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ORIGINAL ARTICLE

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Long-term cardiovascular outcome of Williams syndrome

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Abstract

Objective: Cardiovascular lesions are the leading cause of morbidity and mortality in patients with Williams syndrome. Recent studies have rebutted conventional reports about the natural course of cardiovascular anomalies in Williams syndrome.

Design: Retrospective study.

Setting: Single tertiary center.

Patients: Eighty patients with Williams syndrome followed up for more than 5 years.

Interventions: Not applicable.

Outcome Measures: Long-term outcome of cardiovascular lesions, peak velocity change in obstructive cardiovascular lesions over time, post-interventional courses of disease-specific intervention, and intervention-free survival of obstructive cardiovascular lesions.

Results: The median follow-up duration was 11.0 (5.1-28.3) years. Among 80 patients, supravalvular aortic stenosis (87.5%) was the most common cardiovascular lesion, followed by branch pulmonary stenosis (53.8%), mitral valve prolapse (22.5%), and aortic arch hypoplasia/coarctation (5.0%). During the follow-up period, the peak flow velocity of supravalvular aortic stenosis did not change on peak Doppler echocardiography. Initially, severe supravalvular aortic stenosis was aggravated ($P < .027$). Conversely, the peak velocity of branch pulmonary stenosis decreased (from 3.08 to 1.65 m/s; $P < .001$) within age 3.2 (0.4-6.9) years. Even the group with severe branch PS improved over time. Twenty-two patients (27.5%) with Williams syndrome underwent disease-specific interventions without mortality, mostly for supravalvular aortic stenosis or mitral valve prolapse. No patient in the late-onset and initially mild supravalvular aortic stenosis group needed intervention and 37.5%, 48.4%, and 65.1% in initially moderate and severe supravalvular aortic stenosis groups needed intervention at age 5, 10, and 20 years, respectively. Unlike the conventional therapeutic concept, the intervention for branch pulmonary stenosis was almost unnecessary.

Conclusions: In Williams syndrome, initially severe supravalvular aortic stenosis worsened over time and most branch pulmonary stenoses, including those in the severe group, improved spontaneously. Most patients with branch pulmonary stenosis did not require disease-specific intervention. Surgical repairs for cardiovascular abnormalities in Williams syndrome showed favorable results.

KEYWORDS

branch pulmonary stenosis, cardiovascular lesion, long-term outcome, supravalvular aortic stenosis, Williams syndrome

1 | INTRODUCTION

Williams syndrome (WS) is a multisystem disorder caused by a microdeletion of chromosome 7q11.23.[1] WS is characterized by dysmorphic facies, cardiovascular (CV) lesion, and mental retardation.[2] The elastin gene (*ELN*) is located at the deleted region in WS, and the allelic loss of *ELN* results in CV anomalies in WS.[3] Several studies based on the catheterization data[4-7] reported the natural course of CV anomalies in WS. Supravalvular aortic stenosis (SVAS) in WS appears to worsen, and branch pulmonary stenosis (PS) tends to improve spontaneously.[4-7] However, recent studies rebutted conventional reports about the natural course, as SVAS is more likely to improve than worsen in WS.[8,9] Thus, more investigations about the natural course of CV anomalies in WS was needed. The purpose of this study was to elucidate the natural course and long-term outcomes of CV lesions in WS.

2 | METHODS

In this retrospective study, medical records of patients with WS in Seoul National University Children's Hospital (SNUCH) were reviewed and evaluated. The inclusion criteria were confirmed diagnosis of WS and a follow-up duration of more than 5 years. Confirmed diagnosis of WS was made by either fluorescence in situ hybridization (FISH) or typical CV feature in echocardiography with specific morphology (sunken nasal bridge, upturned tip of nose, long philtrum, full chick, and small chin) for WS.

The outcomes of this study were the peak velocity change in obstructive CV lesions over time, post-interventional courses of disease-specific intervention, and intervention-free survival of obstructive CV lesions. The peak continuous Doppler velocity change was chosen as a parameter in determining the natural course of stenotic lesions.

