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Original Article

Congenital heart defects and postoperative follow-up of patients with Williams syndrome as a single center experience and review of the cases from Türkiye

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ABSTRACT

Background. Cardiovascular system involvement is quite common and the leading cause of morbidity and mortality in patients with Williams syndrome (WS), most of whom need surgery. The present study aimed to provide a detailed evaluation of the features of surgical procedures and outcomes of patients with WS given as single-center experience, and additionally to make a detailed review from Türkiye.

Materials and Methods. Thirty-five children with WS diagnosed between the years 1992 and 2021 were evaluated retrospectively including cardiovascular data, surgical treatment features, and outcomes. A total of six articles from Türkiye were evaluated.

Results. A total of 35 patients with Williams Syndrome (24 male) with a median age of cardiologic diagnosis of 6 months (range, 2 days-6 years) were evaluated. The cardiac defects of the patients with WS were found as supravalvular aortic stenosis (SVAS) (n=30, 85%) and peripheral pulmonary stenosis (PPS) (n=21, 65%). Additional cardiac anomalies were seen in 71% patients. The rate of SVAS and PPS surgery in all patients with WS was 77.1%. The median surgical age of the patients was 2.5 years (range, 7 months-15.5 years). No patients died due to surgery. But one patient died because of ventricular tachycardia due to anesthesia at the beginning of angiography. A total of 138 (63% male) patients with WS were evaluated from the articles published in Türkiye. Of 138 patients, 64.4% had SVAS, 52.1% had PPS, and 39.8% had additional cardiac anomaly. The median follow-up period ranged from 17 months to 18 years, and six (4.3%) patients died in the early postoperative period.

Conclusion. Cardiovascular system involvement is extremely common and is the leading cause of morbidity and mortality in patients with WS, often requiring surgical intervention. As seen in our study including 35 patients with WS and in publications from Türkiye, SVAS in patients with WS generally requires surgery, especially in the first year of life. PPS, on the other hand, requires surgery less frequently than SVAS, and pulmonary stenosis appears to decrease over time.

Key words: Williams syndrome, supravalvular aortic stenosis, peripheral pulmonary stenosis, congenital heart defects.

Williams syndrome (WS), also known as Williams-Beuren syndrome, is a rare genetic disease characterized by typical faces, growth delays, mild intellectual disability, extroverted personality, hypercalcemia, and congenital heart defects (CHD). Although the exact frequency of WS is unknown, it is estimated to be approximately 1 in 7500-15000.[1,2]

The diagnosis of WS is genetically confirmed through fluorescence in situ hybridization. Approximately 90% of patients with WS have a microdeletion of chromosome 7, which includes the elastin gene. Disruption of the elastin gene

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as a result of microdeletion on chromosome 7q11.23 causes a deficiency or abnormal accumulation of elastin during cardiovascular development during the intrauterine period. As a result of the abnormal accumulation of elastin, various CHDs occur in patients with WS.

The most common CHDs in WS are supravalvular aortic stenosis (SVAS), peripheral pulmonary stenosis (PPS), mitral valve prolapse (MVP), and coarctation of the aorta (CoA).[3] Surgery is usually required for these CHDs. In the literature, different surgical techniques such as single patch, Doty, and Brom techniques are used in patients when WS are reported; the type of surgical techniques to be chosen varies from patient to patient and from center to center. Although there are reports including large case series about the long-term follow-up of patients with WS who underwent surgery from different countries in the literature, reports including large series about surgery of patients with WS reported from our country are scant. Our clinic is a tertiary-level congenital heart surgery center, accordingly, we have many patients with WS who have undergone surgery and followed up in our clinic.

This study including 35 patients with WS, most of whom have had surgery, aimed to give detailed data including clinical features, cardiac defects, follow-up periods, and the surgical techniques performed as well as their outcomes as a single-center experience. Additionally, we conducted a literature review of patients with WS reported from Türkiye to date to give more detailed information.

Materials and Methods

Study population

We retrospectively reviewed the current records of 35 patients who were followed up with a diagnosis of WS at our hospital between the years 1992 and 2021. The study was approved by Başkent University Institutional Review Board (Project No: 63 KA20/231). The study protocol was conducted in accordance with the ethical guidelines of the 1975 Helsinki Declaration, as revised in 2008.

