THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Prenatal Diagnosis, Associations and Outcome for Fetuses with Congenital Absence of the Pulmonary Valve Syndrome

ORIGINAL INVESTIGATION

ABSTRACT

Background: The aim of this study is to review the spectrum of the prenatally detected absent pulmonary valve syndrome and its outcome after diagnosis.

Methods: Clinical data and echocardiographic findings of 37 cases with a fetal diagnosis of absent pulmonary valve syndrome between 2008 and 2020 were analyzed in this retrospective multicenter study.

Results: Median gestational age at diagnosis was 25 weeks. Three subtypes of absent pulmonary valve syndrome were observed: (1) with tetralogy of Fallot (n = 30; 81.0%); (2) absent pulmonary valve syndrome with intact ventricular septum (n = 5; 13.5%); (3) with complete atrioventricular septal defect (n = 2; 5.4%). In contrast to 7/25 fetuses (28%) with tetralogy of Fallot-absent pulmonary valve syndrome who had a patent ductus arteriosus, all 5 fetuses with absent pulmonary valve syndrome-intact ventricular septum had a patent ductus arteriosus ($P < .001$). No significant difference was found between the z-scores of pulmonary artery branches in fetuses with or without patent ductus arteriosus ($P > .05$). The analysis did not reveal any correlation between gestational week and z-scores of pulmonary artery, pulmonary artery branches (right pulmonary artery, left pulmonary artery), and ratio of aorta/pulmonary artery ratio. The echocardiographic measurements of survivors did not differ significantly from non-survivors ($P > .05$). Extracardiac anomalies were observed in 8/37 fetuses (21.6%). The incidence of extracardiac anomaly was significantly higher in cases of tetralogy of Fallot-absent pulmonary valve syndrome ($P < .05$). Overall, 9 fetuses (24%) had genetic anomalies. All 6 fetuses (20%) with 22q11.2 microdeletion were within the tetralogy of Fallot-absent pulmonary valve syndrome group. Overall survival after initial diagnosis in the total cases was 36.6% (11/30), with 9 of 30 (30%) tetralogy of Fallot-absent pulmonary valve syndrome cases and 2 of 5 (40%) absent pulmonary valve syndrome-intact ventricular septum cases.

Conclusions: In this largest series of absent pulmonary valve syndrome, extracardiac, and chromosomal anomalies were found to be a common occurrence. The risk of 22q11.2 microdeletion was higher in tetralogy of Fallot cases at 40%. The sizes of the pulmonary artery and its branches and the aorta had no correlation of high mortality antenatally or after birth, which were 63.4% and 47.7%, respectively.

Keywords: 22q11.2 microdeletion, absent pulmonary valve syndrome, echocardiography, fetus, outcome, prenatal diagnosis

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Received: December 14, 2021
Accepted: April 6, 2022
Available Online Date: May 12, 2022

Cite this article as: Babaoğlu K, Doğan Y, Erdem S, Özbarlas N, Başar E, Uzun O. Prenatal diagnosis, associations and outcome for fetuses with congenital absence of the pulmonary valve syndrome. *Anatol J Cardiol.* 2022;26(9):702-709.

DOI:10.5152/AnatolJCardiol.2022.1461

INTRODUCTION

Absent pulmonary valve syndrome (APVS) is an extremely rare congenital heart anomaly characterized by a rudimentary and dysplastic pulmonary valve, resulting in significant pulmonary regurgitation with some degree of stenosis. It is associated with a variable degree of aneurysmal dilation of the pulmonary trunk as well as one or both of its branches. Although APVS has been described as an isolated abnormality, it is more commonly associated with tetralogy of Fallot (TOF). The overall incidence of APVS is not exactly known. Prenatal APVS accounts for 15-20% of all fetuses with TOF, 1% of all congenital cardiac defects, however, the postnatal incidence of APVS is estimated to be 3-6% in all patients with Tetralogy of Fallot.[1-5] It has been associated with significant perinatal morbidity and mortality. The mortality rate is more than 50% and it is closely related to the

bronchomalacia secondary to bronchial compression with respiratory failure and fetal heart failure and chromosome abnormalities. Previously published work has mostly focused on postnatal surgical outcome.[6-9] Because of the rarity of APVS, published data with large series on the outcome of prenatal diagnosis of APVS is scarce. The aim of our research was to further extend the current knowledge about the prenatally detected APVS and its characteristics, associated anomalies, clinical course, and outcome.