This study was approved by the SNUCH's institutional review board (1810-059-978). Informed consent was waived given the retrospective nature of the study.

The definition of vascular stenosis was a peak velocity ≥ 1.6 m/s or peak pressure gradient (PG) ≥ 10 mm Hg. SVAS and branch PS were divided into three categories based on the peak PG at the initial echocardiography: mild (PG, ≥ 10 mm Hg, < 30 mm Hg), moderate (PG, ≥ 30 mm Hg, < 50 mm Hg), and severe (PG, ≥ 50 mm Hg). Mitral valve prolapse (MVP) was diagnosed based on echocardiographic feature, that is, a systolic displacement of total or a portion of the mitral valve beyond the plane of the mitral annulus in the parasternal long-axis view. Coarctation of the aorta (CoA) was defined as a peak PG ≥ 40 mm Hg at the distal aortic arch by Doppler echocardiography.[10] Aortic arch hypoplasia was defined as a small distal aortic arch or isthmus (*z* score ≤ −2.0) with flow acceleration (≥ 3.0 m/s) in echocardiography with or without CoA.

Statistical analysis was performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). To evaluate the peak velocity change, we compared the initial and latest or pre-interventional data using paired Student's *t* test. The Wilcoxon signed-rank test was used for small numbered group. To evaluate the intervention-free survival (probability), we performed the Kaplan-Meier analysis by age. Demographic data were presented as median values with minimum-maximum value in parenthesis, and statistical data were presented as mean values ± standard deviation. We regarded the relationship to be statistically significant when the *P* value was < 0.05.

3 | RESULTS

3.1 | CV lesion in WS

Eighty patients who were diagnosed with WS between 1986 and 2013 were enrolled in this study. Among them, 45 patients were

TABLE 1 The number and percentage of cardiovascular lesions and interventions in Williams syndrome

Cardiovascular lesions	Number of patients (%) (*n* = 80)	Patients with intervention (*n* = 22)
Supravalvular AS	70 (87.5%)	17
Branch PS	43 (53.8%)	2
Mitral valve prolapse	18 (22.5%)	6
Supravalvular pulmonary stenosis	7 (8.8%)	0
HypoArch only	3 (3.8%)	0
HypoArch + CoA	4 (5.0%)	3
Others		
Valvular PS	4	0
VSD	3	0
ASD	3	0
BAV	2	1
Valvular AS	1	0
Subvalvular AS	1	0
Tetralogy of Fallot	1	1
SMA stenosis	1	0

Abbreviations: AS, aortic stenosis; ASD, atrial septal defect; BAV, bicuspid aortic valve; CoA, coarctation of aorta; HypoArch, aortic arch hypoplasia; PS, pulmonary stenosis; SMA, superior mesenteric artery; VSD, ventricular septal defect.

TABLE 2 The severity groups of SVAS and branch PS

Cardiovascular lesions	Mild	Moderate	Severe	Late-onset
SVAS	32/70 (45.7%)	19/70 (27.1%)	13/70 (18.6%)	6/70 (8.6%)
Branch PS	14/43 (32.6%)	16/43 (37.2%)	13/43 (30.2%)	0/43 (0%)

Abbreviations: PS, pulmonary stenosis; SVAS, supravalvular aortic stenosis.