Data collection

The diagnosis of WS was confirmed through fluorescence in situ hybridization or clinical features by a medical geneticist. Cardiovascular data, patient histories, and physical characteristics were reviewed on the medical records of patients identified with WS. Congenital heart disease/abnormalities were diagnosed through echocardiography and cardiac catheterization. We analyzed the variables including age, gender, age at time of diagnosis, and degrees and types of cardiac abnormalities.

Echocardiographic evaluations were performed in accordance with the guidelines of the American Society of Echocardiography. In echocardiographic evaluations, a peak velocity (Vmax) ≥ 1.6 m/s or a peak pressure gradient ≥ 10 mm Hg between pre- and post-stenotic segments was considered vascular stenosis. SVAS and PPS were divided into three categories based on the peak systolic pressure gradient at the echocardiography: mild: Vmax 2 – 2.9m/s, moderate: Vmax 3.0 – 3.9 m/s, and severe: Vmax ≥4 m/s.[4]

Mitral valve prolapse was diagnosed as systolic displacement of one of the mitral leaflet from the plane of the mitral annulus to the left atrium over 2 mm in a parasternal long-axis view on echocardiography.

Surgical records were reviewed to determine anatomic measurements and interventions performed, time and method of surgery, treatment, and follow-up. During the follow-up period, postoperative complications, the development of restenosis, the need for reoperation, mortality rates in surgical patients, and the final status of SVAS and PPS values in non-surgical patients were evaluated.

Literature search

Williams syndrome research in cardiology and cardiovascular surgery from Türkiye was included in this study. The study was conducted by evaluating articles published online. PubMed, Google Academic, TR-Index, and Researchgate databases were searched between the years 1990 and 2022. The latest search was conducted on September 31st, 2022. The searches were performed using the keywords *Williams syndrome*, *Williams-Beuren syndrome*, *supravalvular aortic stenosis*, and *pulmonary arterial stenosis*, which were in either the title, abstract or keywords published in Turkish and English from Türkiye. Articles with incomplete and/or limited information about patients with WS and case reports were not included in the study.

Statistical analyses

Statistical analyses were performed using SPSS version 23.0 software package (SPSS, Inc., Chicago, IL, USA). Qualitative variables are shown as the number of cases (n) with percentages (%), and quantitative variables as mean ± standard deviation (SD). A normality distribution test (Shapiro-Wilk test) was performed for continuous data.

Results

A total of 35 patients with WS who were followed at our clinic were evaluated. The clinical and demographic features of the patients with WS are given in Table I. Twenty-four (68.6%) patients were male. The age of cardiologic diagnosis ranged between 2 days and 6 years (median; 6 months). The presenting symptoms of the patients were murmur (n=18, 51%), cyanosis (n=4,11.4%), and wheezing (n=1, 2.8%). The cardiac defects of the patients with WS were SVAS (n=30, 85%) (isolated SVAS in 12 patients) and PPS (n=21, 65%) (isolated PPS in three patients). Eighteen (51%) patients had both SVAS and PPS. Additional cardiac anomalies were seen in 25 (71%) patients. The most frequently seen additional cardiac abnormalities were coarctation of the aorta (CoA), which was seen in six patients, bicuspid aortic valve (BAV) in five patients, ventricular septal defect (VSD) in four patients, and MVP in three patients (Table I). Hypertension was seen in four (11.4%) patients and no renal pathology was found in these patients.

The rate of SVAS and PPS surgery in all patients with WS was 77.1% (27/35). The surgical age of patients with WS ranged from seven months to 15.5 years (median 2.5 years). The surgical features of patients with WS are given in Table I.

