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ORIGINAL RESEARCH

Risk Factors for Mortality and Circulatory Outcome Among Neonates Prenatally Diagnosed With Ebstein Anomaly or Tricuspid Valve Dysplasia: A Multicenter Study

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BACKGROUND: In a recent multicenter study of perinatal outcome in fetuses with Ebstein anomaly or tricuspid valve dysplasia, we found that one third of live-born patients died before hospital discharge. We sought to further describe postnatal management strategies and to define risk factors for neonatal mortality and circulatory outcome at discharge.

METHODS AND RESULTS: This 23-center, retrospective study from 2005 to 2011 included 243 fetuses with Ebstein anomaly or tricuspid valve dysplasia. Among live-born patients, clinical and echocardiographic factors were evaluated for association with neonatal mortality and palliated versus biventricular circulation at discharge. Of 176 live-born patients, 7 received comfort care, 11 died <24 hours after birth, and 4 had insufficient data. Among 154 remaining patients, 38 (25%) did not survive to discharge. Nearly half (46%) underwent intervention. Mortality differed by procedure; no deaths occurred in patients who underwent right ventricular exclusion. At discharge, 56% of the cohort had a biventricular circulation (13% following intervention) and 19% were palliated. Lower tricuspid regurgitation jet velocity (odds ratio [OR], 2.3 [1.1–5.0], 95% CI, per m/s; P=0.025) and lack of antegrade flow across the pulmonary valve (OR, 4.5 [1.3–14.2]; P=0.015) were associated with neonatal mortality by multivariable logistic regression. These variables, along with smaller pulmonary valve dimension, were also associated with a palliated outcome.

CONCLUSIONS: Among neonates with Ebstein anomaly or tricuspid valve dysplasia diagnosed in utero, a variety of management strategies were used across centers, with poor outcomes overall. High-risk patients with low tricuspid regurgitation jet velocity and no antegrade pulmonary blood flow should be considered for right ventricular exclusion to optimize their chance of survival.

Key Words: congenital heart disease ■ Ebstein anomaly ■ mortality ■ neonate ■ outcome ■ palliation ■ right ventricle ■ tricuspid regurgitation

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CLINICAL PERSPECTIVE

What Is New?

- In this follow-up study of 243 fetuses with Ebstein anomaly or tricuspid valve dysplasia from 23 centers, live-born patients were managed heterogeneously, with overall poor outcomes.
- Among those who had a neonatal intervention, mortality differed by procedure: no patients who underwent right ventricular exclusion died.
- By multivariable analysis of neonatal echocardiographic variables, low tricuspid regurgitation jet velocity and lack of antegrade flow across the pulmonary valve were associated with mortality.

What Are the Clinical Implications?

- Neonatal echocardiographic data should be used to risk stratify patients, particularly with regard to the ability of the right ventricle to function in the circulation.
- Patients with low tricuspid regurgitation jet velocity (<2.5 m/s) and no antegrade pulmonary blood flow should be considered for right ventricular exclusion to optimize their chance of survival.

Nonstandard Abbreviations and Acronyms

EA/TVD	Ebstein anomaly or tricuspid valve dysplasia
MPI	myocardial performance index
RVE	right ventricular exclusion
TR	tricuspid regurgitation
TV	tricuspid valve

Ebstein anomaly or tricuspid valve dysplasia (EA/TVD) is a rare congenital tricuspid valve malformation[1,2] associated with high perinatal mortality. We recently performed a multicenter, retrospective study across North America to assess perinatal outcome and risk factors for mortality among fetuses with EA/TVD.[3] Perinatal mortality, defined as fetal demise or death before neonatal hospital discharge, was high at 45%. Clinical and fetal echocardiographic risk factors included gestational age at diagnosis <32 weeks, larger tricuspid valve (TV) annulus *z*-score, pulmonary regurgitation, and the presence of a pericardial effusion. Among live-born patients, one third died before hospital discharge, which was similar to earlier series[4–7] despite recent advances in care for neonates with congenital heart disease.

Neonates with EA/TVD represent an anatomically and physiologically diverse cohort. For some, careful postnatal medical management and patience during the transition to ex utero life are sufficient. Others require interventional catheterization or surgery before discharge. In these patients, management strategies vary widely, ranging from isolated ductal ligation[8] to TV repair[9,10] to right ventricular exclusion (RVE),[11] and are often guided by institutional preferences. It is currently unclear whether specific strategies may be optimal for individual neonates with particular risk factors. Previously identified risk factors for neonatal mortality have included prematurity and low birth weight,[12,13] as well as neonatal echocardiographic features, such as the right atrial area index, atrial septal defect size, TV annulus size, and lack of antegrade flow across the pulmonary valve.[5,12–17] These findings have been mostly reported in small, single-center case series, often spanning over a decade to accrue enough patients for analysis, but they have not been evaluated in a large cohort with echocardiographic data. Moreover, among surviving patients, factors related to a palliated versus biventricular outcome at the time of neonatal hospital discharge have not been explored.

The aim of this study was to describe the management strategies of this large, multicenter cohort of prenatally diagnosed neonates with severe EA/TVD. In addition, we sought to define clinical and echocardiographic factors associated with neonatal mortality and, among survivors, a palliated versus biventricular circulatory outcome at the time of discharge.

