Pediatric Cardiology (2019) 40:61–70
https://doi.org/10.1007/s00246-018-1961-1

ORIGINAL ARTICLE

Prenatal Diagnosis of Single Ventricle Physiology Impacts on Cardiac Morbidity and Mortality

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Received: 5 May 2018 / Accepted: 10 August 2018 / Published online: 18 August 2018

Abstract

We sought to evaluate the impact of prenatal diagnosis on morbidity and mortality in single ventricle (SV) lesions. All consecutive patients with pre- or postnatally diagnosed SV physiology admitted to our centre between January 2001 and June 2013 were reviewed. Primary endpoints included survival until 30 days after bidirectional cavopulmonary connection (BCPC) without transplant or BCPC takedown. Prenatal diagnosis was performed in 160 of 259 cases (62%). After excluding all cases with termination of pregnancy, intrauterine demise or treated with comfort care, a total of 180 neonates were admitted to our centre for treatment, including 87 with a prenatal and 93 with a postnatal diagnosis. Both groups showed similar distribution regarding diagnosis, dominant ventricle and risk factors such as restrictive foramen or some form of atrial isomerism. A larger proportion of postnatally diagnosed children presented at admission with elevated lactate > 10 mmol/l ($p = 0.02$), a higher dose of prostaglandin ($p = 0.0013$) and need for mechanical ventilation ($p < 0.0001$). Critical lesions such as hypoplastic left heart syndrome were an important determinant for morbidity and mortality. Thirty-days survival after BCPC was better in patients with prenatal diagnosis ($p = 0.025$). Prenatal diagnosis is associated with higher survival in neonates with SV physiology.

Keywords Foetal echocardiography · Single ventricle · Prenatal diagnosis · Outcome

Introduction

Single ventricle (SV) cardiac defects account for a large proportion of prenatally diagnosed cardiac defects in most series [1–5]. SV lesions are easier to detect prenatally than other potentially critical defects such as d-transposition of the great arteries [1, 5]. SV lesions are frequently duct-dependent and may result in dramatic haemodynamic deterioration after birth.

A recent meta-analysis [6] reported a benefit of prenatal diagnosis on outcome of infants with critical cardiac lesions. Timely referral of neonates with congenital heart disease (CHD) to a tertiary cardiac centre, or a planned delivery in a fetomaternal-neonatology–cardiology unit can be achieved if diagnosis is known prenatally [5, 7]. Nevertheless, the effect of prenatal diagnosis on outcome in other specific CHD remains controversial [8–12]. The aim of this study was to evaluate the possible effects of prenatal diagnosis on the perinatal course, morbidity and outcome of patients with SV CHD.

Methods

Population

This retrospective study included all consecutive patients with pre- or postnatal diagnosis of SV physiology who were

Roland W. Weber and Brian Stiasny share first authorship of this manuscript.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00246-018-1961-1) contains supplementary material, which is available to authorized users.

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admitted for treatment in our institution between January 2001 and June 2013. To evaluate if prenatal diagnosis is also beneficial in non-hypoplastic left heart lesions, we included all cases with SV physiology independently from the severity of the lesion.

Our institution is the largest tertiary Pediatric Heart Centre and the referral centre for approximately half of the children with CHD in Switzerland. In cases with prenatally diagnosed duct-dependent cardiac defects, delivery is planned at our maternity, and the neonates are transferred to our cardiac centre immediately after perinatal stabilisation.

Methods

All prenatal or postnatal diagnoses of SV were retrieved from our institutional electronic database. Untreated patients with a weight up to 10 kg at diagnosis were included in the study, in order to also assess late diagnosed cases ($n = 1$). Exclusion criteria were neonates smaller than 1.8 kg, as the results of cardiopulmonary bypass in this patient group are dismal, and this may have represented a confounding factor. Cases were also excluded in which prenatally a SV physiology was predicted, but the infant eventually underwent biventricular repair.

In the prenatally diagnosed group, clinical records were also reviewed for gestational age at diagnosis, chromosomal and/or extracardiac abnormalities, termination of pregnancy, intrauterine demise, parental decision for treatment or primary comfort care and birth location. In Switzerland, termination of pregnancy can be legally performed before 24 weeks of gestation, if a severe maternal or foetal disease is present.

