopathy secondary to severe aortic valve dysfunction, myocardial infarction, or alcoholic cardiomyopathy, or had amyloidosis cardiomyopathy. Patients were analyzed according to type of cardiomyopathy.

Our institutional review board approved the use of clinical data for this study and waived the requirement for informed consent in view of the observational nature of the research. The study was performed in accordance with the ethical standards of the Declaration of Helsinki and its later amendments.

Diagnostic Criteria for BAV and Cardiomyopathy

All patients underwent two dimensional and Doppler echocardiography performed in accordance with American Society of Echocardiography guidelines and local practice routines. BAV was diagnosed by an experienced echocardiographer based on typical characteristics seen on the echocardiogram, namely, when only two cusps were unequivocally

identified in systole and diastole in the short-axis view and there was a clear “fish mouth” appearance during systole.^[13] In patients who underwent aortic valve surgery, the presence of BAV was confirmed using their pathologic specimens. BAV morphology was classified into four types based on the position and pattern of raphe and cusps: type 0, two developed cusps and no raphe; type 1, fusion of the left and right coronary cusps; type 2, fusion of the right coronary and noncoronary cusps; type 3, fusion of the left coronary and noncoronary cusps.^[14] Only patients with confirmed BAV were included.

The study focused on three of the most common inherited cardiomyopathies: HCM, DCM, and LVNC. HCM was diagnosed clinically by experienced cardiologists based on the presence of unexplained myocardial hypertrophy (left ventricular wall thickness ≥ 15 mm) in a nondilated left ventricle without any secondary local or systemic cause of cardiac hypertrophy.^[15] Patients with obstructive HCM were identified according to the presence of left ventricular outflow tract (LVOT) obstruction. DCM was defined as dilatation of the left ventricle or both ventricles that could not be explained by abnormal loading conditions or coronary artery disease;^[16,17] thus, patients with ischemic heart disease, uncorrected or corrected severe aortic stenosis or aortic regurgitation, or other reversible causes were excluded from a diagnosis of inherited DCM. LVNC was diagnosed as per previously published echocardiographic criteria and/or the ratios between noncompacted and compacted layers of the left ventricular wall on cardiac magnetic resonance imaging when LVNC was suspected but not confirmed using echocardiography.^[11]

Data Acquisition

Information on baseline patient demographics, clinical characteristics, and clinical management, including procedures, medications, and other management measures, were extracted from the electronic medical records.

Septal morphology was assessed using the apical long-axis view at end diastole. Resting LVOT obstruction was defined as a peak instantaneous outflow gradient ≥ 30 mmHg under resting conditions.^[18] The severity of aortic valve stenosis and of regurgitation was assessed according to published guidelines.^[19]



Aortopathy was defined as a sinus of Valsalva or ascending aorta dimension ≥ 40 mm, dilation of the sinus of Valsalva, aortic root aneurysm, dilation of the ascending aorta, or ascending aortic aneurysm.^[20,21] Heart failure was diagnosed per guidelines and categorized as heart failure with preserved ejection fraction (left ventricular ejection fraction [LVEF] $\geq 50\%$) or heart failure with reduced ejection fraction (LVEF $< 40\%$), and heart failure with midrange ejection fraction ($40\% \leq \text{LVEF} < 50\%$).^[22] All patient characteristics were prespecified and rigorously verified by the two reviewing cardiologists working independently.

Statistics Analysis

Categorical variables are presented as the frequency and proportion and continuous variables as the mean $\pm$ SD or the median (interquartile range) depending on how the data were distributed. The analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 3533 consecutive patients hospitalized at Fuwai Hospital were diagnosed with BAV based on echocardiographic findings or surgical specimens during the study period. Fifty-seven of these patients were diagnosed to have BAV concomitant with cardiomyopathy and were included in the study. Thirty of the 57 patients had HCM, 19 had DCM, and eight had LVNC, giving a prevalence of 1.6% of coexistent cardiomyopathy in our BAV population, which is higher than that reported in the general population.^[23]

Characteristics of BAV Patients with Cardiomyopathies

The characteristics of patients with BAV and the different types of cardiomyopathy are summarized in Table 1. The mean ages at first diagnosis of BAV and each type of cardiomyopathy were relatively young, particularly for patients with concomitant LVNC (47 years for HCM, 49 years for DCM, and 35 years for LVNC). A male predominance was observed for all three BAV and cardiomyopathy populations (66.7%, 100%, and 87.5% for HCM, DCM and LVNC, respectively). Other congenital heart

diseases (e.g., ventricular septal defect and patent ductus arteriosus) was more prevalent in patients with BAV combined with DCM (36.8%).