METHODS

A multicenter, retrospective cohort study was performed among fetuses diagnosed with EA/TVD throughout North America from January 2005 to September 2011. As previously described,[3] 23 centers participated, and each center obtained institutional board approval with a waiver of informed consent. The data that support the findings of this study are available from the corresponding author (L.F.) on reasonable request. Singleton fetuses with EA/TVD without significant associated lesions were included. Patients who received any form of fetal cardiac therapy (ie, NSAIDs) were excluded. The cohort was composed of 243 fetuses; prenatal clinical data and fetal echocardiographic findings were previously reported.[3] Postnatal clinical data and neonatal echocardiograms were also collected by the lead site and core laboratory and are the focus of the current study. Because the aim was to investigate patients who were intended to and able to be treated, neonates who received comfort care and/or survived <24 hours after birth were not included in quantitative analyses.

Postnatal clinical information included gestational age and weight at birth; Apgar scores; delivery room

and intensive care unit management strategies, including the use of NO, initiation of prostaglandin therapy, intubation, inotropic support, and extracorporeal membrane oxygenation; catheterizations and/or surgeries performed; and survival to neonatal hospital discharge. Patients who underwent neonatal intervention were characterized as having a palliated circulation (ie, ductal stent, aortopulmonary shunt placement with or without pulmonary banding or ligation, or RVE procedure) or a biventricular circulation (ie, no aortopulmonary shunts or additional sources of pulmonary blood flow) at the time of hospital discharge. Patients without neonatal intervention were regarded as having medical management only and a biventricular circulation at discharge. Regardless of intervention, patients with a biventricular circulation at discharge were combined for analysis because they represent patients with an adequate right ventricle (RV).

The first neonatal echocardiogram before any intervention was reviewed at the core laboratory. The right atrial area index was calculated from an apical 4-chamber view at end diastole.[15] The qualitative size and presence of shunting across a patent foramen ovale or secundum atrial septal defect, ventricular septal defect, and/or patent ductus arteriosus (PDA) were noted. The morphological features of the TV were characterized as Ebstein anomaly, TV dysplasia, or unguarded orifice based on the appearance, hinge point, and coaptation of the leaflets[18–21] and with the consensus of 2 echocardiographers (L.F. and W.T.). The degree of displacement of the septal leaflet from the mitral valve annulus was recorded. Standard echocardiographic measurements of the valves and pulmonary arteries were performed. TV area was calculated as Π×(lateral TV annulus diameter/2)×(anteroposterior TV annulus diameter/2) (Figure S1. The peak systolic tricuspid regurgitation (TR) jet velocity was obtained at an optimal angle of insonation, often from the subcostal view in the most apically displaced valves, to estimate RV systolic pressure in m/s. The pulmonary valve was assessed for the presence of leaflets and antegrade flow or regurgitation.

RV systolic function was assessed qualitatively. Left ventricular (LV) size and ejection fraction were calculated by the 5/6 × area × length method. If an aortic valve Doppler waveform was present, then the velocity-time integral was measured for calculation of LV cardiac index [heart rate×Π (aortic annulus/2)^2×velocity-time integral]/body surface area in L/min per m^2. Finally, the LV myocardial performance index (MPI) was calculated by pulse-wave Doppler tracings [(mitral valve closure time–LV ejection time)/LV ejection time], with a lower value corresponding to better myocardial function. Where applicable, quantitative measurements were transformed into body surface area–adjusted *z*-scores.[22]

Statistical Analysis

Data are presented as mean±SD, median (interquartile range), or frequency (percentage), where appropriate. Univariable analysis of clinical and echocardiographic variables between patients who survived and did not survive to hospital discharge was performed by 2-sided *t* tests or χ^2 tests. Multivariable logistic regression models were developed from clinically relevant variables significant on univariable analysis (P<0.05), including up to one variable per 8 to 10 deaths. Two multivariable models were developed on the basis of inherent patient-level risk factors: one with echocardiographic risk factors alone, and another with the same echocardiographic risk factors plus gestational age at birth and/or birth weight. Both models were developed using stepwise forward selection with a threshold P=0.05. As a secondary outcome, type of circulation at neonatal hospital discharge, palliated or biventricular, was assessed among survivors. For this outcome, both neonatal and late gestation (>30 weeks) fetal echocardiographic data were evaluated, as previously defined.[3] P<0.05 was considered statistically significant for all analyses.

RESULTS

Of 176 live-born patients, the families of 7 patients elected for comfort care. Eleven other patients died within 24 hours after birth, including 4 before leaving the delivery room. Four patients were excluded because of insufficient outcome data. The remaining 154 patients comprised the study cohort for analysis. In this cohort, an additional 38 patients (25%) died before neonatal hospital discharge at a median age of 21 days (interquartile range, 6–32 days).

Table 1 demonstrates clinical characteristics and management by neonatal hospital survival. Nonsurvivors were born at an earlier gestational age and with lower birth weight than survivors. The odds ratio (OR) for mortality of patients born at <37 weeks gestational age versus ≥37 weeks was (OR, 4.0 [1.8–8.8], 95% CI, P=0.001). The OR for mortality of patients born <3.0 kg versus ≥3.0 kg was 7.5 (2.0–27.5) (P=0.001). All neonates born at ≥3.5 kg survived (Figure 1).