Gestational age, weight, APGAR score and cardiac diagnosis were recorded in all newborns. Neonatal demise outside of our institution was ruled out by cross-checking cases between the pre- and the postnatal database and by surveying our referring neonatal units.

The primary endpoint consisted of survival until 30 days after bidirectional cavopulmonary connection (BCPC) without transplantation or BCPC take down. We chose this specific time interval for outcome, as in some SV cases with balanced systemic and pulmonary circulation, BCPC may represent the first operation required and these cases would not be comparable to others undergoing neonatal surgery.

Secondary endpoints were neonatal (30 days) mortality and neonatal morbidity including pH, lactate, prostaglandin dose, need for mechanical ventilation at hospital admission.

SV diagnoses were grouped according to the classification proposed by d'Udekem et al. in their large multicentre study on outcome of Fontan patients [13]. Therefore, transposition of the great arteries (TGA) is defined as complex functionally SV cases with TGA as the main feature. Atrioventricular septal defect (AVSD) refers to cases with severe dysbalance or hypoplasia of one ventricle, or complex anatomy of the atrioventricular valves, such as straddling, precluding biventricular repair. The first postnatal echocardiogram determined ventricular dominance as right, left or undetermined. Recorded risk factors included restrictive foramen ovale with abnormal Doppler pattern in the pulmonary veins, total anomalous pulmonary venous return and heterotaxy syndrome. Extracardiac and/or genetic anomalies or syndromes except anomalies belonging to the heterotaxy syndrome were separately recorded in both groups.

Postnatal anatomy was classified as being *critical or non-critical* depending if systemic and or pulmonary underperfusion or cyanosis had to be expected after closure of the arterial duct and/or the foramen ovale.

Parents made the decision for surgical treatment of CHD (with the intention to perform a stepwise Fontan palliation) or for comfort care after appropriate medical counselling. Follow-up ended 30 days after the BCPC operation.

Statistics

Data are described as means and standard deviations or median and range as appropriate. Categorical data are given as frequencies.

Cases with pregnancy terminations, in utero demise, still births and comfort care were considered as "not intended to be treated" and were excluded from comparative statistics.

Categorical data were compared using the Fisher's exact test and χ^2 test as appropriate. Continuous data were compared using the Mann–Whitney U test or unpaired t test, depending on their distribution. Survivals of patients were compared between groups using the χ^2. Kaplan–Meier curves of survival were compared using the Log-rank test. As both the prenatal diagnosis rate increased during the study period, and the quality of intensive care and surgical techniques have evolved, we tested the influence of postnatal diagnosis, era of treatment, presence of critical heart lesion and hypoplastic left heart syndrome as covariates using a Cox proportional hazard model. For testing the era of treatment, patients were divided into two groups, neonates born before or after 31 March 2007 (first and second half of the study period). Statistics were performed using SPSS software (IBM SPSS Statistics, Version 24.0. Armonk, NY: IBM).

Ethics

The ethics authorities of the canton of Zurich, Switzerland, approved this study and waived written consent of the parents for the retrospective use of their clinical and outcome data.

Results

Diagnosis of SV physiology was made in a total of 259 cases including 160 foetuses and 99 neonates (Fig. 1). Thirty-six pregnancies were terminated, three foetuses died in utero and three foetuses were lost to follow-up (Fig. 1). Of the 217 live born, in 36 cases (30 prenatally and 6 postnatally diagnosed) parents refused active treatment and opted for comfort care. One patient died before treatment was possible due to a fulminant viral infection and was considered as death for a non-cardiac reason. Thus 180 patients were admitted with intention to treat. 87 of these neonates (48%) were diagnosed prenatally (Fig. 1). Notably, the prenatal diagnosis rate increased over time during the study period (Fig. 2).

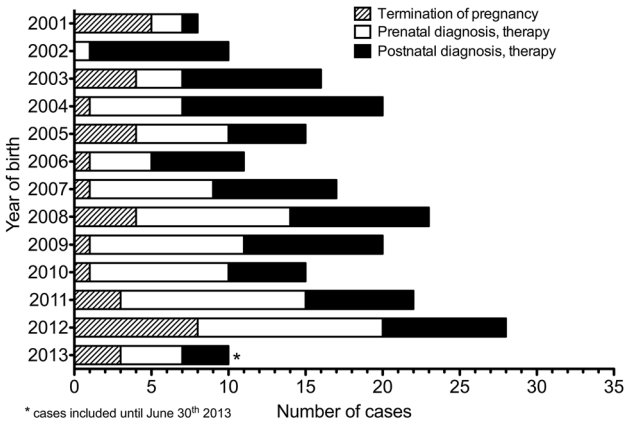

Fig. 2 Terminations and pre- and postnatally diagnosed cases per year of diagnosis