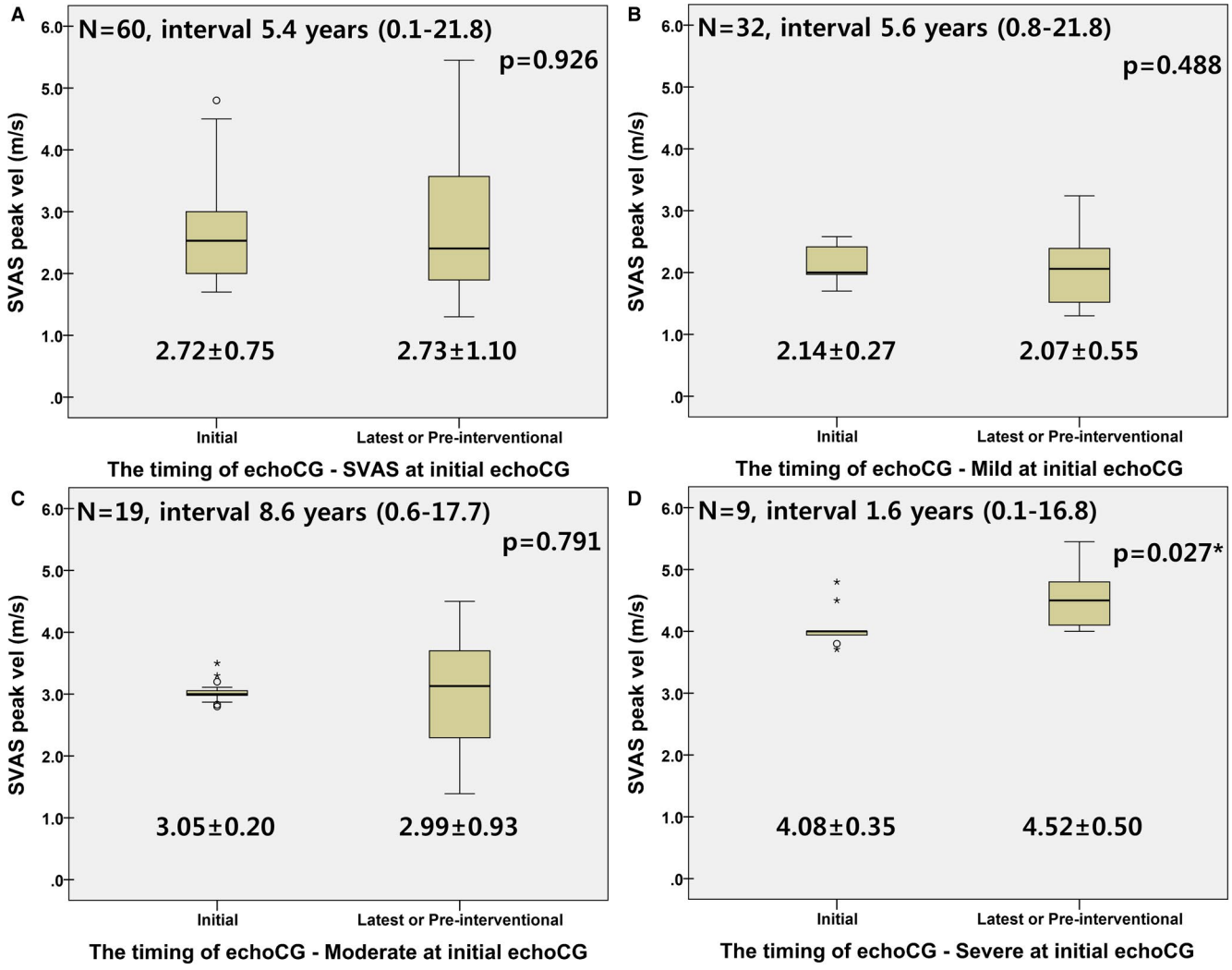

FIGURE 1 Change in mean peak velocity of overall (A), mild (B), moderate (C), and severe (D) SVAS at the initial echocardiography. The interval was presented as the median value. echoCG, echocardiography; SVAS, supravalvular aortic stenosis. **P* value by Wilcoxon signed-rank test

men, and 35 patients were women. The median age at diagnosis was 1.0 year (0-17.3 years). Sixty-four patients (80.0%) were diagnosed with WS by FISH and 16 patients (20.0%) were diagnosed by typical CV manifestation with specific morphology. The median follow-up duration was 11.0 (5.1-28.3) years.