METHODS

Clinical data and echocardiographic findings of 37 cases with a fetal diagnosis of APVS between 2008 and 2020 were analyzed in this retrospective 3-center study. The Institutional Research Ethics Board approved this study.

The perinatal diagnosis of APVS was made on the basis of rudimentary valve leaflets in combination with the concurrent occurrence of pulmonary stenosis and regurgitation demonstrated by to and fro blood flow over the dysplastic valve. Medical records and stored images such as recorded videotapes and pictures were reviewed to determine the spectrum and cardiac features before and after birth.

All cases underwent fetal echocardiography and it was performed by pediatric cardiologists with high-quality ultrasound equipment (Philips Epiq7, Hamburg, Germany; Vivid 7, General Electric Medical Systems, Milwaukee, USA). Two-dimensional grayscale imaging, color Doppler, and pulsed wave Doppler were the modalities used to quantify cardiac morphometry and abnormal flow patterns and velocities. The diagnosis was confirmed by postnatal echocardiography.

The following clinical variables were assessed; indication for referral, gestational age at diagnosis, maternal age, associated cardiac, extracardiac, and chromosomal abnormalities, presence of hydrops fetalis, and fetal/neonatal outcomes. For subjects born alive, postnatal diagnosis, and survival beyond the neonatal period were documented.

The following quantitative echocardiographic parameters were analyzed; cardiothoracic ratio, presence or absence of ductus arteriosus (DA), aortic arch position, maximum diameter of the ascending aorta (Ao), maximum diameter of the main pulmonary artery (PA), maximum diameter of PA branches, the ratio of aortic valve annulus (AV)/pulmonary valve annulus (PV), and pulmonary trunk Doppler velocity (Figure 1). These measurements were compared with established normal sizes (z-score).[10]

Data Analysis

All data were analyzed with Statistical Package for the Social Sciences version 27 for windows. Descriptive statistics for continuous variables were expressed as mean ± standard deviation. The normal distribution of all continuous variables was examined using the Kolmogorov–Smirnov test. The independent samples *t*-test or the Mann–Whitney *U* test was used to assess the between-group significance, according to data distribution. Chi-square or Fisher's exact test was used to compare between-group frequencies for categorical variables. Pearson test was used for inferential comparison. Survival analysis was performed by Kaplan–Meier analysis. A *P*-value <.05 was considered significant.

RESULTS

Study Population

During the study period, 37 cases with APVS were diagnosed prenatally. The mean gestational age at diagnosis was 25 (range 18-37) weeks. Nine out of 37 cases (24%) were diagnosed before 20 weeks of gestation. The main reason for referral was suspected congenital heart disease on a routine obstetric ultrasound scan. Detailed general information of these cases is displayed in Table 1. Thirty fetuses (81.0%) were classified as having TOF/APVS, 5 fetuses (13.5%) as APVS with intact ventricular septum (IVS). In the remaining 2 fetuses (5.4%), 1 had TOF and complete atrioventricular septal defect (CAVSD) and the other had CAVSD and double outlet right ventricle (DORV) accompanying APVS. Additional cardiovascular anomalies were identified in 9 patients (24.3%). There were 7 cases (18.9) with right aortic arch (RAA) and 2 cases with left persistent superior vena cava. Except for the fetus with CAVSD and DORV, all fetuses with RAA were within the group of TOF-APVS.

In 31/37 cases (83.7%), the main PA was significantly dilated. The branches of PA were dilated in all. Although the measurement of z-scores of aorta, main pulmonary artery (MPA), branch pulmonary arteries did not differ significantly in cases with TOF-APVS from cases with APVS-IVS, AV/PV ratio was higher in TOF-APVS cases (P = .002). Echocardiographic measurements of the groups are presented in Table 2. Severe pulmonary valve stenosis (peak systolic velocity more than 1.5 m/s) and regurgitation were present in all fetuses. In 30 of 37 cases (81%), information on patency of the DA was retrieved. In contrast to 7/25 fetuses (28%) with TOF-APVS, all 5 cases with APVS-IVS had a patent DA (P < .001). Z-scores of the MPA and PA branches were not different between the fetuses with or without patent DA (P > .05). The correlation analysis did not identify any significant relationship between gestational age and z-scores of MPA, right pulmonary artery (RPA), left pulmonary artery (LPA), and the ratio of AV/PV. The fetal echocardiographic measurements of survivors did not differ significantly from deceased (P > .05) (Table 3).