Patient Characteristics

Baseline characteristics at admission are presented in Table 1. Patients with a foetal diagnosis presented with a lower gestational age and lower APGAR score, but similar birth weight than postnatally diagnosed neonates. The rate of prenatal diagnosis increased significantly during the study period and was 35% in neonates born before March 2007 and 53% in neonates born after March 2007 ($p = 0.01$). There was no difference in ventricular predominance, anatomic classification or prevalence of risk factors including the number of patients with extracardiac malformations between the prenatally and the postnatally diagnosed groups. In particular, the number of neonates with HLHS was comparable in both cohorts (Table 1). Cardiac anatomy and additional risk factors were also similar between foetuses who were terminated and foetuses with treatment, as well as between

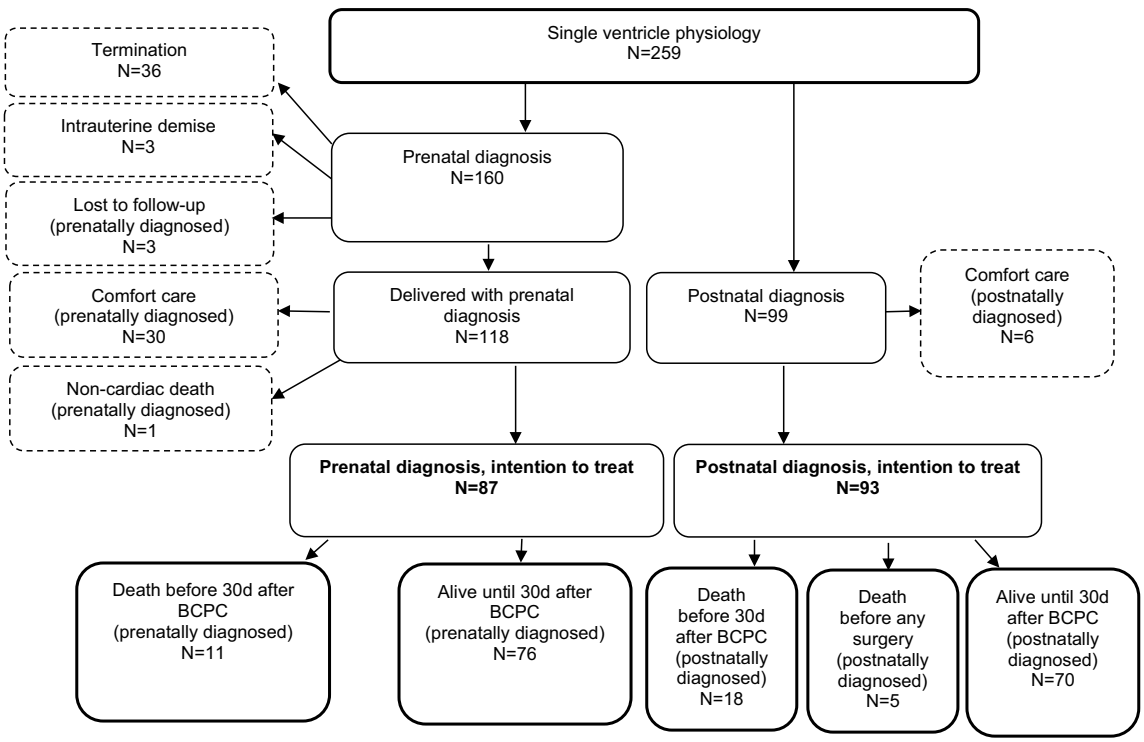

Fig. 1 Outcomes of study population divided into pre- and postnatally diagnosed patients until the primary endpoint 30 days after establishing bidirectional cavopulmonary anastomosis (BCPC)

