Pediatric Cardiology (2019) 40:1509–1515
https://doi.org/10.1007/s00246-019-02176-2

ORIGINAL ARTICLE

Postnatal Outcome Following Prenatal Diagnosis of Discordant Atrioventricular and Ventriculoarterial Connections

Thomas G. Day[1] · Tomas Woodgate[1] · Olatejumoye Knee[1] · Vita Zidere[1,2] · Trisha Vigneswaran[1,2] · Marietta Charakida[1,2,3] · Owen Miller[1] · Gurleen Sharland[1] · John Simpson[1,2,3]

Received: 3 May 2019 / Accepted: 19 July 2019 / Published online: 25 July 2019

Abstract

Discordant atrioventricular and ventriculoarterial connection(s) (DAVVAC) are a rare group of congenital heart lesions. DAVVAC can be isolated or associated with a variety of other cardiac abnormalities. Previous studies examining the outcome of prenatally diagnosed DAVVAC have described only fetal and early postnatal outcome in small cohorts. We aimed to describe the medium-term outcome of these fetuses. Cases were identified by searching the fetal cardiac databases of two centers. Follow-up data were collected from the electronic patient records. We identified 98 fetuses with DAVVAC. 39 pregnancies were terminated and 51 resulted in a liveborn infant. Postnatal data were available for 43 patients. The median length of follow-up was 9.5 years (range 36 days to 22.7 years). The overall 5-year survival of the cohort was 80% (95% confidence interval 74–86%), no deaths were seen after this period. Associated cardiac lesions had a significant effect on both survival and surgery-free survival. Isolated DAVVAC and DAVVAC with pulmonary stenosis ± ventricular septal defect had a low mortality (89% and 100% 5-year survival, respectively). Poorer survival was seen in the group with Ebstein's anomaly of the tricuspid valve, and other complex cardiac abnormalities. Antenatal tricuspid regurgitation had a significant negative impact on postnatal survival. In conclusion, the short- and medium-term outlook for fetuses with isolated DAVVAC, and those with DAVVAC and pulmonary stenosis are good. Antenatal risk factors for postnatal mortality include Ebstein's anomaly of the tricuspid valve, especially if associated with tricuspid regurgitation, and the presence of complex associated lesions.

Keywords Congenitally corrected transposition of the great arteries · Discordant atrioventricular and ventriculoarterial connections · Fetal cardiology

Introduction

Discordant atrioventricular and ventriculoarterial connection(s) (DAVVAC) are a rare group of congenital heart lesions, accounting for less than 1% of major congenital heart disease both antenatally and postnatally [1–3]. It is a heterogeneous condition and may be seen in isolation or accompanied by a wide spectrum of additional structural congenital heart lesions, including ventricular septal defects, pulmonary stenosis/atresia, and Ebstein's anomaly of the tricuspid valve [4]. When present in isolation, it is commonly referred to as congenitally corrected transposition of the great arteries (CCTGA). There are few reports of outcomes following an antenatal diagnosis of DAVVAC, with 4 series in the literature that include 11, 14, 30, and 34 pregnancies (with postnatal data available for 7, 14, 24, and 23 children, respectively) [1, 2, 5, 6]. Although those studies describe the fetal and short-term postnatal outcome (up to 5 years of age) in these patients, longer-term outcomes of prenatally diagnosed patients remain unclear. This information is important to inform fetal counselling of parents. We describe the spectrum of DAVVAC diagnosed during fetal life as well as medium-term outcome (beyond 5 years of age and up to early adulthood) in a large prenatally diagnosed cohort.

✉ John Simpson
john.simpson@gstt.nhs.uk

[1] Fetal Cardiology Unit, Department of Congenital Heart Disease, Evelina London Children's Healthcare, Guy's and St Thomas' NHS Foundation Trust, Westminster Bridge Road, London, UK

[2] Harris Birthright Centre, King's College London NHS Foundation Trust, London, UK

[3] School of Biomedical Engineering, Division of Imaging Sciences, King's College London, London, UK

Methods

Cases of antenatally diagnosed DAVVAC were identified by searching the fetal cardiology databases of the Evelina London Children's Hospital and King's College Hospital between 1 January 1989 and 1 June 2018 (Filemaker Pro, Filemaker Inc.). Fetuses met the inclusion criteria if they were prenatally diagnosed with at least one discordant atrioventricular connection, and at least one discordant ventriculoarterial connection. Data were collected on the antenatal course and pregnancy outcome. For those pregnancies that resulted in a liveborn infant, postnatal data were collected from electronic patient records. Data were recorded using Excel (Microsoft Corp.) and statistical analyses was performed using SPSS (IBM Corp.). Survival was described graphically using Kaplan Meier curves. Survival between groups was compared using the Mantel Cox test.

