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Cover Page Footnote

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ORIGINAL ARTICLE

Discrete Left Ventricle Outflow Tract Obstruction in Children: Incidence and Predictors of Recurrence. A Multi-Center Study

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Abstracts

Objectives: **The purpose of this study is to measure the incidence of recurrence of discrete subaortic stenosis (DSS) after primary resection in two major cardiac centers in Saudi Arabia and to identify risk factors associated with recurrence.**

Methods: **Data on 234 patients who were diagnosed with DSS and underwent surgical resection between 1999 and 2018 were retrospectively reviewed. Patient demographics as well as echocardiographic, surgical, and pathological data were compared between patients with recurrence and non-recurrence.**

Results: **The overall recurrence incidence after primary resection was 44.87% (N=105). Most patients were male (59%). The median age at the 1st operation was 60 months (range 3 months to 133 months). The presence of aortic stenosis at the time of diagnosis was significantly associated with recurrence (p-value=0.002). The overall median peak gradient in which the primary resection was indicated is 60 mmHg (range 11 to 152 mmHg). The median peak gradient pre-operation and post-operation were significantly higher for the recurrence group (p-value=0.018 and p<0.001, respectively). We used univariate and multivariate analysis and controlled for the follow-up time, but there were no significant independent predictors of recurrence.**

Conclusion: **The recurrence rate of DSS after the primary resection is relatively high in this study. Further prospective studies are needed to draw a definite conclusion on risk factors for recurrence after primary resection.**

Keywords: Subaortic stenosis, Discrete subaortic stenosis, Membrane resection, Subaortic stenosis recurrence

1. Introduction

Left ventricular outflow tract obstruction (LVOTO) comprises a collection of stenosis lesions that start in the anatomic left ventricular outflow tract and extend to the descending part of the aortic arch [1,2]; 3–10% of patients with congenital heart diseases have LVOTO [3]. Subaortic stenosis comprises 8–10% of LVOTO in children [4,5]. The obstruction in sub-aortic stenosis can be a long fibrous tunnel or discrete membrane [3,6,7]. In rare cases, discrete subaortic stenosis (DSS) is combined with valvular and supra-valvular stenosis.

Surgical resection with or without septal myectomy is the usual treatment of DSS [4,8]. Patients diagnosed with DSS complicated with aortic

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insufficiency or left ventricular hypertrophy meet the criteria of surgical intervention. However, the surgical timing of referring asymptomatic patients for membrane resection remains controversial and depends on the agreement of both the cardiologist and surgeon [8]. Some surgical decisions depend only on the presence of a sub-aortic membrane. Other studies required additional factors including an increase in the left ventricle-aortic gradient (Doppler echocardiographic measurement of peak gradient more than 24–30 mmHg) or aortic insufficiency or left ventricular hypertrophy as definitive indicators for surgical resection [4,8].

Despite the efficiency of the surgery, 10%–35% of patients may experience DSS recurrence and need re-operation; their risk factors are not yet fully understood [3,9–11]. A Boston study from 2015 tried to define some risk factors [1]. Their findings in the multivariate analysis showed that predictors of DSS reoperation were the left ventricle aortic peak gradient, the distance between the membrane and the aortic valve, and the involvement of the aortic valve leaflets [1].

To the best of our knowledge, there are no studies in Saudi Arabia that estimated the incidence of DSS recurrence. This study aims to measure the incidence of recurrence after successful resection of sub-aortic stenosis in two major highly specialized care centers in Riyadh and to identify possible factors associated with recurrence of DSS. Additional objective was to assess possible predictors of time to recurrence.

2. Materials and Methods

This was a retrospective cohort study conducted at King Abdulaziz Cardiac Center (KACC) in National Guard Health Affairs and King Faisal Specialized Hospital and Research Center (KFSHRC), Riyadh, Saudi Arabia. These centers provide a complete range of high-quality cardiac services to both adults and children.