Table 1 Patient characteristics

Characteristics	Prenatal diagnosis ($n=87$)	Postnatal diagnosis ($N=93$)	P value
Male gender	51 (58%)	55 (59%)	0.94
Gestational age (weeks)	38.2 (±1.44)	39.3 (±1.5)	< 0.0001
Birth weight (g)	3033 (±453)	3167 (±613)	0.09
APGAR score			
1 min	7.45 (±1.5)	7.64 (±1.7)	0.04
5 min	8.60 (±0.8)	8.75 (±1.3)	0.004
10 min	8.91 (±0.6)	9.51 (±0.8)	< 0.0001
Ventricular predominance			
Predominant right ventricle	48 (55%)	52 (56%)	0.92
Predominant left ventricle	29 (33%)	33 (35%)	0.76
Undetermined dominance	10 (12%)	8 (9%)	0.52
Risk factors			
Right atrial isomerism	3 (4%)	2 (2%)	0.7
Left atrial isomerism	5 (6%)	4 (4%)	0.7
TAPVC	4 (5%)	4 (4%)	1
Restrictive foramen ovale	6 (7%)	9 (10%)	0.5
Extracardiac and genetic anomalies or syndrome (except isomerism)	11 (13%)	11 (12%)	1
Anatomy			
HLHS	35 (40%)	33 (36%)	0.56
TA	13 (15%)	9 (10%)	0.28
DILV	12 (14%)	12 (13%)	0.9
AVSD	9 (10%)	11 (12%)	0.75
DORV	8 (9%)	13 (14%)	0.32
DORV–AVSD	3 (4%)	2 (2%)	0.67
PA/IVS	3 (4%)	7 (8%)	0.33
cc-TGA	2 (2%)	1 (1%)	0.61
TGA	1 (1%)	4 (4%)	0.37
Other	1 (1%)	1 (1%)	1.0

TAPVC total anomalous pulmonary venous connection, *TA* tricuspid atresia, *HLHS* hypoplastic left heart syndrome, *DORV* double outlet right ventricle, *AVSD* atrioventricular septal defect, *TGA* transposition of the great arteries, *cc-TGA* congenitally corrected transposition of the great arteries, *DILV* double inlet left ventricle, *PA/IVS* pulmonary atresia/intact ventricle septum

neonates with comfort care with pre or postnatal diagnosis (see additional material).

Clinical characteristics at admission are summarised in Table 2. Despite a similar number of prostaglandin lesions in both groups, postnatally diagnosed patients required higher prostaglandin doses, more often mechanical ventilation and more frequently circulatory support with epinephrine on admission (Table 2). Ten of 93 postnatally diagnosed patients presented with a pH < 7.2 compared to 1/87 prenatally diagnosed patients ($p=0.001$). Similarly, levels of

Table 2 Clinical characteristics at admission

	Prenatal ($n=87$)	Postnatal ($N=93$)	P value
Age (days)	0.22 (±0.47)	7.58 (±14.41)	< 0.0001
Prostaglandin-dependent lesions	74/87 (85%)	74/93 (80%)	0.34
Mechanical ventilation at admission (n)	2/87 (2%)	25/93 (27%)	< 0.0001
Epinephrine use before operation (n)	9/87 (10%)	20/93 (22%)	0.042
PGE dose (mcg/kg/min)	0.0135 (±0.0088)	0.0275 (±0.0306)	0.07
PGE ≥ 0.05mcg/kg/min (n)	2/74 (3%)	14/73 (15%)	0.0013

PGE Prostaglandin

lactate > 10 mmol/l at admission were significantly higher in the postnatal group than in the prenatally diagnosed group ($p = 0.02$) (Fig. 3).

Treatment

The type of surgical intervention performed first was similar in both groups, except for pulmonary artery banding (PAB), which was more frequent in the postnatally diagnosed patients (Table 3).

The Norwood or hybrid procedure for HLHS was performed earlier in neonates who had been diagnosed prenatally (6 vs. 7 days; $p = 0.04$).

During the postoperative course, no significant differences were found between the two groups regarding the duration of mechanical ventilation, the ICU and the total hospital length of stays (Table 3).