Extracardiac anomalies were observed in 8/37 (21.6%) fetuses: 5 of 32 (15.6%) in TOF/AVSD-APVS and 3 of 5 (60.0%)

HIGHLIGHTS

- Patent ductus arteriosus (DA) was detected in 28% of fetuses with tetralogy of Fallot (TOF)-absent pulmonary valve syndrome (APVS). In contrast, all 5 fetuses with APVS-intact ventricular septum had patent DA.
- Extracardiac and chromosomal anomalies are very common that both were identified in one-fifth of the APVS cases and most commonly, 40% of the time in TOF-APVS.
- Overall mortality after initial diagnosis and after birth are still as high as 63.4% and 47.7%, respectively.

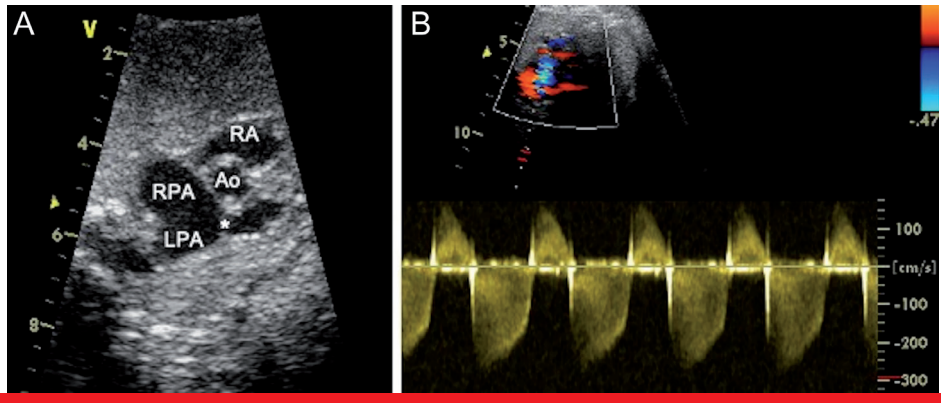

Figure 1. (A) Typical echocardiographic image of fetus with TOF-APVS and dilated pulmonary artery branches; (B) Pulmonary flow by pulsed-wave Doppler showing pulmonary stenosis and regurgitation. TOF, tetralogy of Fallot; APVS, absent pulmonary valve syndrome; RA, right atrium; Ao, aorta; RPA, right pulmonary artery; LPA, left pulmonary artery. *Pulmonary fibrous annulus.

in APVS-IVS. The ratio of the extracardiac anomaly was significantly higher in cases of APVS-IVS (P <.05). The karyotype and 22q11.2 microdeletion were checked in a total of 15 cases, 6 of which were in the antenatal and 9 were in the postnatal period. Overall, 9 fetuses had genetic anomalies: 7 cases (16.6%) with TOF-APVS, 1 case with APVS-IVS, and 1 case with TOF-APVS-AVSD. One fetus with trisomy 18 had TOF-APVS-CAVSD, 1 fetus with 5q35.1del had TOF-APVS, and 1 fetus with t(18;14)(q21;q24) had APVS-IVS. All 6 fetuses with microdeletion 22q11.2 (20%) were within the TOF-APVS group (Tables 1, 4).

The outcome of pregnancy (Figure 2) is unknown in 5 cases since patients were lost to follow-up. The pregnancy was terminated (TOP) in 5 cases with TOF-APVS and in 1 case with APVS-IVS. Among TOPs, there were 2 cases presenting with 22q11.2 del and 5q35.1del, 1 case with hydrops fetalis and 1 case with the extracardiac anomaly. The fetus diagnosed with trisomy 18 who had APVS associated with complete atrioventricular septal defect died during labor. Intrauterine death (IUD) was observed in 2 cases, 1 of whom had hydrops fetalis. Hydrops fetalis was observed in 2 of 37 cases.