Results

There were 98 patients identified who met the inclusion criteria (Fig. 1). Pregnancy was terminated in 39 cases (39.8%), 51 (52.0%) were liveborn, and there were no intrauterine deaths. In 8 pregnancies (8.2%), the outcome was not known. Of the 51 liveborn infants, postnatal data were available for 43 patients (Fig. 1).

The reason for referral for fetal cardiac assessment was suspected congenital heart disease in 88 patients (89.8%), nuchal translucency above the 95th centile in 2 (2.0%), family history of congenital heart disease in 2 (2.0%), extracardiac abnormalities in 3 (3.1%), fetal arrhythmia in 1 (1.0%), and maternal diabetes mellitus in 2 (2.0%). A family history of congenital heart disease was noted in 9 pregnancies (9.2%) of which 2 were a first degree relative of the fetus (2.0%). The median age at fetal cardiac diagnosis was 21 weeks (range 14–36).

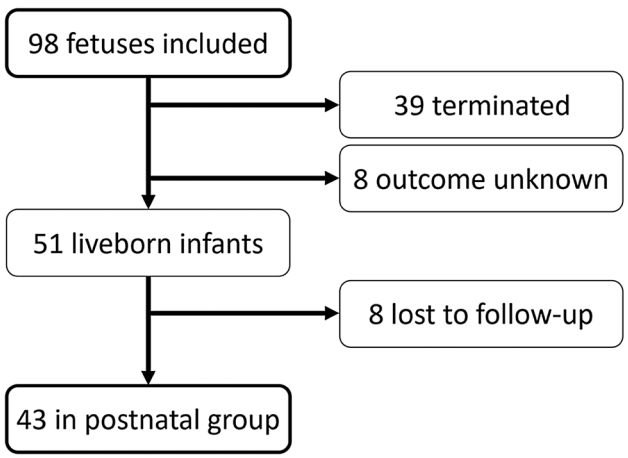

Fig. 1 Inclusion into study cohort

Associated cardiac lesions are shown in Table 1, for both the cohort as a whole and liveborn infants with available postnatal data. A ventricular septal defect (VSD) was the most commonly associated cardiac lesion in both groups, seen in 64 (65.3%) and 29 (67.4%) patients, respectively. The patients were divided into five subgroups based on the associated cardiac features: (a) isolated DAVVAC without an additional structural cardiac lesion ('isolated group'); (b) DAVVAC with a VSD only ('VSD group'); (c) DAVVAC with pulmonary valve stenosis, with or without a VSD ('pulmonary stenosis group'); (d) DAVVAC with Ebstein's anomaly of the tricuspid valve, with or without a VSD ('Ebstein's group'); and (e) DAVVAC with other more complex cardiac lesions ('complex group'). The numbers of patients in each group are shown in Table 2. Of the 36 fetuses in the complex group, 8 had an absent inlet valve (in all cases this was tricuspid atresia), 9 had an absent outlet valve (in all cases this was pulmonary atresia), and 12 had aortic coarctation and/or a hypoplastic aortic arch (6 of whom had a hypoplastic right ventricle). Double outlet right ventricle was seen in 5 cases, and 2 had other additional lesions.

The median postnatal follow-up period was 9.5 years (range 36 days to 22.7 years). The overall survival for the group is shown in Fig. 2. The 5-year survival was 80% (95% confidence interval 74–86%), and there were no late deaths recorded after this period. Figure 3 shows survival based on category of associated lesion. Grouping by associated structural lesion had a significant effect on survival ($p=0.017$). The highest survival was seen in the pulmonary stenosis group ($n=10$), with no deaths observed. The isolated group ($n=9$) had 1 death (at 6 months of age), associated with congenital complete heart block.