Supravalvular aortic stenosis (SVAS)

SVAS was detected in 30 (85%) of 35 patients with WS, 21 (70%) of whom had severe SVAS. All patients with severe SVAS underwent surgery. The median SVAS surgery age of our patients with WS was 42 months. Sixteen (76.1%) of 21 surgical patients with WS due to SVAS were aged younger than 5 years. Of the 21 patients, 10 patients received a single patch, and 11 received double patches (Doty technique) and isthmus expansion. One patient who received a single patch underwent surgery due to stenosis distal of the patch after SVAS surgery (Table I). According to the postoperative SVAS gradient at the last visit, 10 patients showed a decreasing trend in SVAS gradient (mean: 11 mm Hg) and eight patients showed an increasing trend (mean: 8 mm Hg). Nine patients with WS had moderate or mild SVAS, none of whom underwent surgery. The SVAS gradients of patients with mild or moderate SVAS showed a decreasing trend during the follow-up. At the last visit, there were no patients with severe SVAS in the surgical or non-surgical groups (Table I).

Peripheral pulmonary stenosis (PPS)

PPS was detected in 21 of 35 patients with WS. Of 21 patients, surgery was performed for PPS in six (26%) patients (Table I). The mean initial gradients were 53.1 ± 23.7 mm Hg. Pulmonary artery gradients were measured at an average of 13.4 ± 14 mmHg at the last follow-up visits.

Table I. Clinical, demographic characteristics, observed cardiac anomalies, outcome of cardiac surgery, and doppler changes of patients with Williams syndrome.

Clinical features	Number of patients (n)
Cardiologic diagnosis ages	Median: 6 months (2 days-6 years)
Gender	Male: 24(68 %), female: 11(32 %)
Cardiac anomalies	
SVAS	Total: 30 (85.7%) (isolated: 12 (34.2%))
PPS	Total: 21 (60%) (isolated: 3 (8.5%))
SVAS and PPS	18 (51.4%)
Additional cardiac anomalies	25 (71.4%) [CoA: 6 (17.1%), BAV: 5 (14.2%), VSD: 4 (11.4%), MVP: 3 (8.5%), PDA: 2 (5.6%), Hypoplasia of the aorta : 1 (2.8%), Left coronary hypoplasia: 1 (2.8%), Aortic insufficiency (moderate and severe): 3 (8.5%)]
Surgical treatment	
SVAS surgery (total)	21(60%)
Surgery technique of SVAS	Single-patch: 10 (28.5%), Doty technique (Y patch): 11 (31.4%)
Reoperation of SVAS	1 (2.8%)
PPS Surgery	6 (17.1%)
Additional surgery and angioplasty	13 (37.1%) (CoA repair: 5, VSD repair: 2, MVR: 2, AVR: 1, CoA balloon angioplasty: 3)
SVAS Gradient	
Initial	66.1±36 mmHg, mild and modere: 9 (25.7%), severe: 21 (60%)
Last visit	19±13 mmHg, mild and modere: 30 (85.7%), severe: 0
PPS Gradient	
Initial	53.1±23.7 mmHg, mild and modere: 10 (28.5%), severe: 11 (31.4%)
Last visit	13.4±14 mmHg, mild and modere: 20 (57.1%), severe: 1 (2.8%)
Follow-up	
Follow-up time (years)	Median: 5.6y (1.1y-15.6y)
Postoperative follow-up period (years)	Median: 3.6y (1y-14.4 y)
Exitus	1 (2.8%) during anesthesia

AVR: Aortic valve replacement, BAV: Bicuspit aortic valve, CoA: Coarctation of the aorta, MVP: Mitral valve prolapse, MVR: Mitral valve replacement, PDA: Patent ductus arteriosus, PPS: Peripheral pulmonary stenosis, SVAS: Supravalvular aortic stenosis, VSD: Ventricular septal defect

Pulmonary artery gradients were shown to decrease over time during follow-up in most of our patients with PPS. Since the PAP values of our 6 patients remained high even after the age of one year (PAP: 47-115 mmHg), surgery was performed on these patients, whose ages ranged from 12 months to 53 months, after the age of 1 year. Surgical intervention to the pulmonary artery was performed in 4 of 6 patients due to severe pulmonary artery branch stenosis with SVAS, 1 patient due to PPS and CoA, and 1 patient due to right pulmonary arterial stenosis with VSD closure. Surgical intervention in the pulmonary artery was in the form of widening the pulmonary artery with a patch.