The computer databases of both centers were searched for all patients aged under 19 years, as pediatric age defined by WHO, with a diagnosis of membranous discrete sub-valvular aortic stenosis between 1999 and 2018. We included both Saudi and non-Saudis, female and male patients, previously undergoing surgical resection of DSS. We reported all cardiac data that were documented in our patients' medical records. Patients with subaortic tunnel, fibromuscular ridge, hypertrophic subaortic stenosis, or co-existing shone complex were excluded. Follow-up data were collected over a period of at least 12 months to 18 years or recurrence within the study period.

Abbreviations

LVOTO	Left Ventricle Outflow Tract Obstruction
DSS	Discrete Subaortic Stenosis
KACC	King Abdulaziz Cardiac Center
NGHA	National Guard Health Affairs
KFSHRC	King Faisal Specialist Hospital & Research Center
ICIS	Integrated Clinical Information System
SPSS	Statistical Package for the Social Science
IRB	Institutional Review Board
REC	Research Ethics Committee

The data was initially collected from KACC using patients' chart systems including BESTCare and Apollo. The study was expanded to cover the patients' charts in the heart center in KFSHRC using Integrated Clinical Information System (ICIS). Xcelera software was used to obtain the echocardiographic data from both centers. The study variables included demographic data (e.g. nationality, gender, age at the diagnosis, etc.); echocardiographic data (e.g. pre-operative and post-operative peak gradient, aortic annulus, etc.); surgical data (e.g. procedure type, aortic valve abnormality, etc.); and others (e.g. family history, parental consanguinity, chronic illnesses, etc.) Recurrence was identified by the presence of postoperative echo gradient of 30 mmHg or higher. Ethical approval was obtained from the Institutional Review Board (IRB) at King Abdullah International Medical Research Center and the Research Ethics Committee (REC) at King Faisal Research Center.

2.1. Data Analysis

Frequencies and percentages were used to describe categorical variables while median and range (min to max) were used for continuous variables. Percentages reported in results are "valid percent" thus excluding missing data. The Chi squared or Fisher exact tests were used to compare the categorical demographic and clinical characteristics between the recurrence status. A Mann–Whitney test was used in the bivariate analysis between the continuous data and recurrence status. Cut off points were used for the continuous variables significantly associated with recurrence from the bivariate analysis. Univariate logistic regression was used to explore variables associated with recurrence, controlling for the length of follow-up. Variables with a p-value<0.10 were further assessed by multiple logistic regression with forward stepwise selection to determine significant independent predictors of recurrence. Freedom from recurrence survival was calculated from the time of surgery to the time of diagnosis of recurrence and estimated using the Kaplan−Meier method. Additional univariate and multivariable analyses were performed to determine the predictors of time to recurrence using the Cox proportional hazards regression model. Patients with no recurrence status were censored. A P value < 0.05 was considered to be statistically significant. The data were analyzed via Statistical Package for the Social Science (SPSS) version 22 (SPSS Inc., Chicago, IL).

3. Results

The charts of 420 children with subaortic stenosis from 1999 to 2018 were reviewed. After applying the exclusion and inclusion criteria, the 247 patients remained. Of these, 74 patients were obtained from NGHA and 173 patients from KFSHRC. 13 patients were deleted due to insufficient data, the 234 patients remained. Table 1 shows the patient characteristics. The sample included 221 Saudi patients (97.4%) and 6 non-Saudi (2.6%). There were 138 male patients (59%) and 96 females (41%). The median age at diagnosis was 36 months (range, 1−192 months). Overall, 105 patients (44.9%) had recurrence after the primary resection, while 129 patients (55.1%) had not. Of the 105 patients (44.87%) who had recurrence, 90 patients (85.71%) had once recurrence, 14 patients (13.3%) had it twice, and the three-time recurrence were seen in one patient (0.95%); 46 (19.74%) patients needed reoperation after the initial resection.