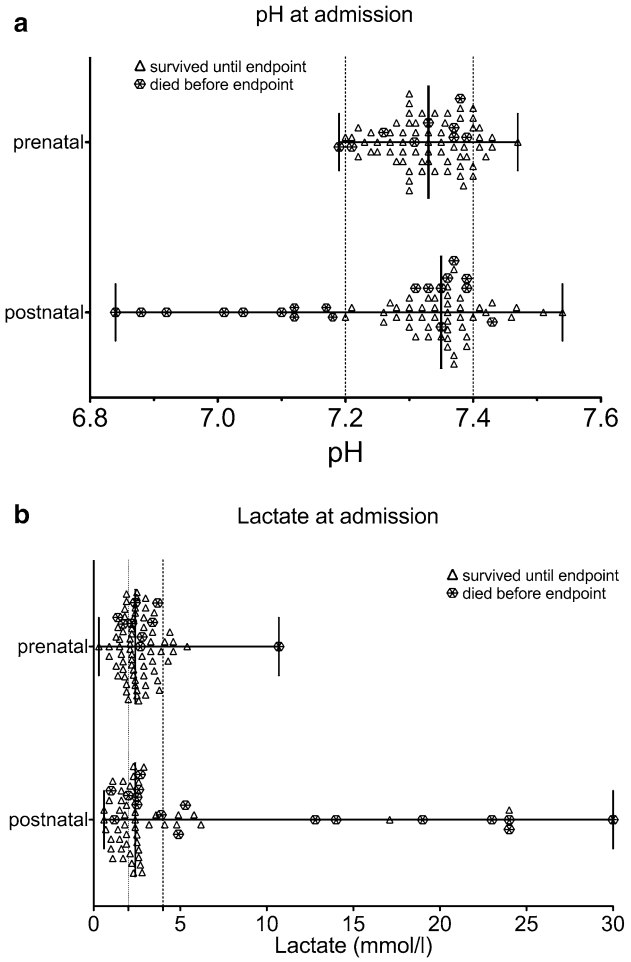

Fig. 3 Distribution (median and range) of pH (**a**) and lactate levels (**b**) in pre- and postnatally diagnosed patients on admission. Cases surviving until the primary endpoint 30 days after BCPC are marked with triangles, patients who died are marked with diamonds

Outcome

Prenatally diagnosed patients showed a better neonatal and mid-term survival, i.e. after BCPC palliation, than postnatally diagnosed cases (Table 4; Fig. 4). All causes of death are summarised in Table 5.

Five postnatally diagnosed neonates died before the intended surgical intervention could be performed, compared to none in the prenatally diagnosed group ($p = 0.06$). All five of these patients had HLHS and presented at admission with severe cardiogenic shock; one of them experienced a supraventricular tachycardia, two presented with a restrictive foramen ovale and another two with a lactate level > 20 mmol/l (Fig. 1).

The results of Cox regression analysis showing the relative effects on survival of prenatal versus postnatal diagnosis, the era of treatment, the diagnose of a critical heart lesion or of hypoplastic left heart syndrome are given in Table 6. The analysis confirmed that postnatal diagnosis significantly increased the mortality risk. To be treated in the older (first) era of treatment had a weaker and statistically not significant negative influence on mortality. To be diagnosed with a "critical heart lesion" had less effect on mortality compared to the main determinant being diagnosed with "hypoplastic left heart syndrome".

Discussion

This single-centre retrospective observational study shows a beneficial effect of prenatal diagnosis on outcomes in infants with SV physiology. Our data demonstrate better neonatal and overall survival up to 30 days after BCPC in prenatally compared to postnatally diagnosed infants. Neonatal morbidity, defined as acidosis, prostaglandin use and intubation rate, was also lower in the prenatally diagnosed group. In contrast, no difference was observed for patient morbidity after the first surgical intervention, including the total duration of mechanical ventilation, and ICU and total hospital length of stay.

In a recent meta-analysis Holland et al. [6] reported that patients with critical CHD with comparable anatomy, standard risk and neonatal care, had a reduced risk of death before cardiac surgery if diagnosis had been made prenatally. In contrast, other studies could not show any benefit of prenatal diagnosis on survival of neonates with severe CHD [3, 10, 11, 14–16]. Most authors suggest that prenatal knowledge of the presence of critical CHD influences neonatal care, and helps prevent clinical deterioration, which usually occurs after closure of the arterial duct and/or the foramen ovale.