Balloon pulmonary angioplasty was performed in one patient due to restenosis after surgery. Balloon angioplasty was performed in this patient at the age of 1 year due to supravalvular pulmonary stenosis, and the gradient, which was 63 mmHg before balloon angioplasty and regressed to 36 mmHg after balloon angioplasty. The pulmonary gradient of this patient, who had no additional problems during follow-up, was measured as 8 mmHg at the last follow-up.

Surgery of other cardiac anomalies

Surgery was performed for CoA in 5/35 (15.6%) patients. Balloon angioplasty for CoA was performed in one patient. During the follow-up, CoA balloon angioplasty was performed in three patients due to recoarctation of CoA. Mitral valve replacement was performed in two patients with mitral valve insufficiency due to MVP. Aortic valve replacement was performed in one patient with aortic valve insufficiency (Table I).

Follow-up period

The follow-up of the patients ranged from 1.1 to 15.6 (median: 5.6) years and postoperative follow-up periods were between 1 and 14.4 (median: 3.6) years. Forty-five percent of the patients with WS had a follow-up longer than 5 years. One patient died because of ventricular tachycardia due to anesthesia at the beginning of angiography but no additional complications during catheterization or surgery were seen.

Published articles from Türkiye

In the review of the literature, published articles related to WS from Türkiye were identified. After excluding case reports, 15 studies were evaluated. Seven SVAS articles were excluded due to incomplete and/or limited information on patients with WS. Two WS studies were excluded due to including the same patients from the same centers in previous years however the last publication of theirs was included in the study. Hence, a total of six articles were included in the study (Fig. 1).

A total of 138 patients (87 (63%) male) with WS from six articles were evaluated. Age at WS diagnosis ranged from 1 month to 14.5 years. Isolated SVAS was reported in 45 (32.6%) patients, isolated PPS in 27 (19.5%) patients, and 44 (31.8%) patients had both SVAS and PPS (Table II).

Supravalvular aortic stenosis (SVAS)

SVAS was seen in 89 (64.4%) patients with WS and 20 (22.4%) underwent surgery. In the 20 surgical patients, the Doty technique was performed in 11 patients, a single patch was used for two patients, and the Brom technique was used in one patient. There was insufficient information about the surgical procedures of SVAS performed on six patients. According to these reports, reoperation was not needed for any patient (Table II).

Peripheral pulmonary stenosis (PPS)

PPS was seen in 72 (52.1%) patients with WS, seven (9.7%) underwent surgery and nine (12.5%) patients underwent balloon angioplasty. Severe PPS was seen in 20 patients with WS at the initial visit and one patient with WS at the last visit. No patients needed reoperation.

The number of patients with additional cardiac anomalies was 55 (39.8%) and the most common additional cardiac anomalies were MVP (n=18, 13%), VSD (n=12, 8%), and CoA (n=6, 4.3%).

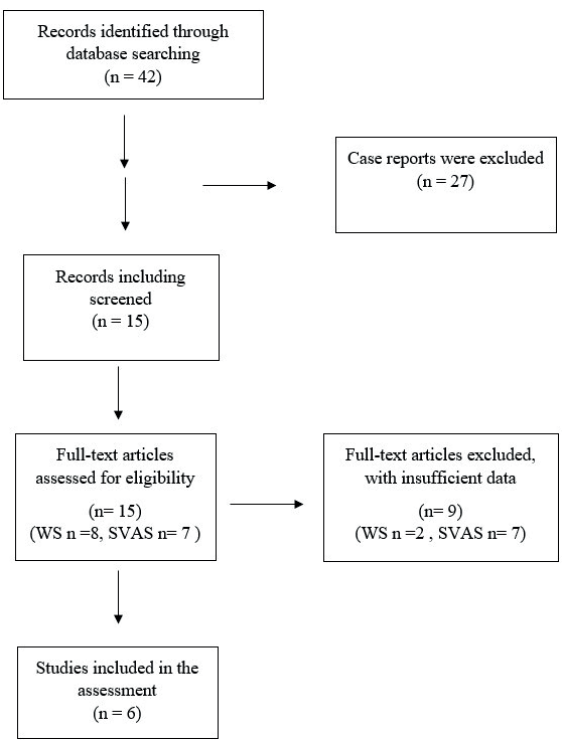

Fig. 1. Diagram of the strategy used for study inclusion.