Among 80 patients, 77 (96.2%) had CV lesion, and only three patients (3.8%) did not have such lesions. The most common CV manifestation was SVAS (70 patients, 87.5%), followed by branch PS (43 patients, 53.8%), MVP (18 patients, 22.5%), supravalvular PS (7 patients, 8.8%), aortic arch hypoplasia/CoA (7 patients, 8.8%/4 patients, 5.0%) (Table 1). There was no described case of coronary artery anomaly in the present study. Among 77 patients with CV lesion, 53 (68.8%) had more than one cardiovascular lesion. The most common association was SVAS with branch PS (38 patients). The severity of SVAS and branch PS at initial echocardiography is presented in Table 2.

3.2 | Natural course of SVAS and pulmonary arterial stenosis

We analyzed data from 60 patients with SVAS and 42 patients with branch PS, who had two or more available echocardiographic records

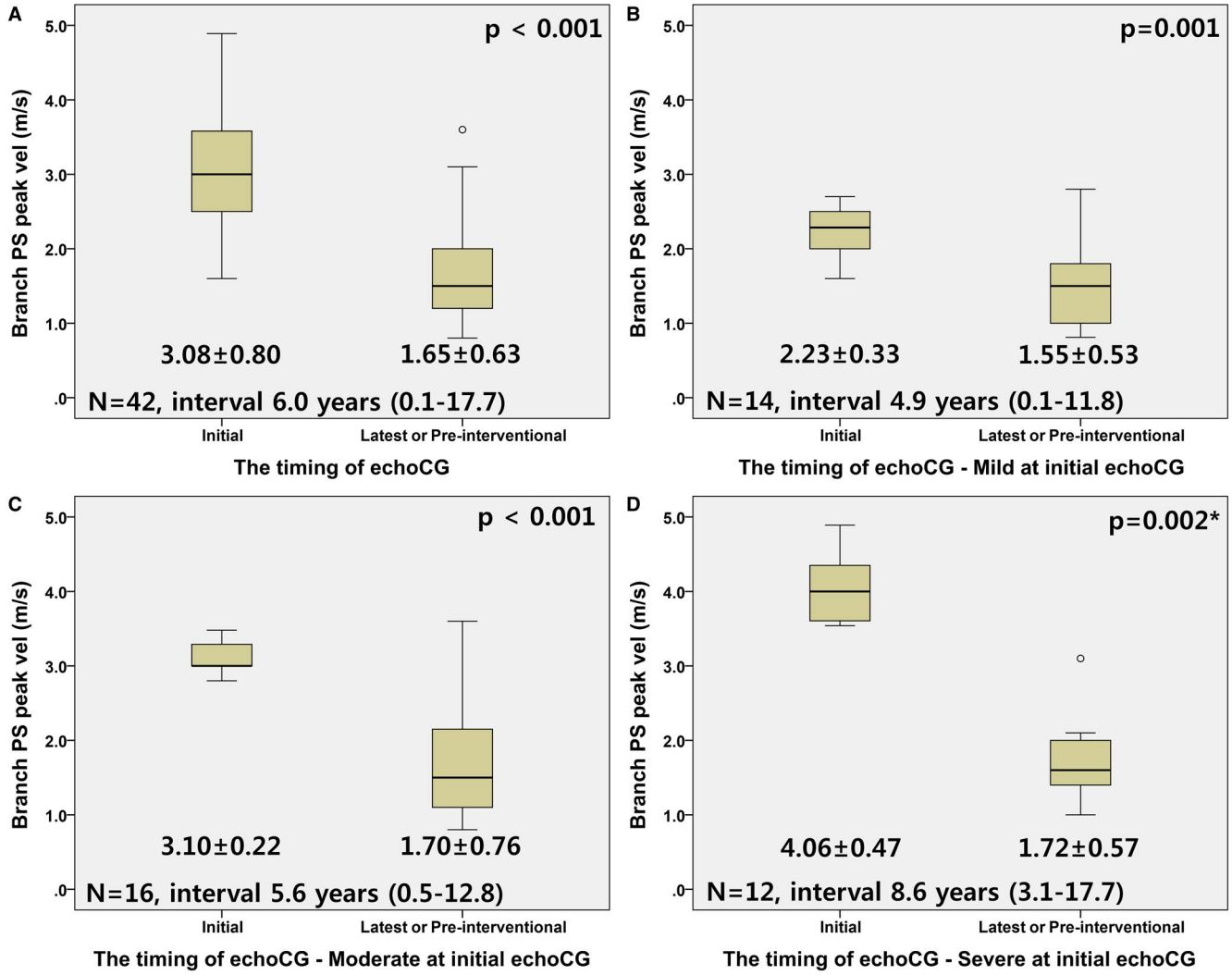

FIGURE 2 Change in mean peak velocity of overall (A), mild (B), moderate (C), and severe (D) branch PS at the initial echocardiography. The interval was presented as the median value. echoCG, echocardiography; PS, pulmonary stenosis. *P value by Wilcoxon signed-rank test

until the time of study or intervention. The median interval between the initial and latest or pre-interventional echocardiography was 5.3 (0.1-21.8) years. There was no significant change in peak velocities of overall SVAS over time (Figure 1A). Only the initially severe SVAS group showed a significant increase in the peak velocity (initial, 4.08 ± 0.35 m/s; latest or pre-interventional, 4.52 ± 0.50 m/s; P = .027) (Figure 1D). The decrease in peak velocity over time was significant in branch PS (initial, 3.08 ± 0.80 