In our study, we have deliberately decided to assess the entire group of neonates with a SV lesion, including many neonates with well-balanced, non-duct-dependent

Table 3 Characteristics of first surgical intervention and postoperative course

	Prenatal ($n=87$)	Postnatal ($N=93$)	P value
Age at first surgical intervention (days)	7 (0–212)	9 (0–238)	0.13
First surgical intervention			
Norwood I with any shunt	29 (33%)	25 (27%)	0.11
Hybrid (Ductal stent/bilateral pulmonary arterial banding)	18 (21%)	10 (11%)	0.09
DKS-operation with/without shunt or with direct BCPC without arch surgery	1 (1%)	7 (8%)	0.07
Any isolated shunt operation or duct stent	17 (20%)	19 (20%)	0.9
BCPC with/without septectomy	8 (9%)	3 (3%)	0.12
PAB	4 (5%)	14 (15%)	0.03
Coarctation repair with/without PAB	7 (8%)	7 (8%)	1.0
Others/unknown	3 (4%)	3 (3%)	1.0
Postoperative course			
Mechanical ventilation (days)	5.2 ± 5.0	6.4 ± 6.5	0.18
ICU-stay (days)	13.5 ± 10.1	15.3 ± 13.8	0.36
Length of first hospitalisation	53.7 ± 40.0	54.1 ± 50.6	0.9
Age at BCPC (days)	147 ± 50	171 ± 81	0.06

BCPC bidirectional cavopulmonary connection, *DKS* Damus–Kaye–Stansel procedure, *ICU* intensive care unit, *PAB* central pulmonary arterial banding

Table 4 Outcome until primary endpoint 30 days after BCPC

	Prenatal diagnosis ($n=87$)	Postnatal diagnosis ($N=93$)	P value
Neonatal (30 days) mortality	4/87 (5%)	13/93 (13%)	0.03
Overall mortality until primary endpoint	11/87 (13%)	23/93 (25%)	0.04
Mortality in			
HLHS ($n=68$)	7/35 (20%)	16/33 (48%)	0.013
TA ($n=22$)	0/13	1/9 (11%)	
DILV ($n=24$)	0/12	2/12 (17%)	
AVSD ($n=21$)	3/9 (33%)	2/12 (17%)	
DORV ($n=20$)	0/8	0/12	
DORV–AVSD ($n=5$)	0/3	0/2	
PA/IVS ($n=10$)	1/3 (33%)	2/7 (29%)	
cc-TGA ($n=3$)	0/2	0/1	
TGA ($n=5$)	0/1	0/4	
Other ($n=2$)	0/1	0/1	

TA tricuspid atresia, *HLHS* hypoplastic left heart syndrome, *DORV* double outlet right ventricle, *AVSD* atrioventricular septal defect, *TGA* transposition of the great arteries, *cc-TGA* congenitally corrected transposition of the great arteries, *DILV* double inlet left ventricle, *PA/IVS* pulmonary atresia/intact ventricle septum

circulation. Our results show that the presence of critical lesions and particularly HLHS are an important determinant of outcome. The importance of immediate postnatal deterioration is demonstrated by the higher rate of neonates who presented with a pH < 7.20 and higher lactate at time of admission (Fig. 3) if prenatal diagnosis had not been made. We suspect these metabolic changes in the very first hours of life could be especially harmful to the myocardial function in infants with a single ventricle, and also have potential implications on long-term cardiac function and mid-term mortality.

Many authors suspect that the prenatally diagnosed cases represent the more severe end of the disease spectrum [10, 14, 17], which may outweigh the potential benefits of prenatal diagnosis on medical management and outcome. Our prenatal and postnatal cohorts were similar regarding the proportion of high-risk cases. An important difference exists in their perinatal management foetuses with a prenatal diagnosis tend to be delivered earlier; duct-dependent cases are usually induced in a tertiary obstetrical centre after 38 completed weeks of gestation [18]. Despite this, the birth weight of our cohort's prenatally diagnosed neonates was