Nonsurvivors received more intensive medical management. Eighteen patients were placed on extracorporeal membrane oxygenation, 8 of which occurred in the postoperative setting. Only 3 of the 18 (17%) survived: 2 were cannulated preoperatively and subsequently underwent RVE, and 1 was cannulated postoperatively following RVE. There was no difference in survival between patients who did and did not have interventional catheterization or surgery performed; however, patients who had >1 neonatal surgery were more likely to die (P=0.001).

Table 1. Clinical Characteristics and Management According to Hospital Survival (n=154)

Variable	Survived (n=116)	Died (n=38)	*P* Value
Gestational age at diagnosis, wk	28.2±6.0	26.1±5.5	0.059
Gestational age at birth, wk*	37.5±2.7	36.3±2.2	0.005
Birth weight, kg	3.0±0.6	2.6±0.5	0.001
Delivery by caesarean section	51 (48)	20 (59)	0.26
Apgar scores			
1 min	6.7±2.3	4.5±2.8	<0.001
5 min	8.0±1.2	6.3±2.4	<0.001
Delivery room intubation	32 (28)	26 (70)	<0.001
Mechanical ventilation in ICU	63 (54)	38 (100)	<0.001
Prostaglandin therapy	69 (59)	30 (79)	0.03
Inotropic support	41 (35)	32 (84)	<0.001
ECMO	3 (3)	15 (39)	<0.001
Any neonatal intervention	50 (43)	21 (53)	0.19
Neonatal catheter intervention	13 (11)	5 (13)	0.74
Neonatal cardiac surgery	40 (35)	19 (50)	0.088
Multiple neonatal surgeries	1 (1)	6 (16)	0.001

Data are presented as mean±SD or number (percentage with available data). ECMO indicates extracorporeal membrane oxygenation; and ICU, intensive care unit.

*Birth weight available for 95 patients.

Figure 2 depicts patient management and outcomes through neonatal hospital discharge. Over half of patients (83/154 or 54%) did not undergo any intervention, either interventional catheterization or surgery. Only 3 patients received NSAIDs to promote PDA closure, with success in 1 who survived. Sixty-six patients who did not undergo intervention survived to hospital discharge, which represents 43% of the entire neonatal cohort and 80% of those medically managed. The median age of death in this cohort was 8 days (interquartile range, 2–27 days).

Of the 154 patients, 71 (46%) underwent ≥1 interventional catheterization or surgery; 34% underwent cardiac surgery alone, 8% had interventional catheterization alone, and 4% had both. The procedures performed are demonstrated in Table 2. Interventional catheterization was performed in 18 patients (12%) at a median age of 6 days (interquartile range, 3–9 days). Of the 18 patients, 15 (83%) underwent balloon pulmonary valvuloplasty, 2 of whom had a PDA occluded at the same catheterization, and 1 underwent surgical PDA ligation before discharge. All 3 of these patients survived, whereas the only patient to subsequently undergo shunt placement died. Cardiac surgery was performed in 59 patients (38%), also at a median age of 6 days (interquartile range, 3–13 days). The most common surgery performed was TV repair; however, no center performed >2 of this operation. No patient underwent neonatal TV replacement. The median age of death for neonates who underwent any intervention was 21 days (interquartile range, 10–30 days).

Figure 3 displays the distribution and mortality of the first neonatal procedure performed. All 15 patients who underwent RVE survived, despite being performed at 7 different centers. Nearly half of patients (10 of 21) who underwent shunt placement or ductal stent (with or without pulmonary artery ligation or banding) died. Similarly, 8 of 19 (42%) died after attempted TV repair. There was no significant difference in survival between neonates who had an initial intervention for a palliated outcome (26 of 37 died, 30%) and neonates who had an initial intervention for a biventricular circulation (10 of 34 died, 29%) (*P*=0.98). Of the 7 patients who underwent >1 surgery, including 4 who underwent attempts at transitioning from a biventricular to a palliated approach, only 1 patient survived.