SVAS: supravalvular aortic stenosis, WS: Williams syndrome.

Eight patients underwent surgery for additional cardiac anomalies.

The median follow-up times of articles ranged between 17 months and 18 years. During the follow-up, six (4.3%) patients died in the early postoperative period (Table II).

Discussion

In the present study, to provide a detailed evaluation of the surgery of patients with WS, we presented our single-center experiences and additionally conducted a detailed review from Türkiye. In our study, 35 patients with WS with follow-up periods between 1.1 and 15.6 years and postoperative follow-up periods between 1 and 14.4 years were evaluated. SVAS was detected in 85%, PPS in 65%, and additional cardiac anomalies were detected in 71% of WS patients. Surgery was performed in 77.1% of these patients. To our knowledge, the present study is the largest study to date regarding the surgical procedures of patients with WS from Türkiye.

Table II. Features of clinical, cardiac abnormalities, and surgery of patients with Williams syndrome in articles reported from Türkiye.

Author		Samanlı et al.[21]	Baykan et al.[15]	Ergul et al.[23]	Sarısoy et al.[18]	Gürses et al.[7]	Gürsoy et al.[19]	Total	Our study
Year of study		1997	2009	2012	2013	2018	2021		2023
Patient (n)		14	31	45	9	12	27	138	35
Sex (male/female)		8 (57%) / 6 (43%)	20 (64%) / 11 (36%)	27 (60%) / 18 (40%)	6 (66%) / 3 (34%)	8 (66%) / 4 (34%)	18 (66%) / 9 (34%)	87 (63%) / 51 (37%)	24 (68%) / 11 (32%)
Age at diagnosis		8y (2m-12y)	1m-13y	4.6y (3m-13y)	19m (3m-9y)	33m (1m-14.5y)	4y (1-8y)	1m-14.5y	6m (2d-6y)
Follow up (year)		3.7y±2.4y	41m ±26m	6.9y (6m-18y)	17m (2-74m)	33m±14m	5y (5-8y)	17m-18y	5.6y (1.1-15.6y)
Exitus		1 (during catheterization)	2 (early period)	2 (early period)	1 (early period)	-	-	6 (4.3%)	-
SVAS	Isolated	3 (21,4%)	12 (38%)	16 (35%)	2 (22%)	2 (16%)	10 (37%)	45 (32.6%)	12 (34.2%)
	Total	8 (57%)	20 (64%)	33 (73%)	7 (78%)	5 (41%)	16 (59.2)	89 (64.4%)	30 (85.7%)
SVAS surgery		1 (7.1%)	3 (9.6%)	8 (17.7%)	6 (66.6%)	-	2 (7.4%)	20 (14.4%)	21 (60%)
PPS	Isolated	6 (42%)	11 (35%)	2 (4.4%)	2 (22%)	3 (25%)	4 (14.8%)	27 (19.5%)	3 (8.5%)
	Total	11 (78%)	19 (61%)	19 (42%)	7 (78%)	6 (50%)	10 (37%)	72 (52.1%)	21 (60%)
PPS surgery			-	1 (2.2%)	6 (66.6%)	-		7 (5%)	6 (17.1%)
SVAS+PPS		5 (35.7%)	8 (38%)	17 (37%)	5 (55%)	3 (25%)	6 (22.2%)	44 (31.8%)	18 (51.4%)
Additional cardiac anomalies (Total)		2 (14%)	8 (38%)	28 (62%)	4 (44%)	5 (41%)	8 (29%)	55 (39.8%)	25 (71.4%)
MVP			4 (13%)	10 (22%)		1 (8%)	3 (11.1%)	18 (13%)	3 (8.5%)
VSD			2 (6.5%)	5 (11%)	1 (11%)	3 (25%)	1 (3.7%)	12 (8%)	4 (11.4%)
CoA		1 (7%)	1 (3.2%)	2 (4.4%)		1 (8%)		6 (4.3%)	6 (17.1%)
BAV			1 (3.2%)	1 (2.2%)			1 (3.7%)	3 (2.1%)	5 (14.2%)
Coronary artery anomaly		1 (7%)						2 (0.7%)	1 (2.8%)
Hypoplasia of the aorta		1 (7%)		4 (8,8%)				5 (3.6%)	1 (2.8%)
Others		2 (14%)		7 (15,5%)	3 (33%)	3 (25%)	3 (11.1%)	18 (13%)	5 (14.2%)