Heart failure was found in 60.0% (18/30), 73.7% (14/19), and 50.0% (4/8) of patients with BAV combined with HCM, DCM, and LVNC, respectively. The mean LVEF was 63.3% for patients with BAV and HCM, 28.4% for those with BAV and DCM, and 48.9% for those with BAV and LVNC; 33.3% (10/30), 42.1% (8/19), and 12.5% (1/8), respectively, were highly symptomatic (NYHA functional class III or higher). Over 70% of patients with DCM had heart failure with reduced ejection fraction. Ventricular tachycardia was found in nine (47.4%) of the patients with DCM, one (3.3%) of those with HCM, and two (25.0%) of those with LVNC. Ten (33.3%) of the patients with HCM, one (5.3%) of those with DCM, and two (25.0%) of those with LVNC had anemia. Less than one third of patients in the overall study population with BAV and cardiomyopathy had hypertension, hyperlipidemia, or diabetes.

Echocardiographic Characteristics of Patients with Coexistent BAV and Cardiomyopathy

Table 2 shows the structural and functional characteristics of the left ventricle, aortic valve, and ascending aorta in patients with coexistent BAV and cardiomyopathy according to the echocardiographic findings. There were significant differences in the left atrial and ventricular dimensions, wall thickness, and valve function among the different types of cardiomyopathy, reflecting their specific disease features. The left atrial diameter and left ventricular end-diastolic dimension were relatively larger in patients with BAV and DCM while the interventricular septum was thicker in patients with BAV and HCM.

BAV with right-left cusp fusion (type 1) was the most prevalent morphology in all groups, followed by right-non cusp fusion (type 2). Aortic valve dysfunction was observed in more than 80.0% of all patients in the study, and 13 (43.3%) of the 30 patients with BAV and HCM and five (26.3%) of the 19 with BAV and DCM had at least moderate to significant aortic valve stenosis. Aortic regurgitation was commonly seen in patients with BAV concomitant with DCM or LVNC and was deemed to be mild in most cases; however, mitral regurgitation was found in nearly half to two thirds of patients with BAV and



Table 1 Clinical characteristics of coexistent BAV and cardiomyopathy.

	HCM (n = 30)	DCM (n = 19)	LVNC (n = 8)
Age, yrs	47.2 ± 19.8	48.7 ± 16.3	35.4 ± 24.2
Male sex	20 (66.7%)	19 (100.0%)	7 (87.5%)
BMI, kg/m ²	25.4 ± 4.2	23.6 ± 4.5%	21.5 ± 4.5
Medical history			
Heart failure	18 (60.0%)	14 (73.7%)	4 (50.0%)
NYHA III/IV	10 (33.3%)	8 (42.1%)	1 (12.5%)
LVEF reduced heart failure	1 (3.3%)	14 (73.7%)	2 (25.0%)
LVEF midrange heart failure	2 (6.7%)	0	0
LVEF preserved heart failure	15 (50%)	0	2 (25.0%)
Hypertension	11 (36.7%)	5 (26.3%)	1 (12.5%)
Hyperlipidemia	7 (23.3%)	4 (21.1%)	1 (12.5%)
Diabetes	6 (20.0%)	6 (31.6%)	3 (37.5%)
Coronary artery disease	10 (33.3%)	9 (47.4%)	1 (12.5%)
Previous CVA	1 (3.3%)	1 (5.3%)	0
Atrial fibrillation	7 (23.3%)	3 (15.8%)	1 (12.5%)
LBBB	0 (0%)	4 (21.1%)	1 (12.5%)
Previous ventricular tachycardia	1 (3.3%)	9 (47.4%)	2 (25.0%)
Anemia	10 (33.3%)	1 (5.3%)	2 (25.0%)
Other congenital heart disease	4 (13.3%)	7 (36.8%)	2 (25.0%)
ASD	2 (6.7%)	1 (5.3%)	1 (12.5%)
VSD	0	2 (10.5%)	0
PDA	0	3 (15.8%)	1 (12.5%)
CoA	2 (6.7%)	1 (5.3%)	0