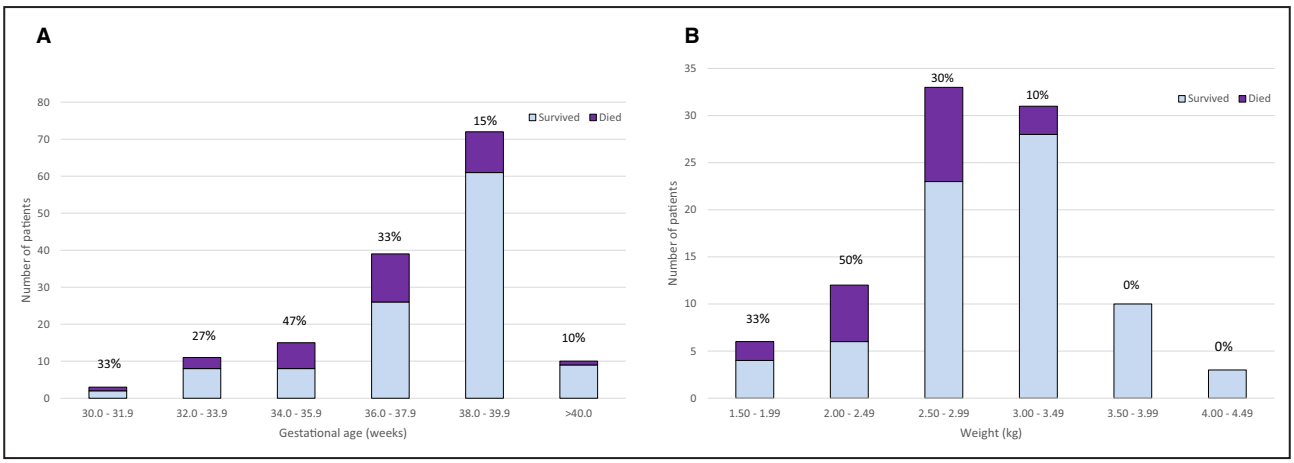

Figure 1. Survival by gestational age (A) and weight at birth (B).
The percentage above the column represents mortality. Birth weight available for 95 patients.

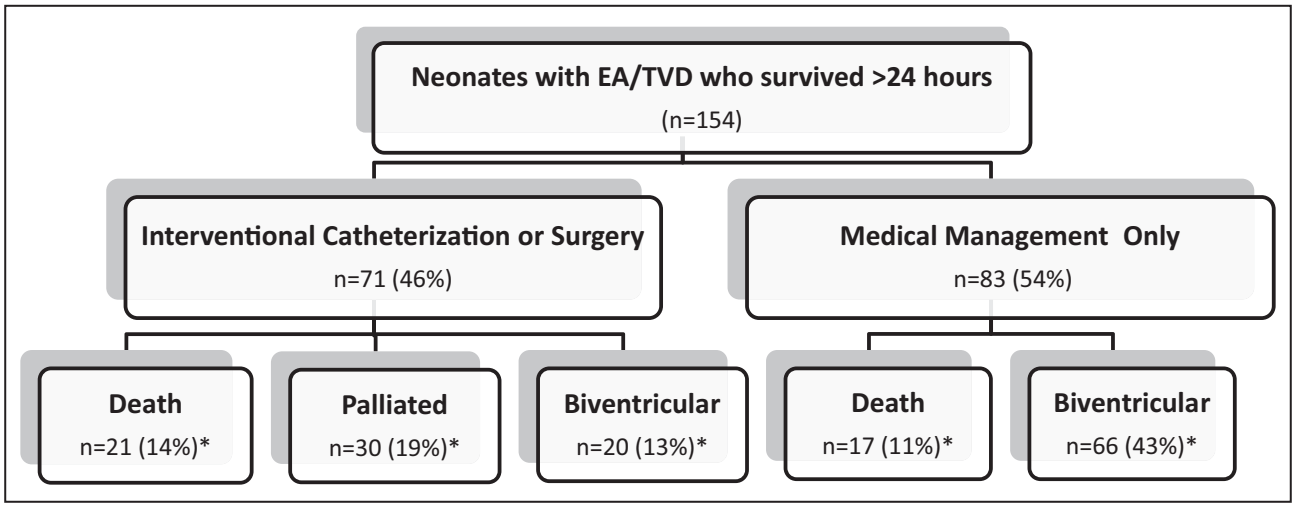

Figure 2. Flow diagram.
Neonatal management and outcome of the cohort at the time of hospital discharge. *Denotes percentage of the original neonatal cohort. EA/TVD indicates Ebstein anomaly or tricuspid valve dysplasia.

Most patients, 132 (86%), had an adequate neonatal echocardiogram performed before any neonatal intervention available for review (median age, 0 days; interquartile range, 0–1 day). A small ventricular septal defect was noted in 11 patients (8%). Among the patients with antegrade pulmonary blood flow (n=58), none had more than trivial pulmonary stenosis at the time of the initial neonatal echocardiogram (peak pulmonary valve velocity, 0.86±0.45 m/s). Almost all patients (126, 95%) had at least a small PDA, all with nonrestrictive right to left shunting. The remaining 6 patients had no PDA on the initial study, and all survived to hospital discharge. Echocardiographic indexes are summarized according to survival status in Table 3. Of note, a higher LV MPI, suggestive of poorer global function, was associated with neonatal mortality on univariable analysis (P=0.039).

Table 2. Interventional Catheterizations and Cardiac Surgeries Performed Before Hospital Discharge

Procedure	No. Performed
Interventional catheterization	
Pulmonary valvuloplasty	15
PDA coil occlusion	2
Ductal stent	2
Hybrid procedure	
Ductal stent with pulmonary artery band	1
Surgery	
Tricuspid valve repair	19
Pulmonary valvotomy (±RVOT patch)	9
Right ventricle to pulmonary artery conduit	6
Isolated PDA ligation	7
Right ventricular exclusion	15
Aortopulmonary shunt only	12
Aortopulmonary shunt with pulmonary artery band or ligation	6

Some patients had ≥1 procedure. PDA indicates patent ductus arteriosus; and RVOT, right ventricular outflow tract.

Multivariable logistic regression of the neonatal echocardiographic indexes demonstrated that lower TR jet velocity (OR, 2.3 [1.1–5.0] 95% CI, per m/s; P=0.025) and lack of antegrade flow across the pulmonary valve (OR, 4.5 [1.3–14.2]; P=0.022) were associated with neonatal mortality, whereas the right atrial area index and TV area z-score were not significant. In the multivariable model that included neonatal echocardiographic indexes, gestational age at birth or birth weight, lower birth weight (OR, 4.5 [1.8–11.1] per kg; P=0.002), and lower TR jet velocity (OR, 4.2 [1.9–9.1] per m/s; P<0.001) were significantly associated with neonatal mortality. There were no significant associations between lower birth weight or gestational age at birth and important echocardiographic factors.