m/s; latest or pre-interventional, 1.65 ± 0.63 m/s; P < .001) (Figure 2A). Each severity group of branch PS also demonstrated a significant decline in peak velocity (Figure 2B-D). Among 12 patients with severe branch PS, 11 patients were improved to a mild degree. The median age for this improvement to a mild degree was 3.2 (0.4-6.9) years.

3.3 | Surgical intervention and post-interventional courses

Among 80 patients, 22 patients (27.5%) underwent intervention. The median age at the first intervention was 5.8 (0-19.9) years. Twenty-eight surgical interventions had been performed in 22 patients. Among the surgical interventions, ascending aortoplasty was most commonly performed (17 ascending aortoplasties in 17 patients) at age 5.9 (2.4-16.9) years. The surgeons used several surgical techniques for ascending aortoplasties, including single patch, modified Brom, double patch, sliding (Myers), and inverted Y-patch techniques. Postoperatively, only one patient exhibited greater than grade II aortic regurgitation (AR) and one patient had remnant moderate SVAS. There was no case of reoperation.

Mitral surgery (mitral valvuloplasty or annuloplasty) for MVP was performed on patients with severe MR (n = 5) or moderate MR (n = 1) with left ventricular (LV) enlargement and left atrial (LA) enlargement among 18 patients with MVP at age 7.6 (2.8-19.9) years. Two patients needed reoperation, including one mechanical valve replacement surgery. After the mitral surgery, all six patients showed less than mild MR. Additionally, five coarctoplasties were performed in three patients and two branch pulmonary angioplasties in two patients. In this study, there was no early mortality. Late mortality