Tricuspid valve regurgitation (TR) subjectively graded as greater than trivial was noted prenatally in 10 fetuses. There were 3 live-births, all with Ebstein's anomaly of the tricuspid valve. The postnatal survival of this group is shown in Fig. 4 and is significantly worse than those without prenatal TR, with 2 early deaths at 36 and 99 days of age ($p=0.002$). These deaths both occurred after cardiac

Table 1 Associated cardiac lesions

Associated lesion	Entire cohort ($n=98$)		Postnatal cohort ($n=43$)	
	N	%	*N*	%
Ventricular septal defect	64	65.3	29	67.4
Pulmonary valve stenosis	28	28.6	14	32.6
Ebstein's malformation	12	12.2	4	9.3
Suspected aortic coarctation	14	14.3	4	9.3
Other cardiac lesions	35	35.7	14	32.6

Table 2 Categories of patients based on additional cardiac lesions

Patient group	Entire cohort ($n=98$)		Postnatal cohort ($n=43$)	
	N	%	*N*	%
Isolated (DAVVAC with no additional structural lesion)	15	15.3	9	20.9
VSD (DAVVAC with VSD only)	17	17.3	6	14.0
Pulmonary stenosis (DAVVAC with PS ± VSD)	21	21.4	10	23.3
Ebstein's (DAVVAC with Ebstein's ± VSD)	9	9.2	3	7.0
Complex group (DAVVAC with other lesions)	36	37.7	15	34.9

DAVVAC discordant atrioventricular and ventriculoarterial connections, *VSD* ventricular septal defect, *PS* pulmonary stenosis, *Ebstein's* Ebstein's malformation of the tricuspid valve

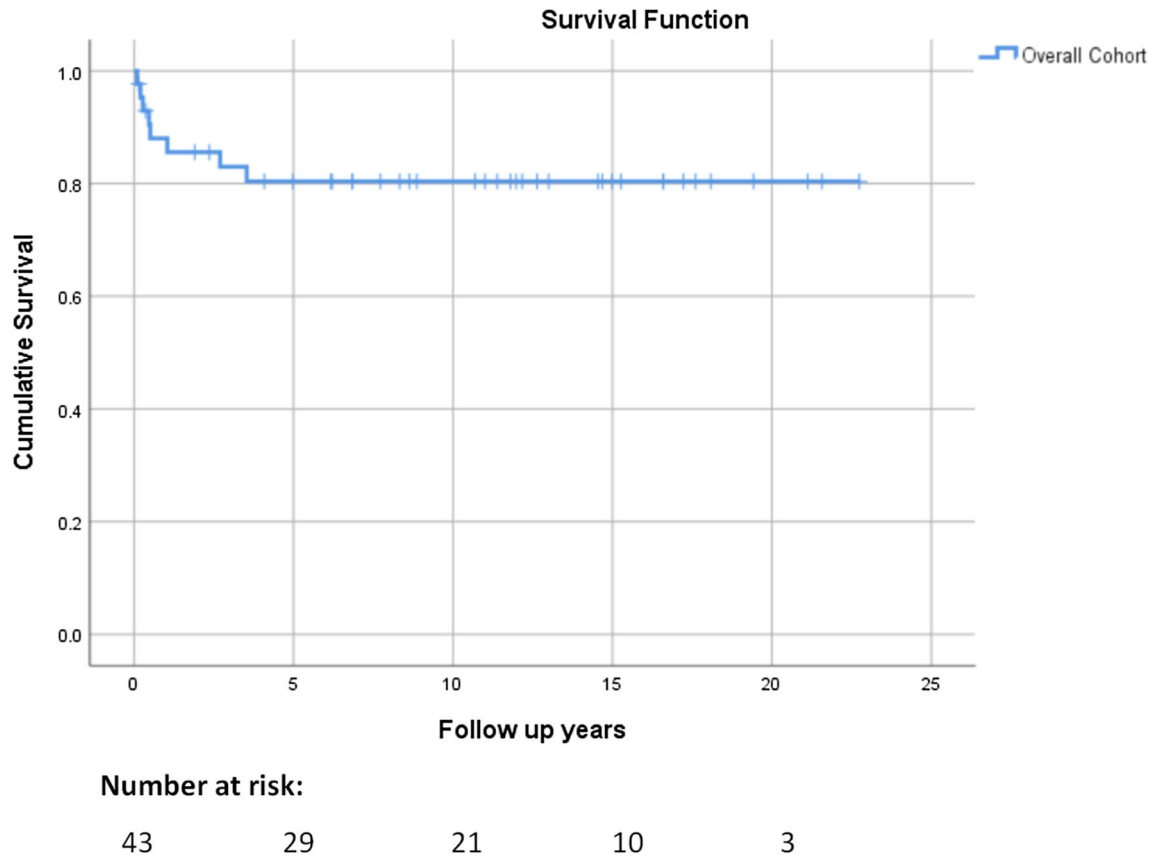

Fig. 2 Survival for postnatal cohort as a whole

surgery. One followed a pacemaker insertion and pulmonary artery banding in the context of complete heart block, and the other followed a hybrid univentricular palliation in the context of functional aortic atresia.