Twenty-one babies were delivered between 36 and 39 gestational weeks. Of the 21 live births, 5 neonates died following birth due to severe respiratory failure in the neonatal period. Eleven babies underwent surgical repair beyond the neonatal period, 5 died after surgery, 6 babies were well

Table 1. General Characteristics of Study Population According to the Type of APVS

	All cases (n = 37)	Group I TOF/AVSD-APVS (n = 32)	Group II APVS-IVS (n = 5)	P[a]
Gestational age	25.54 ± 6.40	25.50 ± 6.27	25.80 ± 7.98	.880
Maternal age	26.05 ± 5.31	26.22 ± 5.43	25.00 ± 4.89	.682
Cardiac anomalies	25			
TOF-APVS	5			
TOF-APVS-RAA	5			
APVS-IVS	1			
APVS-TOF-AVSD	1			
APVS-DORV-AVSD				
Chromosomal anomalies/tested cases	9/15 (60%)	8/11 (72.7%)	1/4(25%)	
22q11.2del	6	6	-	
Trisomy18	1	1	-	
5q35.1del	1	1	-	
t(18;14)(q21;q24)	1	-	1	
Extracardiac anomalies	8/37	5/32	3/5	
TOP	6/37	5/32	1/5	
IUD	2	2	-	
No follow-up	5	5	-	
Stillbirth	1	1	-	

[a]*P* values indicate differences between TOF/AVSD-APVS and APVS-IVS patients.
APVS, absent pulmonary valve syndrome; AVSD, atrioventricular septal defect; DORV, double outlet right ventricle;IUD, intrauterine death;IVS, intact ventricular septum; TOF, tetralogy of Fallot; TOP, termination of pregnancy.

Table 2. Fetal Echocardiographic Measurements According to the Type of APVS

	APVS with TOF/AVSD	APVS with IVS	*P*
Enlarged right ventricle	26/32 (81.2%)	4/5 (80%)	.609
Patent DA	28%	100%	.001
Heart dimensions (Z-score)			
AV annulus	1.50 ± 1.88	1.40±1.78	.509
PV annulus	−0.47 ± 1.90	1.69±1.70	.054
Main PA	3.80 ± 2.19	5.08±2.46	.226
RPA	6.14 ± 2.21	5.5±3.05	.491
LPA	6.08 ± 1.88	5.28±1.94	.363
AV annulus/PV annulus	1.35 ± 0.27	0.80±0.25	.002
Pulmonary regurgitation Peak flow velocity (m/s)	2.65 ± 0.48	2.45±0.46	.752
Pulmonary stenosis Peak flow velocity (m/s)	2.08 ± 0.54	2.20±0.78	.594

APVS, absent pulmonary valve syndrome; AVSD, atrioventricular septal defect; AV, aortic valve; IVS, intact ventricular septum; LPA, left pulmonary artery, RPA, right pulmonary artery; PA, pulmonary artery; PV, pulmonary valve; TOF, tetralogy of Fallot.

Table 3. Comparison of Fetal Echocardiographic Measurements Between the Alive and Non-Surviving Babies After Birth*

	Non-survivors (n=10)	Survivors (n=11)	*P*
Enlarged right ventricle	7 (70%)	8 (72.7%)	.713
Patent DA	6 (60%)	5 (45%)	.670
Dimensions (Z-score)			
AV annulus	1.31 ± 1.11	0.89 ± 2.33	.613
PV annulus	0.41 ± 2.24	−1.13 ± 2.16	.245
Main PA	3.27 ± 1.55	4.75 ± 2.61	.575
RPA	5.84 ± 2.10	6.12 ± 2.92	.260
LPA	5.99 ± 1.31	5.52 ± 2.47	.273
AV annulus/PV annulus	1.15 ± 0.24	1.43 ± 0.52	.214
Pulmonary regurgitation Peak flow velocity (m/s)	2.57 ± 0.41	2.25 ± 0.21	.825
Pulmonary stenosis Peak flow velocity (m/s)	2.30 ± 0.56	2.07 ± 0.60	.727

*Since there are 21 live-born babies with follow-up, the data were evaluated for these babies.
AV, aortic valve; LPA, left pulmonary artery, RPA, right pulmonary artery; PA, pulmonary artery; PV, pulmonary valve; TOF, tetralogy of Fallot.

after the operation. The remaining 5 babies are on medical follow-up awaiting an operation. The overall mortality rate was 63.3% (19/30) including 6 TOP, 2 IUD, and 1 stillbirth. Five cases without follow-up and 2 ongoing pregnancies were not included in this calculation. Overall survival after initial diagnosis in the total cases was 36.6% (11/30), with 9 of 30 (30%) TOF-APVS cases and 2 of 5 (40%) APVS-IVS cases. The Figure 3 illustrates the current survival rate for TOF-APVS and APVS-IVS in our series.