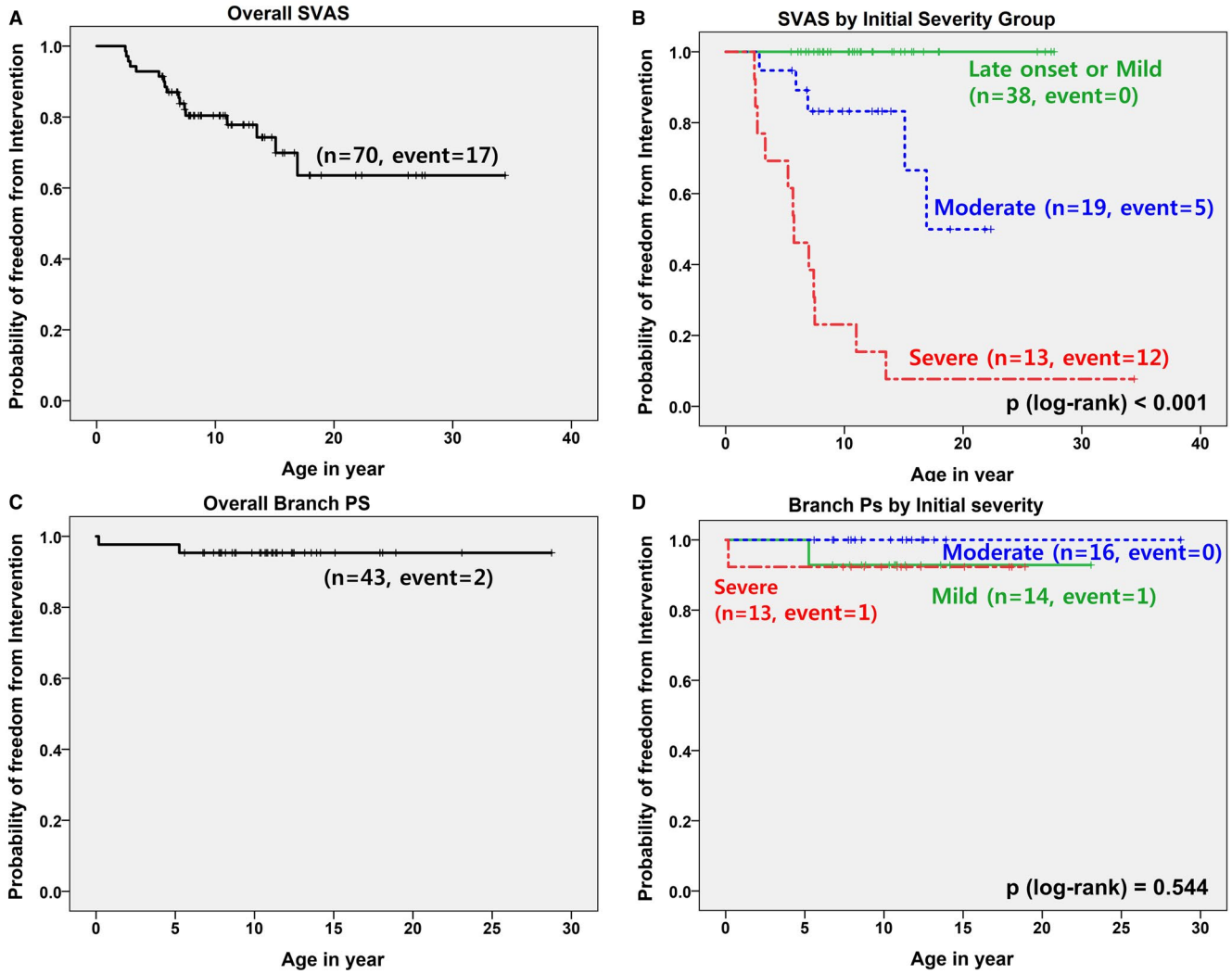

FIGURE 3 Intervention-free probability of overall SVAS (A), SVAS by the initial severity group (B), overall branch PS (C), and branch PS by the initial severity group. PS, pulmonary stenosis; SVAS, supravalvular aortic stenosis

was not analyzed because some patients were lost to follow-up. Moreover, only one patient underwent catheter-based intervention (CBI), such as CoA ballooning.