BAV: Bicuspit aortic valve, CoA: Coarctation of the aorta, MVP: Mitral valve prolapse, PDA: Patent ductus arteriosus, PPS: Peripheral pulmonary stenosis, SVAS: Supravalvular aortic stenosis, VSD: Ventricular septal defect.

In the literature, the rate of cardiovascular system involvement in patients with WS was reported as 60-80% and was the leading cause of morbidity and mortality.[5,6] From Türkiye, Dolunay et al. reported the frequency of cardiovascular system involvement in patients with WS as 83%.[7] The most common cardiac abnormalities in patients with WS are reported as SVAS, PPS, and CoA.[3] In addition, other congenital heart diseases such as BAV, MVP, VSD, atrial septal defect, and atrioventricular septal defect have been reported in patients with WS.[2] A detailed cardiac examination should be performed on every patient suspected of having WS because it is associated with high rates of CHDs and cardiac involvement. In addition, it should be recommended to evaluate the possibility of WS in children with anomalies such as SVAS and PPS, which were frequently seen in patients with WS.

Supravalvular aortic stenosis is the most common cardiac anomaly in patients with WS, reported with a frequency of 37-75%. Patients with severe SVAS often require surgery in the first years of their lives.[5] Patients with SVAS with moderate and mild stenosis are generally diagnosed later, and it has been reported that stenosis gradients tend to decrease over time, and the need for surgery decreases in advanced ages. When we evaluated the articles in Türkiye, 72.4% of patients with WS were diagnosed as having SVAS, and surgery was performed on 22.4% of them. In the present study, SVAS was found in 85% of patients with WS, of which 70% underwent surgery due to severe stenosis. The high SVAS incidence in patients with WS and high surgical rate due to severe SVAS in our study is related to our center being a tertiary pediatric cardiovascular surgery center. The median SVAS surgical age of our patients with WS was 42 months. We had only five patients who underwent surgery for SVAS aged over 5 years. The stenosis gradients of our patients with moderate or mild SVAS also showed a tendency to decrease over time, in line with the literature.

The first technique used in SVAS surgery is the single-patch aortoplasty technique described by McGoon et al.[8] Later, Doty et al. used an inverted Y-shaped patch that extended towards the non-coronary and right coronary sinus.[9] It has been reported that the Doty technique is more successful than McGoon et al.'s method and the frequency of reoperation is less. Brom et al. improved the technique by patching all three sinuses.[10] Myers sliding aortoplasty is an autologous technique where the aorta is reconstructed without the need for prosthetic material.[11] The Doty technique and Brom technique are seen as more preferred in SVAS surgery throughout recently published articles from Türkiye.[12] Koçyildirim et al. found no significant difference between the two techniques in an SVAS article, in which single-patch and three-patch techniques were compared.[13] Bostan et al. reported that reoperation was required for a patient who underwent single-patch surgery during the follow-up period.[14] We used the single-patch aortoplasty technique in 10 patients with WS in our clinic in the first years, but the Doty technique was preferred in 11 WS patients in procedures performed after the year 2010. The SVAS type of most patients in our study (71%) was the hourglass-type. In this cohort, only one patient required reoperation. This patient was our patient with hourglass-type SVAS who was operated on with a single patch and developed stenosis distal to the patch. We observed no restenosis in our patients who underwent SVAS surgery performed with the Doty technique.