Complete heart block was noted in 4 fetuses before birth (4.1%). This was noted at the time of diagnosis (20 weeks' gestation) in 1 fetus, and in the remaining 3 fetuses was only noted on subsequent scans (at 20, 25, and 36 weeks' gestation). Of these, 2 are included in the postnatal cohort. The survival of these patients had a non-significant trend toward being worse than the remainder of the cohort ($p=0.18$). Complete heart block developed in a further 6 patients after birth (13.9% of postnatal cohort), either spontaneously (3 cases) or after cardiac surgery (3 cases). In total 5 out of 43 postnatal patients were either born with or spontaneously developed compete heart block (11.6%). Of these, 2 have required permanent pacemaker insertion. Four other patients have undergone permanent pacemaker insertion for other indications including postoperative complete heart block, exercise-induced 2:1 atrioventricular block, and 1 following an ablation of tachyarrhythmia in the context of a Fontan circulation. Excluding postoperative complete heart block,

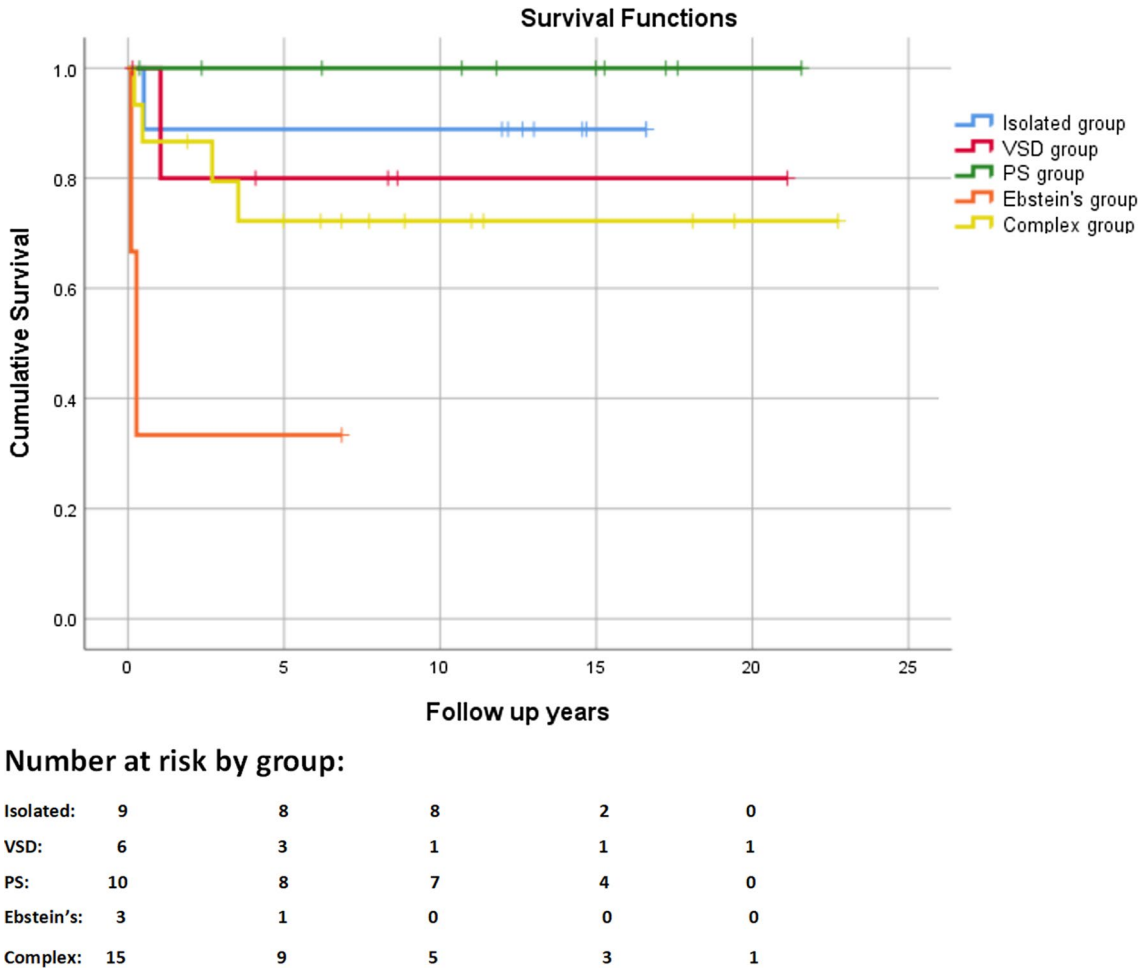

Fig. 3 Survival by grouping of associated cardiac lesions

complete heart block-free survival (and 95% confidence intervals) were 83% (77–89%) at 1 year, 76% (69–83%) at 5 years, and 73% (66–80%) at 10 years.