3.4 | Long-term outcome: probability of freedom from intervention

The intervention-free probabilities of SVAS are presented in Figure 3A. When the intervention-free probabilities in each severity group at the initial echocardiography were compared, a significant difference was found between the subgroups (Figure 3B). No patient in the late-onset and mild SVAS groups at the initial echocardiography needed intervention for SVAS during the long-term follow-up. Patients with initially severe SVAS showed lowest intervention-free probability (Figure 3B). In the initially moderate and severe SVAS groups, 37.5%, 48.4%, and 65.1% patients needed intervention at age 5, 10, and 20 years, respectively. Figure 3C shows the intervention-free probability in branch PS. When the intervention-free probability in each severity group in branch PS was compared, no difference was noted between the groups (Figure 3D).

When the intervention-free survival between SVAS and branch PS was compared, the intervention-free probability of SVAS was significantly lower than that of branch PS (P = .014) (Figure 4A). The same comparison of four CV lesions in WS also showed significant difference (P = .016) (Figure 4B), but this result was obtained from the difference in intervention-free probability between branch PS and other three CV lesions (SVAS, MVP, and hypoplastic aortic arch). Between the other three CV lesions (SVAS, MVP, and hypoplastic aortic arch), there was no significant difference in intervention-free probability.

4 | DISCUSSION

Since Giddins et al. reported on the natural course of SVAS and branch PS in WS in 1989,[4] several studies had reported similar results.[5-7] SVAS in WS universally tends to progress, and branch PS generally improves spontaneously and rarely progresses.[4-7]

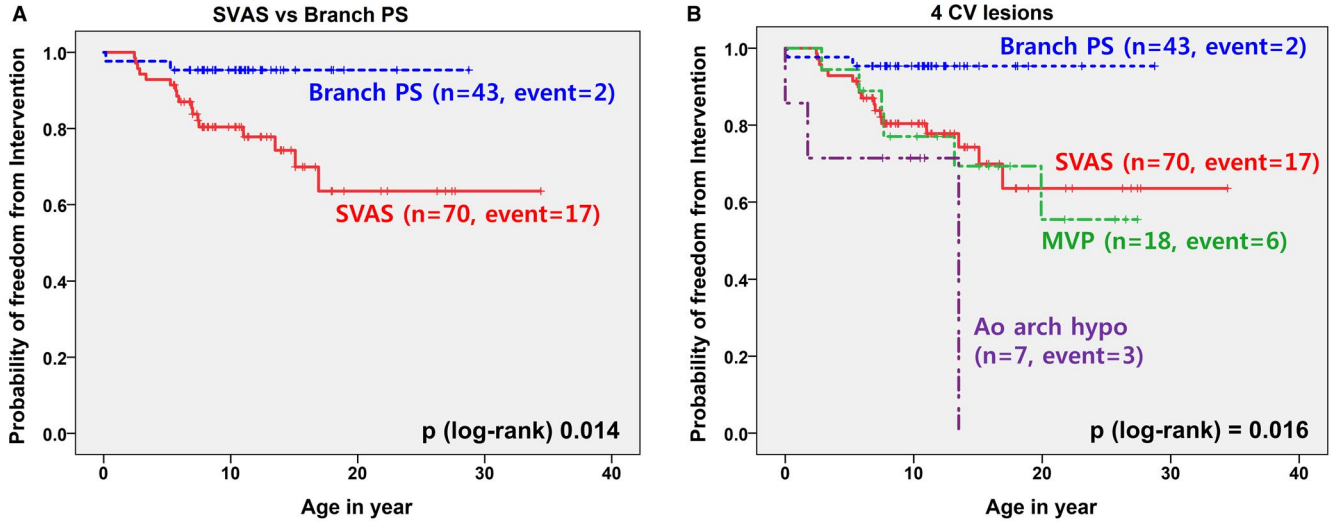

FIGURE 4 Intervention-free probability of SVAS and branch PS and four cardiovascular lesions. Ao arch hypo, aortic arch hypoplasia; CV, cardiovascular; MVP, mitral valve prolapse; PS, pulmonary stenosis; SVAS, supravalvular aortic stenosis

However, recent studies from Taiwan[8] and the Children's Hospital of Philadelphia[9] rebutted the common belief about the natural course of SVAS; they demonstrate that SVAS in WS is more likely to improve than worsen, although this finding was not statistically significant.