In all patients, the overall median age at diagnosis and at the 1st operation was 36 months (1−192 months) and 58 months (3−202 months), respectively. The median age at 1st operation for the recurrence group was 50 months (3−133 months), which is significantly lower than that of the non-recurrence group at 60 months (4−202 month) (p-value = 0.048). In the recurrence group, the median weight and height at the 1st operation were 16.4 kg (2.6−49 kg) and 104.5 cm (43−171 cm); both were significantly lower than the median weight and height at the 1st operation for the non-recurrence group (p-value = 0.027 and p-value = 0.010, respectively). However, BMI did not differ significantly between the groups (p-value = 0.497). There were 145 normal term subjects (92.4%).

The presence of aortic stenosis at the time of diagnosis was significantly associated with higher recurrence (p-value = 0.002). Of the 14 patients who had associated aortic stenosis at the time of DSS diagnosis, 12 patients had recurrence (85.7%). The presence of other cardiac lesions including valvular

Table 1. Patient characteristics.

Variable	All Patients (N = 234)	Non- Recurrence (N = 129)	Recurrence (N = 105)	P Value
Nationality				
Saudi	221 (97.4)	120 (54.3)	101 (45.7)	NS
Non-Saudi	6 (2.6)	3 (50)	3 (50)	
Sex, male	138 (59)	75 (54.3)	63 (45.7)	NS
Age at diagnosis, months	36 (1−192)	40 (1−192)	32.5 (3−132)	NS
Age at 1st operation, months	58 (3−202)	60 (4−202)	50 (3−133)	0.048
≤96	194 (83.6)	101 (52.1)	93 (47.9)	0.031
>96	38 (16.4)	27 (71.1)	11 (28.9)	
BMI, kg/m^2	15.2 (7.3−26.6)	15.5(7.3−26.6)	14.9(7.9−25.8)	NS
No prematurity	145 (92.4)	75 (51.7)	70 (48.3)	NS
Presence of cardiac lesions				
Aortic Stenosis (valvular)	14 (6)	2 (14.3)	12 (85.7)	0.002
Pulmonary Regurgitation	30 (12.9)	18 (60)	12 (40)	NS
Tricuspid Regurgitation	87 (37.5)	42 (48.3)	45 (51.7)	NS
Mitral Regurgitation	45 (19.4)	30 (66.7)	15 (33.3)	NS
VSD	9 (3.9)	5 (55.6)	4 (44.4)	NS
PDA	12 (5.2)	6 (50)	6 (50)	NS
Dilated Atrium	13 (5.6)	6 (46.2)	7 (53.8)	NS
Dilated Ventricle	20 (8.6)	10 (50)	10 (50)	NS
Others	58 (24.8)	27 (46.5)	31 (53.5)	NS
Chronic illness (including genetic disorders)	40 (19)	21 (52.5)	19 (47.5)	NS
Family history relevant to the problem	85 (52.1)	47 (55.3)	38 (44.7)	NS
Parent consanguinity	88 (59.9)	45 (51.1)	43 (48.9)	NS

Abbreviation: NS: Not significant, **BMI:** Body Mass Index, **VSD:** Ventricular Septal Defect, **PDA:** Patent Ductus Arteriosus.
Others: Double Outlet Right Ventricle, Post-stenotic dilatation, Supra-mitral membrane, mitral stenosis, pulmonary stenosis, tricuspid stenosis, atrial septal defect, or accessory mitral tissue. Data are presented as N(%) or median (range).

Table 2. Echocardiographic characteristics.