Pulmonary artery stenosis is the second most common cardiac anomaly, reported with a frequency of 37-75% in patients with WS. It is more common in the first year of life. Many studies have reported that pulmonary arterial stenosis improves over its natural course in time and PPS needs less surgery than SVAS in patients with WS.[6] In the articles reported in Türkiye, PPS is the second most common cardiac anomaly in patients with WS, and surgery was performed in 12.5% of patients with PPS. Baykan et al. performed balloon

valvuloplasty on seven of 10 WS patients with PPS and observed no restenosis.[15] In our study, PPS was the second most common cardiac anomaly, shown in 60% of patients with WS, and surgery was required in only 28.5% of patients. Similar to the literature, it has been reported in articles reported from Türkiye that PPS gradients tend to decrease at follow-up, which we also observed in our study. The upper limits of the incidence of pulmonary arterial stenosis in patients with WS in the present study compared to the literature in general might be due to the fact that our clinic is known as a tertiary cardiac surgery center and most of our patients are referred to our clinic from different centers from Türkiye due to their severe clinical findings.

In the literature, the most common cardiac anomalies other than SVAS and PPS in patients with WS have been reported as CoA, MVP, and VSD.[3,5,16] In the articles reported from Türkiye, the rate of other cardiac anomalies is 39.8%, and MVP, VSD, and CoA are the most common, respectively. In our study, CoA, bicuspid aortic valve, and VSD were the most common cardiac anomalies in patients with WS, respectively. In our study, CoA was the third most common cardiac anomaly, which also required surgery in patients with WS.

MVP in patients with WS was reported at different rates in previous studies. In the study of Collins et al., which included 270 patients with WS, MVP was reported as third among the cardiac anomalies at a rate of 15%.[6] Cha et al. reported the frequency of MVP in patients with WS as 22.5% (18/80) in their study, six of whom underwent mitral surgery.[17] When the studies from Türkiye are evaluated, the frequency of MVP is seen as 12% but no patient who was operated on for MVP was reported.[18,19] In our study, unlike the literature, MVP was shown only in three (8.5%) patients, two of whom required mitral valve replacement due to severe mitral insufficiency.

Coronary artery anomalies in WS are usually seen as coronary artery stenosis, especially ostial stenosis in patients with WS.[3] Coronary ostial narrowing may be present, leading to myocardial ischemia and a higher risk for sudden cardiac death. Coronary artery anomalies have been reported in approximately 5% of patients with WS.[5] Collins et al. reported 6% coronary artery anomalies in their study. By contrast, Cha et al. observed no coronary artery anomalies in their study of around 80 patients.[6,17] In studies from Türkiye, Akkaya et al. reported a coronary anomaly in one patient in their study and Samanlı et al. reported a single coronary root with tetralogy of Fallot, pulmonary artery hypoplasia, and PPS.[20,21] Ergul et al. detected coronary artery anomalies in 26% (10/38) of patients with WS using computed tomography angiography studies in patients with WS.[22] In our study, we described left coronary hypoplasia in a 5-year-old patient with WS who was diagnosed as having SVAS and PPS and underwent surgery for SVAS. No coronary artery intervention was performed in this patient and we observed no additional problems at follow-up.

Elastin haploinsufficiency results in systemic arteriopathy in Williams syndrome. Hypertension is a clinical condition reported in 3-30% of patients with WS and increases with older age. Although the cause is mostly unknown, diffuse aortic stenosis, CoA, and renal artery stenosis have been reported as causes of hypertension.[3,5] Two of the studies conducted in Türkiye mentioned the hypertension rate in patients with WS as 22% (Ergul et al.) and 12.9% (Baykan et al.).[15,23] The incidence of hypertension in our cohort was found as 11.4% (4 patients). However, renal or thoracic artery stenosis or any renal pathology was not detected in any of these four patients. While, among our other patients in whom hypertension was not observed, we had four patients in whom we detected anomalies on urinary USG. (Right renal agenesis in two patients, double ureter in one patient, nephrocalcinosis in one patient). Due to the high incidence of renal and urinary abnormalities in Williams syndrome, performing a urinary and renal analysis and sonographic evaluation of the patients is recommended.