To our knowledge, this is the first report to demonstrate that only the initially severe SVAS in WS had a tendency to progress and the mild and moderate SVAS at the initial echocardiography did not progress. The overall SVAS in WS also did not show significant progression. Branch PS, even in the initially severe group, improved spontaneously during the follow-up periods, usually at age 3.2 years. Determining the natural course of SVAS and branch PS by echocardiographic data is also unique, because most previous studies about the natural course of CV lesion in WS were based on catheterization data.[4-7] However, catheterization for diagnosis of CV lesion in WS was substituted by echocardiography nowadays because of its invasiveness.

In addition, to our knowledge, this study is the first to show that balloon or surgical angioplasty for branch PS may not be necessary in WS on many occasions. The conventional therapeutic concept for severe branch PS in WS is balloon pulmonary angioplasty initially. In a previous study, 50% of patients with branch PS underwent disease-specific intervention, and most interventions were CBI.[9] In this study, only 4.7% of patients with branch PS underwent disease-specific intervention, and branch PS in WS improved over long-term follow-up, even in the initially severe group. Moreover, the intervention-free probability showed that most patients with branch PS in WS did not need the intervention.

Another interventional issue in WS is MVP. In this study, the second most common surgical intervention was mitral valve surgery for MVP, which showed favorable results. Although a study from Argentina reported four cases of surgical intervention for MVP,[11] most previous studies reported no mitral surgery in WS[9,12,13] because most patients with MVP in WS had lesser than mild MR.[14] In the present study, however, among 18 patients with MVP, six showed moderate-to-severe MR accompanied with LV and LA enlargement. In this circumstance, mitral valve surgery is an inevitable option even in children.

In the present study, ascending aortoplasty for SVAS was the most common surgical intervention, similar to previous studies.[9,11,12] The result of ascending aortoplasty in WS is good regardless of surgical types. There was no case of reoperation. The postoperative AR or remnant SVAS was minimal and was not related to various surgical techniques.

Intervention-free probability of SVAS suggested that the severity of SVAS at the initial echocardiography was related to the risk of intervention in the long-term follow-up. The requirement of intervention was increased with an increase in initial SVAS severity. A previous study reported a similar trend in SVAS with WS,[9] although the authors did not focus on this relationship. However, this trend was not significant in branch PS. We also demonstrated that patients with SVAS had higher probability of disease-specific intervention than those with branch PS.

Despite its novel findings, this study has limitations. First, results were based on a single-center experience. Therefore, selection bias of subjects could arise. Second, this study was conducted retrospectively. Thus, some patients enrolled had only one echocardiogram preinterventionally and the interval of echocardiograms for each patient was irregular. However, prospective studies on the natural progression of cardiovascular disease in WS from birth would be very difficult to conduct.[9] In real-world practice, most patients with WS undergo cardiology evaluations prior to the diagnosis of WS as in the present study and in another study.[9] Finally, a proportion of the enrolled patients (16/80, 20%) did not underwent gene test for WS, because these patients were diagnosed with WS in the era that FISH test was not popular. This also could influence the selection bias.

In conclusion, in WS, only the initially severe SVAS worsened over time and most of the branch PS including the severe group improved spontaneously. Surgical repairs for SVAS in WS showed favorable

results. Unlike the conventional therapeutic concept, most patients with branch PS did not require disease-specific interventions, and mitral valve surgery would be a treatment of choice in severe cases.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Concept/design: Bae, Kim

Data analysis/interpretation: Bae, Kim, Cha

Data collection: Cha

Statistics: Cha

Drafting article: Cha, Bae, Kim

Critical revision of article: Kim, Bae, Lee

Approval of article: Bae, Cha, Song, Lee, Kim, Kwak, Kim

All authors read and approved the final version of the manuscript.

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