Variable	All Patients (N = 234)	No Recurrence (N = 129)	Recurrence (N = 105)	P Value
Peak gradient of pre-op, mmHg	60 (11−152)	49 (11−150)	70.5 (22.1−152)	0.018
Peak gradient of post-op, mmHg	13 (0−71)	10 (0−56)	15.9 (3.9−71)	<0.001
>13 mmHg	94(46.3)	29(30.9)	65(69.1)	<0.001
Diameter of Aortic Annulus pre-op, cm	1.2 (0.10−9.8)	1.3 (0.11−2)	1 (0.10−9.8)	NS
Severity of stenosis				
Mild	53 (29.3)	35 (66)	18 (34)	NS
Moderate	40 (22.1)	22 (55)	18 (45)	
Severe	87 (48.1)	42 (48.3)	45 (51.7)	
Critical	1 (0.6)	0 (0)	1 (100)	
Aortic regurgitation pre-op				
No	25 (11)	12 (48)	13 (52)	NS
Mild	188 (82)	107 (56.9)	81 (43.1)	
Moderate	15 (6.6)	8 (53.3)	7 (46.7)	
Aortic regurgitation post-op				
No	42 (18.3)	21 (50)	21 (50)	NS
Mild	178 (77.7)	100 (56.2)	78 (43.8)	
Moderate	9 (3.9)	5 (55.6)	4 (44.4)	
AoV morphology				
Bicuspid	17 (7.6)	10 (58.8)	7 (41.2)	NS
Tricuspid	207 (92.4)	113 (54.6)	94 (45.4)	
AoV abnormality				
Thickened, prolapsed, or malformed	93 (39.8)	48 (51.6)	45 (49.4)	NS

Abbreviations: NS: Not significant, **Pre-Op:** Before the surgery, **Post-Op:** After the Surgery, **AoV:** Aortic Valve.
Data are presented as N(%) or median (range).

regurgitation or stenosis, atrial septal defect, ventricular septal defect, patent ductus arteriosus, or dilated chambers were not associated with recurrence. There was a trend toward a higher rate of parental consanguinity (51.1% vs 48.9%, p = 0.112) and presence of tricuspid regurgitation (48.3% vs 51.7%, p = 0.102), but these were not significant. Sex and family history did not differ significantly between the patients who had recurrence and the ones who did not.

The overall median peak gradient in which the primary resection was indicated is 60 mmHg, or less in the presence of aortic regurgitation (11−152 mmHg). The median peak gradient pre-operation for the recurrence group (70.5 mmHg [22.1−152 mmHg]) was significantly higher compared to non-recurrence group (49 mmHg [11−150 mmHg], p-value = 0.018). The median peak gradient post-operation for the recurrence group (15.9 mmHg, range 3.9−71 mmHg) was significantly higher than that of non-recurrence group (10 mmHg, range 0−56 mmHg) (p-value <0.001) (Table 2). After applying the bivariate analysis, patients with a post-operative peak gradient of more than 13 mmHg, 65 (69.1%) had a recurrence versus 29 (30.9%) patients with nonrecurrence (p-value<0.001). There was no significant difference between the patients who had recurrence and the ones who did not in terms of aortic regurgitation pre-operation and post-operation.

There were 61 (45.5%) patients who had recurrence and underwent a simple membrane resection

Table 3. Surgical and pathological characteristics.

Variable	All Patients (N = 234)	No Recurrence (N = 129)	Recurrence (N = 105)	P Value
Procedure used at 1st operation				
Simple membrane resection	134 (57.5)	73 (54.5)	61 (45.5)	NS
Membrane resection with myectomy	99 (42.5)	55 (55.6)	44 (44.4)	
Type of extracted surgical tissue				
Fibrous	32 (27.8)	19 (59.4)	13 (40.6)	NS
Fibromuscular	51 (44.3)	22 (43.1)	29 (56.9)	
Others	32 (27.8)	14 (43.75)	18 (56.25)	
Complications after the 1st operation	83 (37.1)	47 (56.6)	36 (43.4)	NS

Abbreviations: NS, Not Significant.
Others: Fibromyxoid, Fibrocollagenous with myoxid changes, or Fibroelastic with myoxid changes.
Data are presented as N(%).