Data are presented as mean ± SD or n (%). ASD: atrial septal defect; BAV: bicuspid aortic valve; BMI: body mass index; CoA: coarctation of the aorta; CVA: cerebrovascular accident; DBP: diastolic blood pressure; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; LBBB: left bundle branch block; LVNC: left ventricular non-compaction; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; PDA: patent ductus arteriosus; SBP: systolic blood pressure; VSD: ventricular septal defect.

cardiomyopathy. LVOT obstruction was present in 17 (56.7%) of the 30 patients with HCM; 10 (33.3%) of these patients had coexistent aortic stenosis. BAV-related aortopathy was present in 13 (43.3%) of the patients with HCM, five (26.3%) of those with DCM, and two (25.0%) of those with LVNC; in most cases, the aortopathy presented as dilatation or aneurysm of the ascending aorta. The mean dimensions were 34.0 mm, 34.1 mm, and 32.1 mm for the sinus of Valsalva and 34.9 mm, 37.6 mm, and 31.4 mm for the ascending aorta in patients with HCM, DCM, and LVNC, respectively.

Clinical Management of BAV with Cardiomyopathy

The clinical course varied according to the type of

cardiomyopathy because of the heterogeneity of clinical manifestations and main complaints (Table 3). During the index hospitalization, 24 (42.1%) of the 57 patients underwent surgery. Twenty of the patients were had BAV with HCM; 14 underwent surgical aortic valve replacement, 16 had a Morrow procedure, and four had a procedure involving the ascending aorta. One patient in each group underwent heart transplantation.

DISCUSSION

This cohort study investigated the clinical characteristics and management of inherited cardiomyopathy in patients with BAV at a large cardiovascular referral center. Our main findings were as fol-



Table 2 Echocardiographic findings of coexistent BAV and cardiomyopathy.

	HCM (n = 30)	DCM (n = 19)	LVNC (n = 8)
LAD, mm	39.3 ± 7.6	45 ± 7.4	37.4 ± 11.9
LVEDD, mm	46.1 ± 10.5	70.8 ± 13.6	62.1 ± 20.4
IVS thickness, mm	18.6 ± 10.6	9.6 ± 2.3	8.4 ± 2.5
LVEF	63.3% ± 10.5%	28.4% ± 6.4%	48.9% ± 20.9%
BAV morphology			
Type 1 (LCC+RCC)	17 (56.7%)	9 (47.4%)	4 (50.0%)
Type 2 (RCC+NCC)	8 (26.7%)	5 (26.3%)	2 (25.0%)
Type 3 (LCC+NCC)	1 (3.3%)	0	0
True bicuspid	0	2 (10.5%)	1 (12.5%)
Missing	1 (3.3%)	1 (5.3%)	0
Valve function			
Normal AV function	7 (23.3%)	3 (15.8%)	1 (12.5%)
Aortic stenosis, mild	6 (20.0%)	8 (42.1%)	0
Aortic stenosis, moderate	3 (10.0%)	5 (26.3%)	0
Aortic stenosis, significant	10 (33.3%)	0	0
Aortic regurgitation, mild	5 (16.7%)	7 (36.8%)	5 (62.5%)
Aortic regurgitation, moderate	2 (6.7%)	4 (21.1%)	0
Aortic regurgitation, significant	2 (6.7%)	0	2 (25.0%)
Aortic valve mean gradient, mmHg	65.5 ± 42.6	31.0 ± 23.9	NA
Aortic valve velocity, cm/s	394.8 ± 153.1	269.2 ± 91.2	NA
LVOT obstruction	17 (56.7%)	NA	NA
Mitral stenosis	2 (6.7%)	0	1 (12.5%)
Mitral regurgitation	15 (50.0%)	9 (47.4%)	6 (75.0%)
Aorta features			
Aortopathy	13 (43.3%)	5 (26.3%)	2 (25.0%)
Ascending aorta dilatation	5 (16.5%)	3 (15.8%)	1 (12.5%)
Ascending aortic aneurysm	5 (16.5%)	2 (10.5%)	0
Aneurysm of Valsalva sinus	1 (3.3%)	0	1 (12.5%)
Aortic root aneurysm	2 (6.7%)	0	0
Aortic dissection	0	1 (5.3%)	0
Aortic valve annulus diameter, mm	21.6 ± 3.6	23.7 ± 3.2	24.1 ± 8.8
Aortic sinus, mm	34.0 ± 9.3	34.1 ± 4.9	32.1 ± 13.3
Ascending aorta diameter, mm	34.9 ± 8.7	37.6 ± 5.7	31.4 ± 11.6