Cardiac surgery was performed in 23 patients (53.5%), of whom 14 underwent > 1 surgery, 7 > 2 surgeries, and 3 > 3 surgeries. Freedom from surgical intervention, by diagnostic group, is illustrated in Fig. 5. Associated structural cardiac lesions had a significant effect on freedom from surgery ($p \leq 0.01$). The type of surgery included three "double switch" operations, one in the isolated group (aged 4 years), one in the VSD group at 2.9 years following pulmonary artery banding, and one in the complex group at 3 years, following a previous PA band and coarctation repair. All 15 patients in the complex group underwent cardiac surgery. Out of the 23 operated patients overall, 3 had a biventricular circulation with a systemic left ventricle (i.e. following a 'double-switch' type operation), 5 had a biventricular circulation with a systemic right ventricle, and 15 had a functionally single ventricle circulation. No patient underwent heart transplantation.

Catheter intervention was performed in 8 patients. In 1 patient, this was a definitive procedure (a balloon pulmonary valvuloplasty performed at 10 days of age). A balloon atrial septostomy was performed in 2 patients and the other 5 patients required cardiac catheter interventions to optimize a functionally single ventricle circulation.

Overall, 18 patients (41.9%) did not undergo any cardiac surgery, cardiac intervention, or pacemaker insertion over the study period (8 isolated group, 4 VSD group, 5 pulmonary stenosis group, and 1 Ebstein's group). Of these, 16 were alive at the time of the study. Two patients were receiving beta blockers, with none were taking any other cardiac medications.

Discussion

The present study describes the largest cohort of antenatally diagnosed discordant atrioventricular and ventriculoarterial connections (DAVVAC) reported to date. There was a