Cardiovascular abnormalities are the leading cause of morbidity and mortality in WS patients. In the literature, it was reported that anesthesia-related rhythm problems, sudden cardiac arrest, and postoperative complications were seen as causes of early mortality in patients with WS. The rate of early mortality in patients with WS has been reported as 2-11% in the literature. In the cohort study of Wessel et al., the incidence of sudden death in patients with WS was reported as 1/1000 patient-years.[24] In the articles reported from Türkiye, a total of 6(4.3%) patients died, five were in the early postoperative period, one was during catheterization. We saw no early mortality postoperatively in our series. One of our patients with WS died of cardiac arrest after ventricular tachycardia during anesthesia before catheterization. Careful preoperative preparation of patients with WS should be undertaken before every elective procedure and physicians should be aware of anesthesia-related rhythm problems.

The follow-up period is important for WS. The present study included 29 years of experience with a median of 5.6 years of follow-up; 45% of our patients were followed for more than 5 years after surgery. Our patients with WS with mild and moderate SVAS did not require surgery during follow-up. Similarly, in the articles from Türkiye, it was reported that there was a tendency for SVAS and PPS gradients to decrease in their mean follow-up period ranging from 17 months to 6.9 years. According to literature about follow-up of WS patients, it is recommended that the cardiology evaluation for elastin arteriopathy occurs at least annually until age five years and every two to three years thereafter; and renal and bladder ultrasound examination every ten years.[25] In patients with WS, surgery may be required for supravalvar aortic or pulmonary artery stenosis, mitral valve insufficiency, and/or renal artery stenosis.[25] Anesthesia consultation and electrocardiogram are recommended prior to sedation and surgical procedures.[25] At our clinic, follow-up periods of WS patients, and outpatient clinic controls with echocardiography and electrocardiography are performed, usually at between 6-month and one-year postoperative intervals, however neonatal period and patients with serious cardiac findings may be evaluated more frequently.

Limitations

Our study has some important limitations due to its retrospective design and long study period. Since Williams syndrome is a very rare syndrome, we conducted a scan of the first patient diagnosed with Williams syndrome in our clinic, and this period consisted of 29 years. First of all, some changes were observed in the diagnosis, surgical method, and treatment applied to patients with WS during the study period. Second, we could not make a clear assessment of the frequency of cardiac anomalies and the incidence of WS in our patients with WS. Thirdly, the follow-up period we stated in our study is the period from the diagnosis of the cardiac disease of the patients to the last check-up at our clinic. Due to our clinic being a reference tertiary center in the diagnosis and surgical treatment of congenital heart diseases, we have patients from many parts of Türkiye, and some of these patients applied only for evaluation of surgery. For this reason, unfortunately, the follow-up period of some of our patients in our clinic was very short. This caused the average follow-up period of the current study to be short, and the rate of surgical intervention in our patients to be higher compared to the literature. Additionally, since we are a pediatric cardiology clinic, our patients over the age of 18 are transferred to adult cardiology clinics. Lastly, in this study, we only evaluated original articles about patients with WS from Türkiye to provide homogeneity; however, because WS is a rare syndrome, publications from Türkiye have usually been reported as case reports in the literature. Larger series and longer follow-up times are needed to give more detailed information about children with WS.

Conclusion

Cardiovascular system involvement is quite common and the leading cause of morbidity and mortality in patients with WS, frequently requiring surgery. The present study provides a detailed evaluation of the features of surgical procedures and outcomes of patients with WS through our single-center experiences and provides a detailed review from Türkiye. SVAS usually requires surgery, especially in the first year of life, PPS requires less surgery than SVAS, and pulmonary stenosis is seen to decrease over time. Aortic hypoplasia causes stenosis distal to the patch after SVAS surgery and increases the frequency of reoperations. The Doty technique and isthmus dilation process decrease the frequency of this stenosis. To the best of our knowledge, the present study is the largest reported to date about surgical procedures of patients with WS from Türkiye.

Ethical approval

The study was approved by Başkent University Institutional Review Board (Project No: KA20/231).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: AO, NKT; data collection: AO, İE, MÖ; analysis and interpretation of results: AO, İE, MÖ, BV; draft manuscript preparation: AO, İE, BV, SA, NKT. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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