Among surviving neonates (n=116), 86 (74%) were discharged with a biventricular circulation (66 without intervention), and 30 (26%) were palliated. Comparison of clinical and neonatal echocardiographic variables between these 2 outcome groups is presented in Table 4. All patients with an unguarded TV orifice underwent palliation. In addition, patients who had a lower TR jet velocity, lack of antegrade flow across the pulmonary valve, absence of pulmonary valve leaflets, and smaller pulmonary valve and main pulmonary artery z-scores were more likely to be palliated. There was no significant difference in the qualitative impression of RV dysfunction between the 2 groups. Among patients with a biventricular circulation, there was no significant difference in the TR jet velocity between

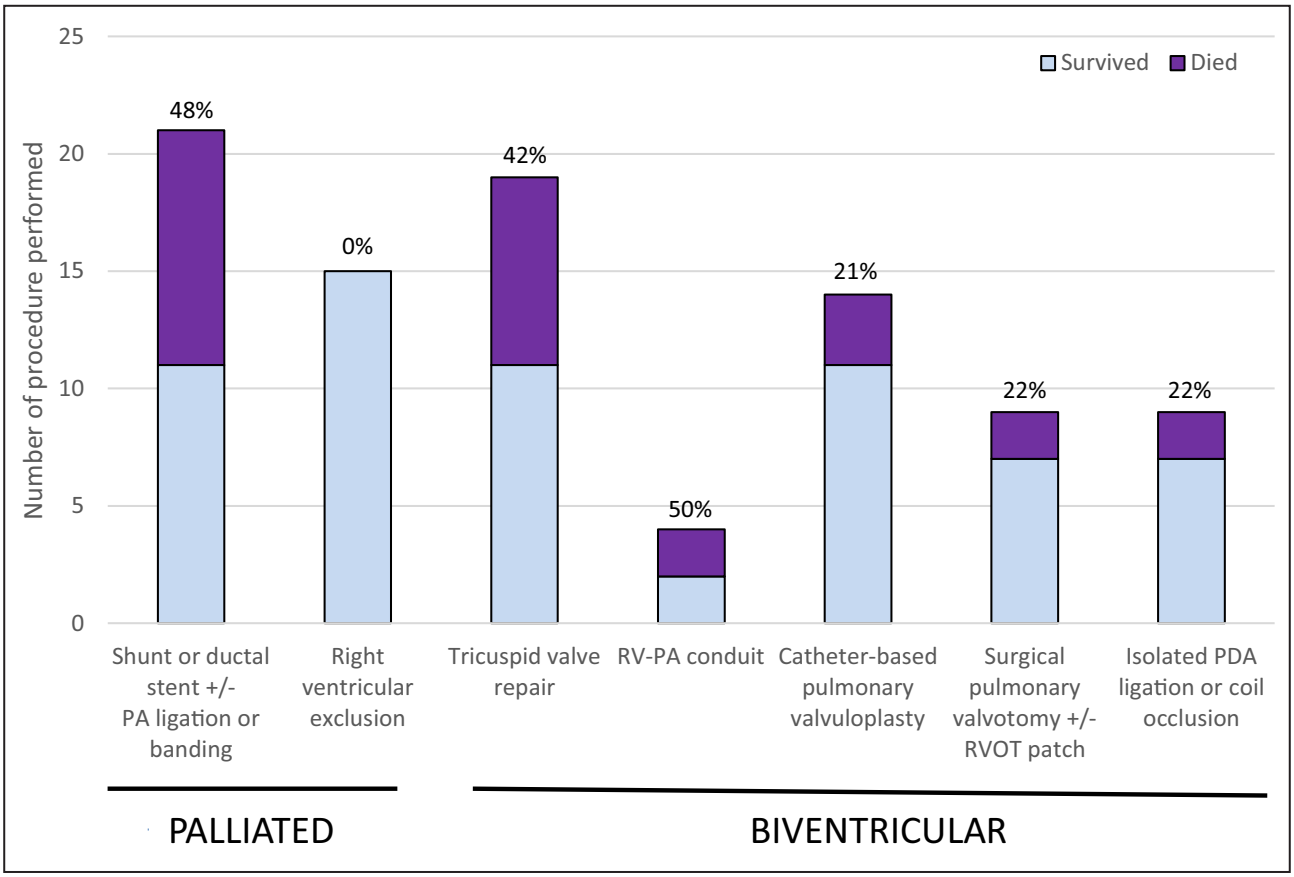

Figure 3. Neonatal procedure and survival.
The number of each neonatal procedure performed is displayed, stratified by survival (gray=survived, black=died). The percentage above the column represents mortality. Only the first procedure performed was included, and some patients were listed in >1 procedure group. The circulatory strategy below each procedure type, palliated or biventricular, is also noted. PA indicates pulmonary artery; PDA, patent ductus arteriosus; RVOT, right ventricular outflow tract; and RV-PA, right ventricle to pulmonary artery.

those who attained this circulation as a result of intervention and those who received medical management only (P=0.96).