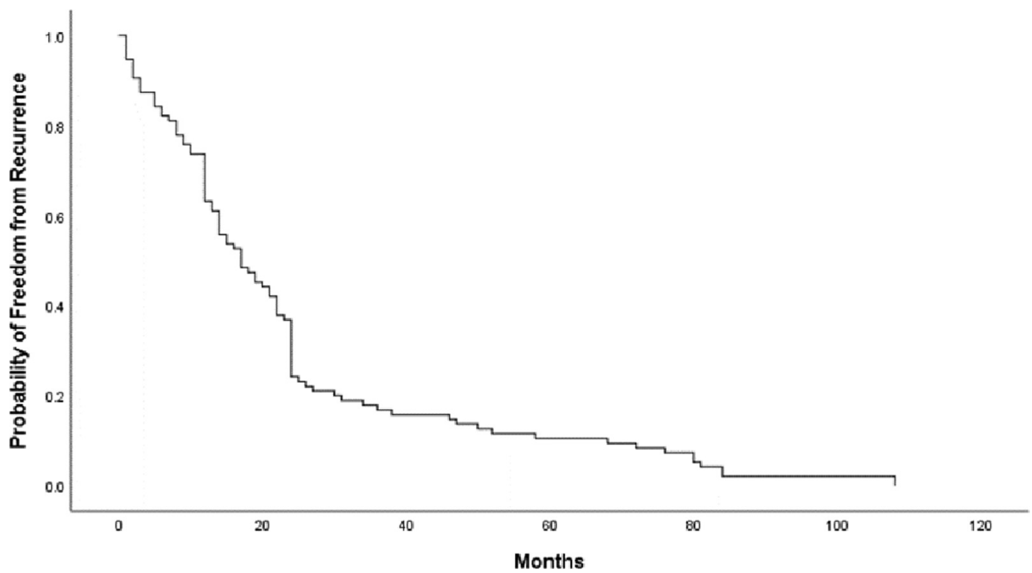

Fig. 1. Kaplan−Meier curve illustrating the freedom from recurrence after DSS.

as a primary intervention; 44 patients (44.4%) underwent membrane resection with septal myectomy (Table 3). There was no significant difference between the patients who had a recurrence and the ones who did not in this type of extracted tissue.

All variables significantly associated with recurrence in the bivariate analysis were examined using univariate logistic regression model. The univariate analysis showed no significant risk factor for recurrence. The minimum p-value obtained was for age at the 1st operation (≤96 months) (OR = 1.02, 95%CI 0.540−1.92, p-value = 0.06). All calculated p-values were above 0.2 and hence no variables could be introduced into the multiple logistic regression.

The median time to recurrence was 17 months (range 1−108 months). The overall freedom from recurrence for the study cohort is represented by a Kaplan−Meier curve (Fig. 1). The solid line shows the overall probability of being free from recurrence versus time. In univariate analysis using Cox proportional hazards model, there was no statistically significant difference in terms of time to recurrence according to the patients' characteristics, pre-operative, or post-operative variables (p-value>0.05).

4. Discussion

This multi-center retrospective cohort study analyzed data of 234 patients with DSS to estimate the incidence of DSS recurrence after primary resection and determined the associated risk factors. The rate of recurrence and need for reoperation after the initial resection reported in previous studies range from 22.7% to 43%. The rates of recurrence and reoperation are demonstrated in Table 4. During the period of our study, the rate of recurrence was 44.9%.

In our study, the age at the 1st operation was not a significant risk factor. Geva A et al. [14] confirmed our findings and suggested that some patients had a different underlying pathophysiology and may need earlier surgery; thus, they were more likely to experience recurrence and need reoperation unlike those whose clinical course progresses more slowly. In contrast, Pickard et al. [1] and Donald et al. [12] reported that a younger age during the 1st operation was a significant risk factor for recurrence.

We found no significant association between recurrence and the presence of other cardiac

Table 4. A review of studies of Discrete Subaortic Stenosis.