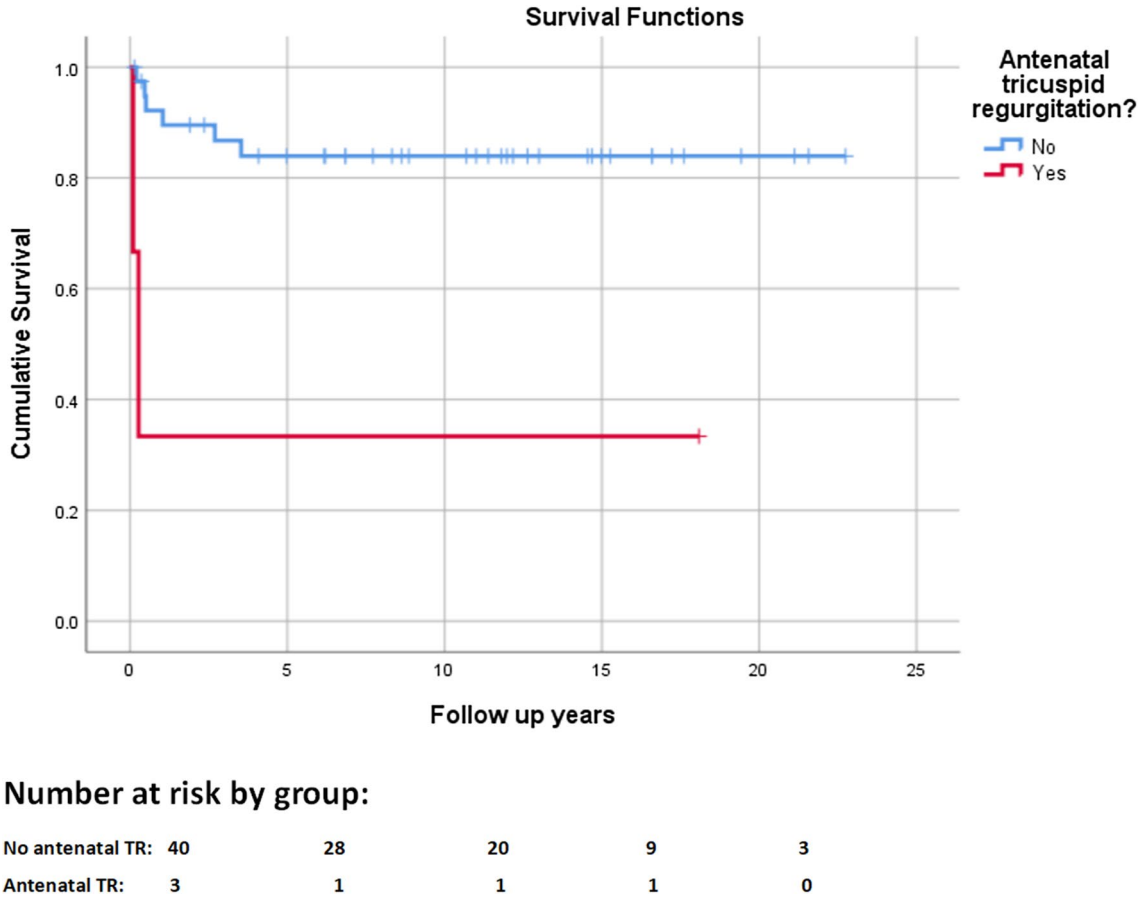

Fig. 4 Postnatal survival by the presence of antenatal morphological tricuspid valve regurgitation

relatively high termination rate reflecting the complexity of the lesion and uncertain prognosis. Only a relatively small group of our cohort had "isolated" DAVVAC, making up 15% and 20% of our entire and postnatal cohorts, respectively. This is higher than in previously described cohorts of postnatally diagnosed [4, 7–10] and antenatally diagnosed patients [1, 2]. One reason for this may be improved screening programmes and ultrasound technology, meaning that the more subtle features of isolated DAVVAC are being more commonly identified.

This is the first study to describe the medium-term outcomes for patients who were prenatally diagnosed with DAVVAC. These data are of great importance to guide parental counselling following antenatal diagnosis. The medium-term postnatal survival of fetuses with isolated DAVVAC, DAVVAC with pulmonary stenosis, and DAVVAC with VSD are encouraging, with 10-year survivals of 89%, 100%, and 80%, respectively, albeit with small numbers in each subgroup. The low mortality in the pulmonary stenosis group has been observed by other investigators [10], and may be due to natural restriction of pulmonary blood flow avoiding pulmonary over-circulation. In addition, the increased afterload to the left ventricle caused by the pulmonary stenosis may cause shift of the ventricular septum resulting in less tricuspid regurgitation and improved right ventricle performance, and may partly explain the favorable outcome seen in this group [11, 12].

We observed a relatively high mortality in the small number of liveborn cases with Ebstein's anomaly and other more complex cardiac lesions. The postnatal overall survival and surgery-free survival of both the Ebstein's and complex groups were worse than the remainder of the cohort. In the group with more complex additional cardiac lesions, all patients had either died or undergone cardiac surgery before the age of 1 year. The reason for the poor survival of the Ebstein's group probably relates to regurgitation of the systemic tricuspid valve, with severe hemodynamic consequences. This is supported by our finding that the presence of TR before birth is associated with a significantly worse postnatal survival, with two out of three patients dying within the first 4 months of life. Poor survival in the context of significant TR has also been found by other groups [4, 9].

A striking finding of our study was the lack of deaths past the age of 4 years. Although this finding is encouraging