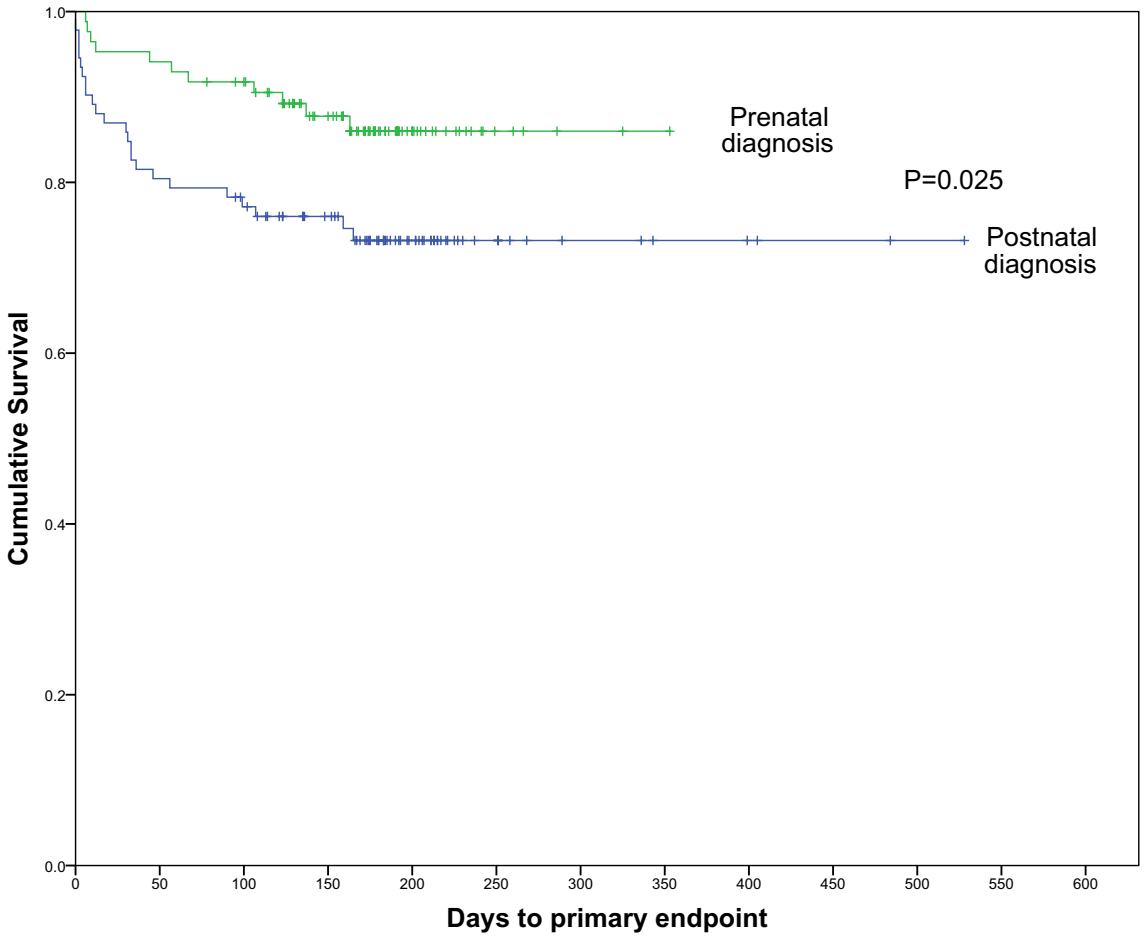

Fig. 4 Kaplan Meier curve of survival to 30 days after bidirectional cavopulmonary anastomosis

not significantly different from those diagnosed postnatally. Interestingly, prenatally diagnosed neonates had a lower APGAR score; one potential reason for this could be that neonatologists who are aware that there is a prenatal diagnosis of a single-ventricular cardiac defect may be sensitised and tend to be stricter in their perinatal clinical judgement.

More patients with a postnatal diagnosis received PAB as the first surgical intervention. This may lead to the hypothesis that there were less duct-dependent cases and less severe lesions in the postnatally diagnosed group. However, our data do not confirm this hypothesis, as in each group a similar number of patients with a duct-dependent lesion were present (see Table 2). Due to the relatively small number of patients in the study, we consider this difference more as a hazard rather than a true bias in the distribution of diagnoses severity within the pre- and postnatal groups. The literature is totally lacking in specific data discussing this aspect.

In comparison with the literature [11, 12, 19, 20], our study shows a high rate of parental choice for comfort care; this was 17% in the overall group, 25% in the prenatally diagnosed group and 6% in the postnatally diagnosed group (Fig. 1). This observation is also in contrast with data from an Australian study, which reported that parents faced with a postnatal diagnosis of HLHS more often choose comfort care compared to families in which diagnosis was made prenatally [21]. In addition, the rate of termination of pregnancy in our cohort was lower (27%) than that reported by others (range 30–63%) [4, 9, 20, 22]. We therefore hypothesise that some families may have opted for comfort care instead of termination of pregnancy for religious or personal ethical attitude, and/or others may have received a prenatal diagnosis too late for legal termination. Moreover, in the prenatally diagnosed cases who received comfort care, additional malformations or additional risk factors were more frequent (47% vs. 16%). Additional risk factors and/or malformations could be important modulating factors that influence prenatal counselling and parental decision-making.