Data are presented as mean ± SD or n (%). AV: bicuspid aortic valve; BAV: bicuspid aortic valve; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; IVS: interventricular septum; LAD: left atrium diameter; LCC: left coronary cusp; LVEDD: left ventricular end-diastolic dimension; LVEF: left ventricular ejection fraction; LVNC: left ventricular non-compaction cardiomyopathy; LVOT: left ventricular outflow tract; NA: not available; NCC: non-coronary cusp; RCC: right coronary cusp.

lows: the prevalence of inherited cardiomyopathy in patients with BAV was approximately 1.6%; HCM was the most common type of cardiomyopathy; patients with coexisting BAV and cardiomyopathy were relatively young, with a high prevalence of heart failure; and the clinical and echocardiographic fea-

tures and clinical course varied according to type of cardiomyopathy, particularly in patients with BAV and HCM, over half of whom required surgical intervention at the time of first diagnosis.

To the best of our knowledge, our study is the largest to investigate the prevalence, clinical character-



Table 3 Surgery for patients coexistent BAV and cardiomyopathy.

	HCM (n = 30)	DCM (n = 19)	LVNC (n = 8)
Surgical treatment	20 (66.7%)	1 (5.3%)	3 (37.5%)
Isolated AVR	2 (6.7%)	0	2 (25.0%)
AVR + Morrow	2 (6.7%)	0	0
AVR + Morrow + MVR	2 (6.7%)	0	0
AVR + Morrow + CABG	2 (6.7%)	0	0
Isolated Bentall procedure	1 (3.3%)	0	0
Bentall + Morrow	2 (6.7%)	0	0
Wheat + Morrow	1 (3.3%)	0	0
Ross + Morrow	2 (6.7%)	0	0
Isolated Morrow procedure	5 (16.7%)	0	0
Heart transplantation	1 (3.3%)	1 (5.3%)	1 (12.5%)

Data are presented as n (%). AVR: aortic valve replacement; BAV: bicuspid aortic valve; CABG: coronary artery bypass graft; DCM: dilated cardiomyopathy; HCM: hypertrophic cardiomyopathy; LVNC: left ventricular non-compaction; MVR: mitral valve replacement.

istics, and current management of concomitant cardiomyopathy in adult patients with BAV. Our study highlights a potential association between BAV and inherited cardiomyopathy, particularly HCM, and raises questions regarding their genetic and pathophysiologic relationship. Our findings also point to a need for further investigations concerning the optimal clinical management of these patients.

Information on the prevalence of inherited cardiomyopathy in patients with BAV is rather limited. In a study of 1186 patients with BAV at a single tertiary center in South Korea, Jeong, *et al.*^[24] found that cardiomyopathy had a prevalence of 5.6% and that LVNC was the most common type of cardiomyopathy (3.4%), followed by HCM (1.4%) and DCM (0.8%). The prevalence and distribution of the different types of cardiomyopathy and the patient profiles reported by Jeong *et al* are different from those in our study, potentially reflecting the nature of single-center patients and referral bias. In our study, HCM was the most common coexisting cardiomyopathy with a prevalence of 0.8%, which is significantly higher than the estimated 0.2%–0.3% in the general adult population,^[25] and somewhat higher than the prevalence of 0.4% reported by Padang *et al* in 2640 patients with BAV identified by echocardiography at a single HCM referral institution.^[12] The previous literature suggests a possible common genetic etiology for coexistent BAV and HCM.^[26] Our present findings provide evidence for this potential associ-

ation and call for comprehensive genetic studies in all patients with BAV and HCM as well as their family members to investigate this observation further.