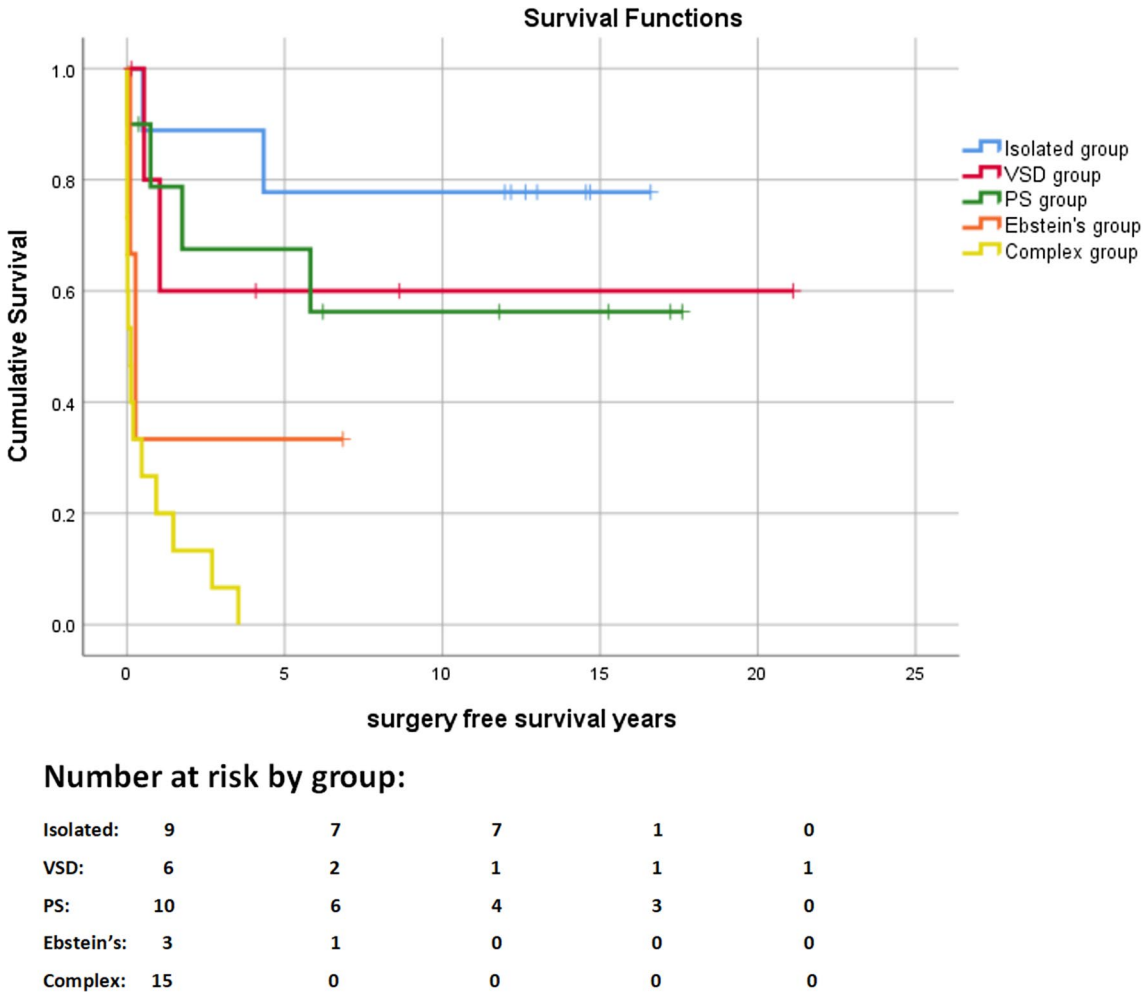

Fig. 5 Postnatal freedom from cardiac surgery by grouping of associated cardiac lesion

with respect to medium-term survival in our group, with the longest follow-up beyond 22 years (median 9.5 years), this may not translate into longer-term event-free survival. Data from other groups focusing on longer-term outcome of large cohorts of postnatally diagnosed DAVVAC have described a significant mortality rate in adulthood [4, 8]. Rutledge et al. found a 20-year survival rate of 75%, and this was significantly worse in those with right ventricular dysfunction or significant TR [4]. Graham et al. found that by age of 45, 67% of those with associated lesions and 25% of isolated cases had clinically diagnosed congestive cardiac failure [8]. They also found an increasing incidence of systemic right ventricular failure as age increased, with 32% of isolated patients having at least mild RV dysfunction by the age of 45. However, it is worth noting that several case reports of very late diagnosis of asymptomatic isolated DAVVAC have been described in the 8th and 9th decade of life, so clearly the long-term outcome for selected patients can be very good [13, 14].

Concerns regarding the ability of the morphological right ventricle to sustain the systemic circulation have led to the development of the 'double switch' procedure, involving both atrial and arterial switch operations. Several studies have examined postnatal outcomes following this procedure [15–17]. Encouraging long-term outcomes have been described, although with a significant reoperation rate, as well as a number of late deaths. For example Sharma et al. describe 4 late deaths out of a total cohort of 37 patients following a double-switch procedure [18]. There were only a small number ($n=3$) of double switch operations in our cohort; thus, the impact of this procedure on prognosis cannot be gauged from our series.

This is a large prenatal cohort of DAVVAC, but limitations include small numbers in individual subgroups due to the heterogeneity of the condition. Although we present data on mortality, surgery and heart block we lack structured data on morbidity and quality of life. These additional measures of outcome are of great importance to parents during fetal

counselling, and further studies are required to investigate this in more detail.

In conclusion, DAVVAC is associated with a wide spectrum of associated cardiac anomalies in cases diagnosed during fetal life. Antenatal risk factors for postnatal mortality include Ebstein's anomaly of the tricuspid valve, especially if associated with tricuspid regurgitation, and the presence of complex associated lesions. In the absence of congenital complete heart block, the short- and medium-term outlook for fetuses with isolated DAVVAC, and those with DAVVAC and pulmonary stenosis are good. It is hoped that these data will assist counselling parents of affected fetuses.

Compliance with Ethical Standards

Conflict of interest None of the authors have any conflict of interest with respect to this paper.