DISCUSSION

This study shows that APVS can also occur with AVSD which was not recorded in other series. Absent pulmonary valve syndrome has a high prenatal and postnatal preoperative mortality. Absence of the DA or dilatation of the PA or the branches has no significant impact on the survival outcomes. Frequent extracardiac and genetic anomalies are more likely to affect the clinical course of this unique anomaly. Prenatal diagnosis of the APVS should be rather straightforward because of its typical features of a dilated MPA and its branches, and color Doppler detection of severe stenosis and insufficiency of the functionally absent pulmonary valve.

Although APVS is mostly seen with TOF, it can also be associated with complete AVSD and tricuspid atresia or as an isolated lesion in the context of an intact ventricular septum.[2,4,11,12] In this current study, 81% of the cases occurred with TOF, and 13.5% with APVS-IVS. This distribution is similar to the results of Axt-Fliedner et al[13] who published the largest study in the literature with 71 APVS cases (83.1% and 16.9%). The coexistence of APVS-AVSD, which was not found in other series, was detected in 2 (5.4%) cases in our study.

The effect of DA on physiopathology, pulmonary vascular structure, and hemodynamics in pulmonary valve absence syndrome is poorly defined. Furthermore, it is debatable whether ductal agenesis is due to underdevelopment of the pulmonary valve leaflets or it leads to their rudimentary formation. While DA is restrictive or even absent in fetuses with TOF-APVS, it is large in APVS-IVS. It is postulated that hydrops fetalis is likely to develop early in gestation because of aortopulmonary shunting and biventricular volume overload by the DA in TOF-APVS with patent DA.[13,14] Our study detected hydrops only in 2 cases who had TOF-APVS with patent DA at early gestational weeks of 15 and 18. It can be assumed that the absence of DA in TOF cases has a hemodynamically protective effect from heart failure and hydrops. Supporting this concept, Zach et al[14] proposed that intrauterine closure of the DA would be essential for survival in APVS as patency of the arterial duct would result in substantial aorto-pulmonary shunting and right-sided cardiac failure.[14] On the contrary, in our study, although the ductus was patent in 22% of the TOF group, hydrops/heart failure was observed just in 2 cases, suggesting that the DA may not be the only factor affecting it.

Table 4. Detailed Information About all Extracardiac and Genetic Anomalies in all Fetuses with APVS

	Cardiac Anomalies	Genetic Anomalies	Extracardiac Anomalies	Outcome
1	TOF-APVS	22q11.2del	-	Death, 4 months, surgery (+)
2	TOF-APVS	22q11.2del	-	Death, 5 months, surgery (+)
3	TOF-APVS	22q11.2del	Short long bones	Death, 6 months, surgery (-)
4	TOF-APVS	22q11.2del	-	TOP
5	TOF-APVS	22q11.2del	-	No follow-up
6	TOF-APVS	22q11.2del	-	No follow-up
7	TOF-AVSD-APVS	Trisomy18	Polycystic kidneys, absent ductus venosus	Still birth
8	APVS-IVS	Not identified	TEF	Alive
9	APVS-IVS	t(18;14)(q21;q24)	Rocker-bottom foot, SUA rectal malformation,	Death, 50 days, surgery (+)
10	TOF-APVS	Not identified	Right persistant UV, duodenal atresia	Cont. pregnancy
11	TOF-APVS	Not identified	Esophageal atresia with TEF, SUA	Alive
12	APVS-IVS	Not identified	Congenital cataract	Death, 9 months, surgery (+)
13	TOF-APVS	Not identified	Low set ears	TOP
14	TOF-APVS	5q35.1del	-	TOP

APVS, absent pulmonary valve syndrome; AVSD, atrioventricular septal defect; IVS, intact ventricular septum; SUA, single umbilical artery; TEF, tracheoesophageal fistula; TOF, tetralogy of Fallot; TOP, termination of pregnancy; UV, umbilical vein.

One of the most important issues in APVS is the aneurysmatic dilatation in the PA and its branches. The absence of DA has been claimed to be responsible for this enlargement.[15-17] Although the presence of a patent and non-restrictive DA seems to prevent massive dilatation of the branch PAs, PA dilatation can be also seen in patients with either IVS or TOF having patent DA (4.11). Therefore, factors other than DA also affect the extent of the width of the PA branches. It has been hypothesized that aneurysmatic dilatation of branches of PA results from both primary underdevelopment of the pulmonary valve leaflets with an obstructive ring and high RV stroke volume with severe pulmonary regurgitation and high pulmonary vascular resistance.[15-19] Our findings corroborate this hypothesis, we have failed to demonstrate any link between the presence or absence of the arterial duct and the size of the PA branches.