Study	Study period	Patients N	Recurrence N(%)	Reoperation N(%)
Our study	1999−2018	234	105 (44.9)	46 (19.7)
Geva A et al. [14]	1984−2001	111	NR	16 (14)
Pickard S et al. [1]	1984−2009	155	38 (24)	32 (21)
Mukadam S et al. [13]	1991−2015	104	NR	9 (8.4)
Donald J et al. [12]	1989−2015	69	20 (29)	13 (18.8)
Nawaytou H et al. [18]	2006−2014	35	15 (43)	NR
Uysal F et al. [15]	1994−2010	66	15 (22.7)	1 (1.5)

Abbreviations: NR: Not reported.

lesions—this could be due to the small sub-populations of each lesion. Similarly, Geva et al. [14] found no significant association between the presence of other cardiac lesions and recurrence requiring re-operation. However, Mukadam et al. [13] found a higher incidence of DSS recurrence in patients with pre-operative mitral regurgitation. Mukadam et al. [13] identified a significant association between the presence of genetic diseases and the recurrence of DSS. Nevertheless, our findings did not support the association between recurrence and any extra-cardiac anomaly or associated genetic disorders. However, there was a trend toward a higher rate of parental consanguinity in our sample (60%). Future genetic studies are required to identify the mode of inheritance or responsible genes.

Pickard et al. [1], Geva et al. [14], and Uysal et al. [15] reported that a higher pre-operative peak gradient at the echocardiogram was a significant risk factor for recurrence. Donald et al. [12] reported that a higher post-operative peak gradient was a significant risk factor. This could be due to different surgical techniques over time. However, our study found that pre-operative and post-operative peak gradients were not significant risk factors.

Parry et al. [10] and van Son et al. [16] reported that performing myomectomy during the primary surgery decreases the rate of recurrence. However, Brauner et al. [6] and Coleman et al. [17] did not confirm this finding. There was no significant association between recurrence and the use of myectomy in the primary surgery. These findings might be due to different definitions of outcomes used in the previous studies or the fact that more aggressive underlying disease may lead surgeons to use myectomy.

5. Study Limitations

Our study is subject to the same limitations as other cohort retrospective studies. Some of the data were missing or documented inappropriately such as the distance of obstruction from aortic valve, the left ventricle outflow tract angle, and post-operative aortic annulus. A larger study with a prospective design would better identify risk factors for recurrence in DSS. Although our study was conducted in large national cardiac centers in Saudi Arabia, the results of this study cannot be generalized to the Saudi population.

6. Conclusion

To the best of our knowledge, this is the largest retrospective study conducted to estimate the incidence of discrete subaortic stenosis (DSS). Our results suggest that the rate of recurrence after the initial resection of discrete subaortic membrane in children is relatively high (44.9%). In our study, the age at first operation as well as peak-gradient pre- and post-operation were significantly associated with recurrence. However, no significant independent risk factors of recurrence were identified when the time to recurrence was controlled for in the analysis. We strongly recommend larger prospective studies to determine the risk factors for recurrence in DSS.

Author contribution

Conception and design of study: Kamal MK Ayoub, Abdullah A. Al Sehly. Literature review: Gadah M. Alqurashi, Rema S. Almohanna, Arwa A. Alkhuraiji, Najla A. Almasoud, Amjad R. Alsubaie. Acquisition of data: Gadah M. Alqurashi, Rema S. Almohanna, Arwa A. Alkhuraiji, Najla A. Almasoud, Amjad R. Alsubaie. Analysis and interpretation of data: Alaa M. Althubaiti. Data collection: Gadah M. Alqurashi, Rema S. Almohanna, Arwa A. Alkhuraiji, Najla A. Almasoud, Amjad R. Alsubaie. Drafting of manuscript: Gadah M. Alqurashi, Rema S. Almohanna, Arwa A. Alkhuraiji, Najla A. Almasoud, Amjad R. Alsubaie. Revising and editing the manuscript critically for important intellectual contents: Kamal MK Ayoub, Alaa M. Althubaiti, Abdullah A. Al Sehly. Supervision of the research: Kamal MK Ayoub, Alaa M. Althubaiti, Abdullah A. Al Sehly. Research coordination and management: Gadah M. Alqurashi, Rema S. Almohanna.

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Perspective

In literature, there was a relatively high rate of recurrence of DSS after primary resection. Thus, we aim to measure the incidence and identify possible factors associated with recurrence of DSS in our population. Larger studies might be better to stratify risk factors for recurrence in DSS and identify causality.

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