There were 66 neonates who had a late gestation fetal echocardiogram: 48 with a biventricular circulation and 18 who were palliated. The median gestational age at the fetal echocardiogram was 35.0 (interquartile range, 33.8–36.0) weeks. Late gestation fetuses who were discharged with a biventricular circulation, regardless of neonatal intervention, had a higher TR jet velocity at the time of their last study in utero than those who were palliated (3.0±0.1 versus 2.5±0.3 m/s; P=0.04). Patients with a biventricular circulation were also more likely to have antegrade flow across the pulmonary valve in late gestation (63% versus 5%; P<0.001) and to have larger pulmonary valve z-scores than palliated patients in utero (–1.6±0.2 versus –2.5±0.4). The late gestation cardiothoracic area ratio, TV annulus z-score, main pulmonary artery z-score, and the presence of pulmonary regurgitation or RV dysfunction were not associated with circulatory outcome at discharge.

The distribution of neonatal right atrial area index, TV area z-score, and TR jet velocities among patients who died or had a palliated or biventricular outcome by the time of discharge is demonstrated in Figure 4. There was a progressive trend of lower right atrial area index (P=0.003), lower TV area z-score (P=0.002), and higher TR jet velocity (P<0.001) toward survival and, in particular, a biventricular outcome.

The mean TR jet velocity of neonates who died was 2.5 m/s, which was lower than 2.6 m/s among those who survived with a palliated outcome and 3.0 m/s among those who survived with a biventricular circulation (P<0.001). From a descriptive standpoint, all patients who underwent palliation with RVE had a TR jet velocity ≤3.0 m/s and no antegrade flow across the pulmonary valve. Among patients who underwent TV repair as part of a biventricular approach, those with a TR jet velocity ≤2.5 m/s had 50% mortality (3 of 6), whereas all 4 patients with TR jet velocity ≥3.0 m/s survived. Overall, patients who required surgery to maintain a biventricular circulation and survived had a mean TR jet velocity of

Table 3. Neonatal Echocardiographic Parameters According to Hospital Survival (n=132)

Variable	Survived (n=99)	Died (n=33)	Univariable *P* Value	Multivariable *P* Value
Right atrial area index	0.88±0.37	1.22±0.52	<0.001	
Right atrial area index <1	60 (63)	13 (41)	0.039	
Atrial septal defect			0.29	
None	2 (2)	0 (0)		
Patent foramen ovale or small	89 (91)	28 (85)		
Moderate to large	7 (7)	5 (2)		
Atrial septal defect flow direction			0.006	
Right to left	57 (58)	29 (88)		
Bidirectional	33 (34)	4 (12)		
Left to right	8 (8)	0 (0)		
Type of tricuspid valve anomaly			0.30	
Ebstein anomaly	56 (57)	21 (64)		
Tricuspid valve dysplasia	39 (39)	9 (27)		
Unguarded orifice	4 (4)	3 (9)		
Tricuspid valve displacement, mm	0.90±0.56	0.94±0.63	0.34	
Tricuspid valve *z*-scores				
Anteroposterior diameter	5.1±3.0	6.6±2.5	0.029	
Lateral diameter	4.6±2.3	6.4±2.5	0.001	
Area	9.5±5.7	13.7±5.6	0.002	
TR jet velocity, m/s	3.0±0.6	2.4±0.9	<0.001	0.025
TR jet velocity ≤2.5 m/s	19 (21)	19 (60)	<0.001	
≥Moderate RV dysfunction	31 (31)	21 (66)	0.003	
Pulmonary valve *z*-score	–1.2±1.1	–1.0±1.0	0.34	
Presence of pulmonary valve leaflets	94 (95)	24 (73)	<0.001	
Antegrade pulmonary blood flow	54 (54)	4 (12)	<0.001	0.022
≥Moderate pulmonary regurgitation	23 (23)	13 (39)	0.071	
≥Moderate patent ductus arteriosus	75 (77)	32 (97)	0.011	
Main pulmonary artery *z*-score	–0.7±1.6	–1.0±1.8	0.39	
LV end-diastolic volume *z*-score	–0.3±1.8	–0.3±1.9	0.88	
LV end-systolic volume *z*-score	–6.9±1.5	–7.5±1.9	0.094	
LV ejection fraction	0.55±0.09	0.58±0.08	0.11	
LV cardiac index, L/min per m^2	3.34±0.22	2.92±0.28	0.35	
LV MPI	0.42±0.35	0.62±0.57	0.039	
Ventricular septal defect	9 (9)	2 (6)	0.73	
Pericardial effusion	7 (7)	7 (21)	0.044	
Pleural effusion	2 (2)	4 (12)	0.034	
Ascites	2 (2)	6 (18)	0.003	

Includes only patients with a neonatal echocardiogram available for review. Data are presented as mean±SD or number (percentage with available data). For the multivariable analysis, only significant *P* values (<0.05) are depicted. LV indicates left ventricle; MPI, myocardial performance index; RV, right ventricle; and TR, tricuspid regurgitation.

2.9 m/s, and those who survived with medical management only had a mean TR jet velocity of 3.1 m/s.