Another controversial issue is whether dilatation in the PA and its branches progress during pregnancy. Wertaschnigg reported that z-score values of PA did not change significantly from diagnosis till birth.[20] They suggest that PA dilatation occurs early in pregnancy. Similarly, the diameters of PA branches of fetuses in advanced gestational weeks were not greater than those with earlier pregnancies and there was no correlation between gestational age and z-scores in our study. Furthermore, we observed that there was no significant change in the z-scores of the fetuses with repeated measurements during the fetal period.

The association between APVS and chromosomal anomalies has been documented in different studies. Volpe et al[21] detected chromosomal anomalies in 9 of 21 patients, 4 of them had 22q11.2 microdeletion. In our study, we found 9 (24.3%) chromosomal anomalies in 37 cases, however, invasive tests were performed only in 15 cases antenatally. There were 6 cases (16.2%) with 22q11.2 microdeletion and all of them were in the TOF-APVS group, as in the study of Axt-Fliedner et al.[13] It should be noted that these rates will be higher when we set the denominator to only the 15 cases tested. According to the number of cases tested, 22q11.2 microdeletion was 40% in our study, 25% and 20.6% in the other 2 studies.[13,21] In a cohort of patients with conotruncal lesions, 22q11.2 deletion was found in 16% of TOF patients,[22] current results suggest a higher rate of 22q11.2 deletion in TOF-APVS.

The incidence of extracardiac anomalies and genetic abnormalities in APVS is contradictory. Galindo et al[23] underlined that extracardiac anomalies are rarely associated with APVS, while a high number of associated anomalies and chromosomal problems were reported by Volpe et al.[21] Axt-Fliedner et al[13] found a rate of 50.7%, they stated that there was a higher rate of extracardiac anomalies in the TOF-APVS group compared to the APVS-IVS group. Extracardiac anomalies were less common (21.6%) in our study. Interestingly, we found that the ratio of extracardiac anomalies in APVS-IVS group was higher than TOF-APVS group in contrast to the study of Axt-Fliedner et al.[13] It should also be kept in mind that the number of extracardiac anomalies will be higher in patients with chromosomal anomalies.

The clinical course and prognosis of patients with TOF and absent pulmonary valve are variable and usually poor. Pulmonary regurgitation promotes aneurysmal dilatation of the pulmonary arteries. Thus, highly pulsatile enlarged pulmonary arteries often cause external compression of the airways, sometimes completely obliterating the bronchial