Table 5 Summary of cases who died during treatment

Case	Cause of death	Age at endpoint (days)	Anatomy
Prenatal diagnosis			
48	Thrombotic complication	6	HLHS
68	Myocardial infarction	7	HLHS
79	Catheter sepsis	137	HLHS
111	Interstage cardiogenic shock	57	HLHS
120	Myocardial infarction	9	PA/IVS
149	Low cardiac output	123	HLHS
152	Low cardiac output (post)	106	AVSD
185	Prolonged SVT	44	HLHS
223	Endocarditis of AV-valves	163	AVSD
252	Hybrid conversion to Norwood, postoperative low cardiac output	67	AVSD
260	Myocardial infarction	12	HLHS
Postnatal diagnosis			
15	Thrombotic complication	107	TA
20	Cardiogenic shock	1	HLHS
22	Restrictive foramen ovale and severe chylothorax	159	HLHS
32	Cerebral bleeding	10	DILV
35	Low cardiac output	6	HLHS
38	Thrombotic shunt occlusion	2	PA/IVS
49	Anomalous left coronary artery from pulmonary artery, infarction	36	HLHS
51	Myocardial infarction	31	DILV
76	JET and low cardiac output	12	HLHS
85[a]	Cardiogenic shock	2	HLHS
86[a]	Cardiogenic shock	4	HLHS
93	Retroperitoneal bleeding after catheter intervention	30	PA/IVS
94	Myocardial infarction	33	HLHS
110	Thrombotic complication after BCPC	46	AVSD
113	BCPC failure	99	AVSD
119	Cardiogenic shock after late diagnosis	6	HLHS
134	Low cardiac output	17	HLHS
142[a]	Cardiogenic shock	1	HLHS
146	Thrombotic shunt occlusion	90	HLHS
151	Thrombotic shunt occlusion	33	HLHS
157[a]	SVT	2	HLHS
220[a]	Cardiogenic shock	3	HLHS
256	Low cardiac output	56	HLHS

AV atrioventricular, *BCPC* bidirectional cavopulmonary connection, *JET* junctional ectopic tachycardia, *SVT* supraventricular tachycardia

[a]Preinterventional demise

Table 6 Risk factors for mortality until primary endpoint analysed with Cox proportional Hazard model

Risk factor	Hazard ratio	95% Confidence interval	*P* value
Postnatal diagnosis	2.49	2.11–2.87	0.015
Treatment in first era (before 3/2007)	1.44	1.08–1.80	0.3
Critical heart lesion	1.80	1.02–2.59	0.45
Hypoplastic left heart syndrome	5.12	4.70–5.54	< 0.0001

Limitations

This study has a retrospective design and is not population based. This increases the risk that some non-diagnosed postnatal cases may have been missed if they died before having reached our centre. We minimised this limitation by cross-checking missing cases with the referral obstetrical units. Moreover, Switzerland has short geographical distances between hospitals, excellent primary health care including a neonatal oximetry screening programme [23] and an efficient medical emergency transportation service so that our centre is in the middle of a well-developed and tightly bound medical network. Thus, we do not expect to have any significant referral bias in the study cohort.

The retrospective design makes the first enrolled cases an historical group with therefore potentially worse outcomes. The influence of the era of treatment was tested with an additional Cox proportional hazard model. The results of a covariates analysis confirmed that prenatal diagnosis reduces the risk of adverse outcome; the era of treatment did not have a significant influence on survival.

Conclusion

Prenatally diagnosed patients with SV CHD have lower neonatal morbidity and a higher survival to 30 days after BCPC than postnatally diagnosed cases. Diagnosis of critical CHD, particularly HLHS, remains an important determinant of mortality independent from a prenatal diagnosis.

Acknowledgements We would like to thank Dr. Janet F. Kelly from the department of intensive care at the University children's hospital of Zurich for her constructive and critical review of this manuscript as a native speaker.

Compliance with Ethical Standards

Conflict of interest None of the authors has a conflict of interest to disclose. There is no relationship with industry or funding sources. All authors were involved in the study design, manuscript preparation, data collection and data analysis.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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