It is now widely recognized that LVNC can occur alongside a variety of other cardiac abnormalities, particularly in patients with congenital heart defects. However, the prevalence of LVNC depends on the criteria used for diagnosis, as well as the ethnicity and comorbidities in the study population. It is generally accepted in the literature that the prevalence of LVNC is around 0.2%.^[27] To date, there have only been isolated reports of LVNC in patients with BAV.^[28,29] Agarwal, *et al*,^[11] reported that LVNC had a prevalence of 11% based on echocardiographic criteria in 109 patients with BAV (almost all of whom were white with a mean age of 33 ± 17 years at diagnosis) this figure was higher than the annual prevalence of LVNC of 0.3% among patients referred to the same center, the 0.2% in our study, and the 3.4% in the study by Jeong, *et al.*^[24] These differences in prevalence may reflect the characteristics of the study population, particularly age and ethnicity, as well as limited numbers of patients and variation in the diagnostic criteria used in different centers. Future large-scale studies are needed in different ethnic groups and using standardized definitions to understand the true prevalence of LVNC in patients with BAV.

DCM in patients with BAV has been less well studied. In the present study, we excluded patients with DCM that was secondary to ischemic heart disease,



significant aortic valve dysfunction, or other reversible causes and focused primarily on patients with idiopathic DCM. Therefore, the actual prevalence of coexisting DCM in patients with BAV might have been underestimated when compared with studies performed in different populations.^[24] The coexistence of BAV and cardiomyopathy may have significant clinical implications, given that management of these conditions when they occur together differs from that when they occur alone. In our study, nearly 70% of patients with coexisting BAV and HCM presented with heart failure; 43% of these patients had less than moderate aortic stenosis or aortopathy and half had mitral regurgitation. Hemodynamic changes resulting from structural abnormalities of the mitral valve, aortic valve, and aorta caused by cardiomyopathy contribute significantly to heart failure, and mitral regurgitation could further increase diastolic dysfunction. Furthermore, 16 of our 30 patients with HCM had a Morrow procedure, which was combined with aortic valve and/or aortic surgery in 11 cases. The high proportion of patients undergoing combined surgery is attributed mainly to primary valve dysfunction and the need to avoid aortic regurgitation, which is a common complication of septal myectomy.^[30] There were no deaths or other major adverse cardiovascular events among the 42.1% of patients (24 of 57) who underwent surgery or in the 28% (16 of 57) who had aortic valve and/or aortic surgery during the index hospitalization. However, the long-term outcomes remain unknown. Given the additional surgical complexity of concomitant myocardiopathy and BAV, management of these patients requires case-by-case decision-making by a heart team that includes a cardiovascular surgeon, echocardiographer, anesthesiologist, and perfusionist. We also call for more investigations regarding the long-term survival and outcomes of patients with coexistent BAV and HCM who had or had not undergone surgery.

LIMITATIONS

This study has several limitations. First, although it represents the largest population of patients with coexistent BAV and cardiomyopathy studied to date, the cohort was still small and the prevalence could have been overestimated or underestimated

because of referral bias resulting from a large tertiary referral population. Larger pooled studies are needed to identify the true prevalence of cardiomyopathy in the BAV population and to help understand the basis for their correlation. Second, a comparative analysis between the study population and cohorts was not feasible given the small number of patients. Third, long-term follow-up is required to further understand the clinical course and outcomes in patients with these combined conditions. A detailed follow-up plan may be beneficial for early identification of patients who need timely intervention.

CONCLUSION

In this study, we found that inherited cardiomyopathy had a prevalence of 1.6% in patients with BAV and that HCM was the most common type of cardiomyopathy. The clinical and echocardiographic features and the clinical course varied in these patients according to the type of cardiomyopathy. There was a high prevalence of heart failure, and over half of the patients with BAV and HCM required surgical intervention at the first diagnosis. Our findings highlight a potential association between inherited cardiomyopathy, particularly HCM, and BAV. Further studies regarding their genetic and pathophysiologic relationship as well as the optimal clinical management strategy are required to promote better understanding of these conditions.

DISCLOSURE

Founding

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Author Contributions

Di Zhang, Jianyu Qu, and Xianliang Zhou designed the study, and modified the manuscript. Di



Zhang, Yiting Lu, Zemin Zhou, Yuxiao Hu, Yi Qu, and Xinchang Liu collected clinical data. Di Zhang performed data analysis. Di Zhang mainly wrote the manuscript with the support from Yaxin Liu, Jinyu Qu, and Xianliang Zhou. All authors contributed to the final manuscript and reviewed this work.

Conflict of Interests

None.

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