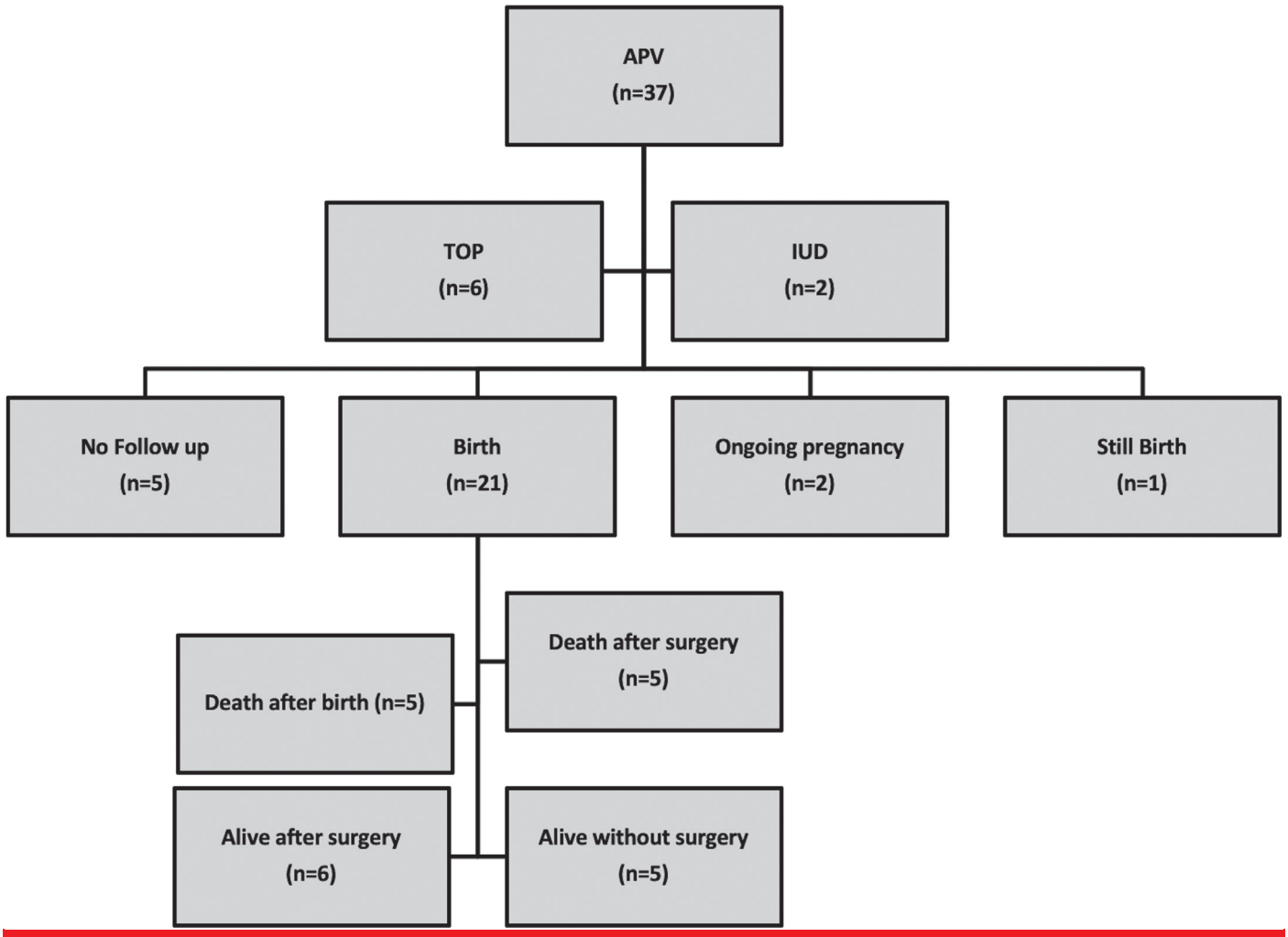

Figure 2. Flowchart of overall study population and outcome.

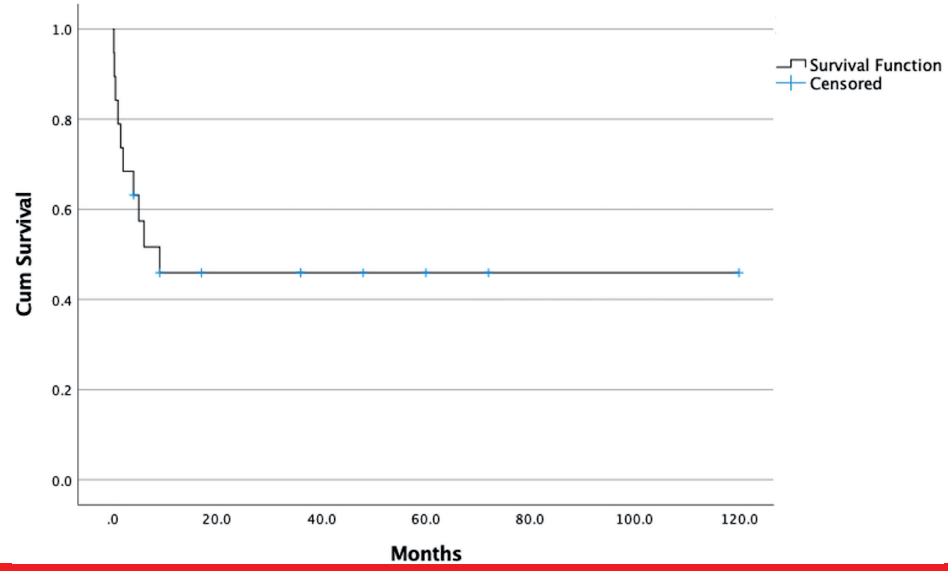

Figure 3. Kaplan–Meier survival curve for subjects born alive for whole cases.

lumens during systole. This leads to varying degrees of tracheobronchial malacia and air trapping.[22] The clinical spectrum of APVS is bimodal. Some patients are able to survive the neonatal period and infancy with mild or even no respiratory symptoms, while others suffer from severe airway complications immediately after birth. Patients who present with severe respiratory compromise immediately after birth or in the first weeks of life will generally require urgent intervention and have a worse outcome than those who escape early intervention with relatively minor respiratory involvement.[22] It is commonly advocated that the prognosis is largely dependent on the size of the pulmonary trunk and branches and the degree of bronchial compression. However, respiratory distress may not develop even in fetuses with massively large PA branches. We observed that some babies with large PA branches were symptom-free but some of them became ventilator dependent. The severity of bronchial compression cannot be predicted accurately by fetal echocardiography. There are conflicting results regarding a higher PA valve-to-aortic valve annular ratio and its effect on the severity of the clinical symptoms (11.13). Our findings support that a significant association could not be established between the presence of the duct and the size of the pulmonary arteries and the ratio of PA valve-to-aortic valve annular ratio. Therefore, we believe that PA diameters alone do not determine the clinical symptoms.