References

1. Paladini D, Volpe P, Marasini M et al (2006) Diagnosis, characterization and outcome of congenitally corrected transposition of the great arteries in the fetus: a multicenter series of 30 cases. Ultrasound Obstet Gynecol 27:281–285. https://doi.org/10.1002/uog.2715
2. Sharland G, Tingay R, Jones A, Simpson J (2005) Atrioventricular and ventriculoarterial discordance (congenitally corrected transposition of the great arteries): echocardiographic features, associations, and outcome in 34 fetuses. Heart 91:1453–1458. https://doi.org/10.1136/hrt.2004.052548
3. Allan LD, Sharland GK, Milburn A et al (1994) Prospective diagnosis of 1,006 consecutive cases of congenital heart disease in the fetus. J Am Coll Cardiol 23:1452–1458. https://doi.org/10.1016/0735-1097(94)90391-3
4. Rutledge JM, Nihill MR, Fraser CD et al (2002) Outcome of 121 patients with congenitally corrected transposition of the great arteries. Pediatr Cardiol 23:137–145. https://doi.org/10.1007/s00246-001-0037-8
5. Chiappa E, Micheletti A, Sciarrone A et al (2004) The prenatal diagnosis of, and short-term outcome for, patients with congenitally corrected transposition. Cardiol Young 14:265–276
6. Wan AW, Jevremovic A, Seda E et al (2009) Comparison of impact of prenatal versus postnatal diagnosis of congenitally corrected transposition of the great arteries. Am J Cardiol 104:1276–1279. https://doi.org/10.1016/j.amjcard.2009.06.047
7. Egloff L, Rothlin M, Arbenz U et al (1980) Congenitally corrected transposition of the great arteries: a clinical and surgical study. Thorac Cardiovasc Surg 28:228–232
8. Graham TP, Bernard YD, Mellen BG et al (2000) Long-term outcome in congenitally corrected transposition of the great arteries. J Am Coll Cardiol 36:255–261. https://doi.org/10.1016/S0735-1097(00)00682-3
9. Lundstrom U, Bull C, Wyse RKH, Somerville J (1990) The natural and "unnatural" history of congenitally corrected transposition. Am J Cardiol 65:1222–1229. https://doi.org/10.1016/0002-9149(90)90978-A
10. Bjarke BB, Kidd BS (1976) Congenitally corrected transposition of the great arteries. A clinical study of 101 cases. Acta Paediatr Scand 65:153–160. https://doi.org/10.1177/1073191116659134
11. Cools B, Brown SC, Louw JJ et al (2012) Pulmonary artery banding as "open end" palliation of systemic right ventricles: an interim analysis. Eur J Cardio-thoracic Surg 41:913–918. https://doi.org/10.1093/ejcts/ezr078
12. Kutty S, Danford DA, Diller GP, Tutarel O (2018) Contemporary management and outcomes in congenitally corrected transposition of the great arteries. Heart 104:1–8. https://doi.org/10.1136/heartjnl-2016-311032
13. Orchard EA, Ormerod O, Myerson S, Westaby S (2010) Congenitally corrected transposition of the great arteries presenting in a nonagenarian. Circulation. https://doi.org/10.1161/CIRCULATIONAHA.109.919068
14. Matsumura Y, Kawahito K, Nakamura K, Hashimoto K (2013) Congenitally corrected transposition of the great arteries with coexisting aortic valve stenosis in a 77-year-old woman. Eur J Cardio-thoracic Surg 43:442. https://doi.org/10.1093/ejcts/ezs477
15. Brizard CP, Lee A, Zannino D et al (2017) Long-term results of anatomic correction for congenitally corrected transposition of the great arteries: a 19-year experience. J Thorac Cardiovasc Surg 154:256–265.e4. https://doi.org/10.1016/j.jtcvs.2017.03.072
16. Hiramatsu T, Matsumura G, Konuma T et al (2012) Long-term prognosis of double-switch operation for congenitally corrected transposition of the great arteries. Eur J Cardio-thoracic Surg 42:1004–1008. https://doi.org/10.1093/ejcts/ezs118
17. Murtuza B, Barron DJ, Stumper O et al (2011) Anatomic repair for congenitally corrected transposition of the great arteries: a single-institution 19-year experience. J Thorac Cardiovasc Surg 142:1348–1357.e1. https://doi.org/10.1016/j.jtcvs.2011.08.016
18. Sharma R, Talwar S, Marwah A et al (2009) Anatomic repair for congenitally corrected transposition of the great arteries. J Thorac Cardiovasc Surg 137:404–412.e4. https://doi.org/10.1016/j.jtcvs.2008.09.048