Among neonates who died <24 hours after birth or received comfort care (n=18), limited data were available on management and only 5 neonatal echocardiograms were available for review. Three had a pericardial effusion, and 1 had both a pericardial effusion and ascites, suggestive of prior hydrops. Four had TR jet velocities <2.0 m/s and no antegrade pulmonary blood flow, and 3 had pulmonary regurgitation. Thirteen of the neonates had late gestation fetal echocardiograms at a median gestational age of 30.0 weeks (interquartile range, 29.3–33.0 weeks). Nearly half (n=6) had a pericardial effusion or hydrops in utero, and most had additional concerning physiologic findings, including low TR jet velocity ≤2.6 m/s (n=12), no antegrade

Table 4. Neonatal Clinical and Echocardiographic Data Among Hospital Survivors According to Biventricular Versus Palliated Circulation at the Time of Discharge (n=116)

Variable	Biventricular (n=86)	Palliated (n=30)	*P* Value
Gestational age at diagnosis, wk	28.9±6.2	26.1±4.9	0.028
Gestational age at birth, wk	37.4±2.4	37.8±1.6	0.48
Apgar scores			
1 min	6.7±2.3	6.6±2.3	0.92
5 min	7.9±1.1	8.1±1.4	0.64
Birth weight, kg	3.0±1.6	3.1±1.6	0.76
Right atrial area index	0.86±0.38	0.96±0.32	0.50
Right atrial area index >1	47 (64)	13 (57)	0.24
Type of tricuspid valve anomaly			0.001
Ebstein anomaly	44 (59)	12 (50)	
Tricuspid valve dysplasia	31 (41)	8 (33)	
Unguarded orifice	0 (0)	4 (17)	
Tricuspid valve *z*-scores			
Anteroposterior diameter	4.7±3.1	6.1±2.5	0.079
Lateral diameter	4.3±2.4	5.3±2.2	0.088
Area	8.8±5.8	11.5±5.2	0.079
TR jet velocity, m/s	3.1±0.6	2.6±0.8	0.002
TR jet velocity ≤2.5 m/s	11 (16)	8 (42)	0.014
≥Moderate RV dysfunction	20 (27)	11 (46)	0.099
Pulmonary valve *z*-score	−0.9±0.8	−1.3±1.3	0.046
Presence of pulmonary valve leaflets	74 (99)	20 (83)	0.003
Antegrade pulmonary blood flow	51 (68)	3 (13)	<0.001
≥Moderate pulmonary regurgitation	15 (20)	8 (33)	0.18
≥Moderate patent ductus arteriosus	45 (68)	22 (100)	0.002
Main pulmonary artery *z*-score	−0.5±1.3	−1.3±2.2	0.039
LV end-diastolic volume *z*-score	−0.3±1.6	−0.2±2.1	0.78
LV end-systolic volume *z*-score	−6.8±1.5	−7.3±1.6	0.28
LV ejection fraction	0.55±0.09	0.55±0.09	0.74
LV cardiac index, L/min per m^2	3.15±0.22	3.87±0.60	0.27
LV MPI	0.41±0.37	0.47±0.27	0.55
Ventricular septal defect	9 (12)	0 (0)	0.11
Pericardial effusion	7 (9)	0 (0)	0.12

Data are presented as mean±SD or number (percentage with available data). LV indicates left ventricle; MPI, myocardial performance index; RV, right ventricle; and TR, tricuspid regurgitation.

pulmonary blood flow (n=10), and/or pulmonary regurgitation (n=7).

DISCUSSION

In this multicenter study, we report the postnatal management and risk factors for neonatal outcome in a large cohort of patients diagnosed with EA/TVD in utero. More important, we had the opportunity to review the postnatal echocardiograms to better understand patient-level factors associated with both mortality and circulatory outcome at the time of neonatal hospital discharge.

Neonatal Mortality

As we previously reported, nearly one third of live-born patients died before neonatal hospital discharge.[3] Of the cohort who survived >24 hours after birth and were intended to or able to be treated, the neonatal mortality remained high at 25%, which is not significantly different from other series over the past several decades.[4–7,13,17,23] Notable risk factors for mortality included earlier gestational age at birth and lower birth weight, particularly <37 weeks and <3.0 kg, respectively. Lower birth weight remained significant in the multivariable analysis with neonatal echocardiographic factors and has been previously identified as a risk