Survival rates in cases with APVS are widely variable in different studies, that ranges from 14.2% to 50%.[13,20,21] In the current study, the overall survival rate after the initial diagnosis was 36.6% (11/30) in the total cases, with 9 of 30 (30%) in TOF-APVS cases and 2 of 5 (40%) in APVS-IVS cases. Our results are comparable to the 28.1% overall survival rate reported by Axt-Fliedner et al[13] from the initial diagnosis. The survival rate of babies born alive was 52.9% in the TOF-APVS group and 50.0% in the APVS-IVS group. Consequently, the survival rate of subjects born alive in the total case was 52.3% (11/21). These numbers are much higher than the reported 14% by Galindo et al[23] but also much less than the reported 86.2% by Axt-Fliedner et al[13] Besides termination of pregnancy, the perinatal risk factors for mortality include the presence of a genetic syndrome or abnormal karyotype, heart failure due to hydrops fetalis, and respiratory failure in the postnatal period. Various degrees of segmental or lobar air trapping and atelectasis are expected findings in all newborns with respiratory distress. In our study, hydrops, genetic or extracardiac anomalies were present in 4 out of 6 fetuses (75%) in addition to APVS. Of the 21 live births, 5 neonates died following birth due to severe respiratory failure in the neonatal period.

The yield of echocardiographic parameters for prediction of outcome is controversial. Z-scores of MPA, RPA, LPA, and PA valve to aortic valve annular ratio of survivors did not differ significantly from non-survivors in our series. Contrary to our results, Szwast et al[11] found a higher PA valve to Aortic valve annular ratio to be a factor in poor outcomes. There is evidence that early neonatal ventilator dependency predicts mortality independent of the surgical result.

Surgical mortality was 60% in the 1980s. However, during the last decade survival of the patients with APVS has improved by modern surgical strategies and improvements in intensive care management. Nevertheless, the need for reinterventions is not rare, especially after surgery, due to respiratory problems and pulmonary insufficiencies.

Study Limitations

It is plausible that a number of limitations might have influenced the results obtained. First, this was a retrospective study conducted at 3 different tertiary referral centers in which fetal examinations are performed by experienced fetal cardiologists, our results might not be applicable to the general population. Secondly, chromosome analysis was not performed in all patients, although genetic testing was offered to all families, some declined; therefore, our data may not show the true prevalence of genetic anomalies in our series. Third, some patients were lost to follow-up, and data on postnatal outcome is difficult to ascertain due to the multicentric approach.

CONCLUSION

In conclusion, we have reported one of the largest case series with prenatally diagnosed APVS in the literature. Our study provides further information on APVS diagnosed in the prenatal period. Extracardiac anomalies were seen in one-fifth of cases, and chromosomal anomalies were also common. It should be kept in mind that 22q11.2 microdeletion can be found in 40% in APVS with TOF cases. This information is important during prenatal parental counseling and for decision-making with respect to genetic testing. This study also confirmed that there is no relation between the degree of PA enlargement and the presence of DA neither the dilatation of PAs do not progress during pregnancy based on the fact that z-scores of PA and branches do not change with gestational age. Consequently, the prognosis is still not at the desired level despite advances in prenatal diagnosis and surgery. Overall mortality after initial diagnosis and after birth are still as high as 63.4% and 47.7%, respectively.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Kocaeli University Non-Invasive Clinical Research (approval no: KÜ GOKAEK-2021/5.37- 2021/46).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – K.B., N.Ö.; Design – K.B., O.U.; Supervision – K.B., O.U.; Materials – E.B., O.U., S.E.; Data Collection and/or Processing – Y.D., N.Ö., S.E.; Analysis and/or Interpretation – E.B., S.E.; Literature Review – E.B, S.E, Y.D.; Writing – K.B., Y.D., O.U.; Critical Review – K.B, N.Ö., O.U.

Declaration of Interests: The authors declare that they have no competing interest.

Funding: This study received no funding.

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