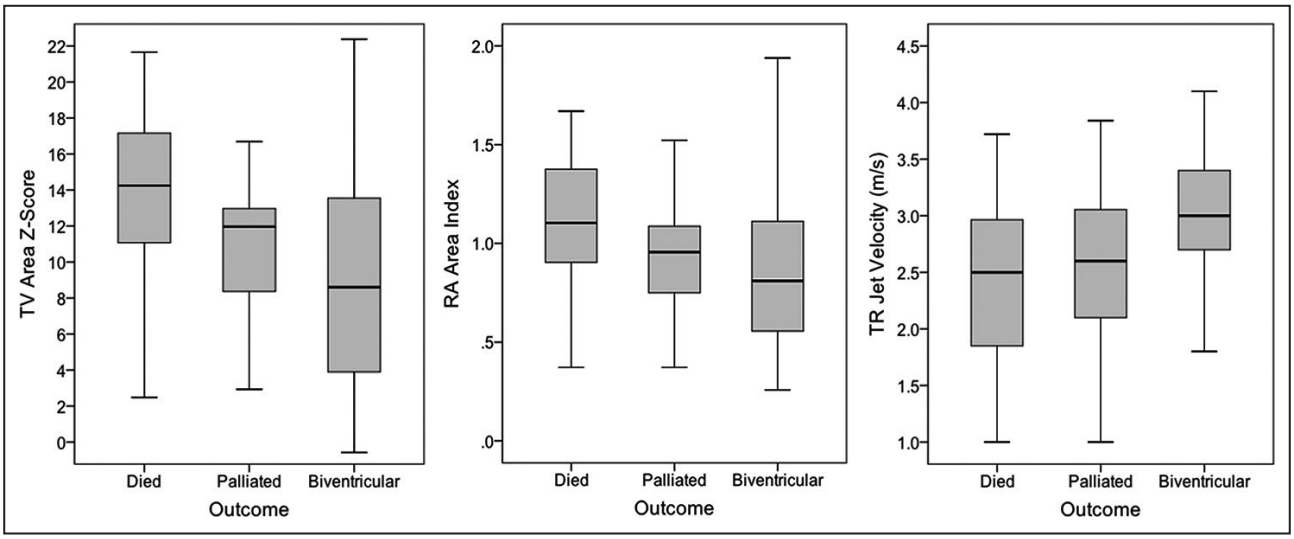

Figure 4. Echocardiographic indexes and outcome.
Distribution of neonatal right atrial (RA) area index, tricuspid valve (TV) area *z*-score, and tricuspid regurgitation (TR) jet velocity by ultimate outcome (mortality or palliated or biventricular circulation at neonatal hospital discharge). The solid line represents the median, the box represents the interquartile range, and the whiskers represent the entire range. P=0.003 (RA area index), P=0.002 (TV area *z*-score), and P<0.001 (TR jet velocity).

factor among neonates undergoing congenital heart surgery.[24,25] Its close association with gestational age at birth highlights the importance of optimal perinatal management and delivery timing for fetuses with this complex disease.[3] Of note, we did not find an association between caesarean delivery and survival.

Postnatal Management

More than half of the patients in this series were managed with careful intensive medical therapy alone during the transition to ex utero life. There was no difference in mortality between neonates managed medically versus those deemed to require interventional catheterization or surgery, nor between neonates who underwent initial intervention for a palliative or biventricular approach. However, patients who needed to return to the operating room for additional cardiac surgery had poor outcomes. Most of these cases involved transitioning from a biventricular to a palliated approach, which underscores the need for better preoperative risk stratification, including evaluation of estimated RV pressure.

There was substantial heterogeneity of interventional management for this complex group of neonates. With regard to palliative approaches for patients with low RV pressure, the difference in mortality was striking: placement of an aortopulmonary shunt or ductal stent with or without pulmonary artery band or ligation had nearly 50% mortality, whereas RVE had no mortality. Starnes et al originally described the approach of RVE in 1991,[11] and subsequent modifications, particularly with fenestrated closure of the tricuspid valve, have yielded more promising results.[26–28] More important, this experience has been replicated at other centers.[29–31] Although RVE may commit a patient to single-ventricle palliation, it provides a significantly more stable circulation in the high-risk neonatal period. The procedure reduces RV volume overload to allow for more effective LV filling and function. Placement of an aortopulmonary shunt with ligation of the main pulmonary artery interrupts circular shunting by eliminating pulmonary regurgitation. On the other hand, placement of a shunt or ductal stent without main pulmonary artery ligation exacerbates volume overload and may perpetuate circular shunting, systemic steal, and poor cardiac output in the presence of pulmonary regurgitation.

Among interventional strategies to maintain a biventricular circulation, TV repair was performed commonly, but it was associated with high mortality of 42%. This is likely because of several factors, including low volume per center for a technically challenging operation[32] and failure to identify the best candidates. In particular, half of the neonates with TR jet or RV pressure ≤2.5 m/s died, whereas all those ≥3.0 m/s survived. This underscores the importance of evaluating the ability of the RV to eject antegrade, because, even with a potentially successful TV repair, the RV may be unable to tolerate this approach and provide effective pulmonary blood flow. Knott-Craig et al have encouraged TV repair in this population since 2000.[33,34] They have been able to achieve durable technical success in a subset of patients[33]; however, overall early mortality was 28% in their most recent publication.[34]

Use of an RV to pulmonary artery conduit was infrequently performed (n=6) across multiple centers

and was associated with mortality of 50%, which is higher than previously reported in this population.[34] The higher mortality of this procedure, as opposed to catheter-based or surgical relief of RV outflow tract obstruction, may be dictated by the severity of the underlying abnormality (ie, anatomic pulmonary atresia) or the burden of a ventriculotomy on an already fragile RV.

In contrast, PDA ligation or coil occlusion had a mortality of 22%. Two different centers performed coil occlusion for high-risk patients in the catheterization laboratory, both of whom survived. One of 3 patients who received NSAIDs for PDA closure survived without further intervention, and another subsequently underwent surgical ligation and survived. Therefore, the mortality of all patients who underwent PDA closure by any means was 20%. Wald et al previously described the strategy of limiting ductal patency in patients with EA/TVD.[8] Using an algorithmic approach at their institution, the authors noted a striking reduction in mortality from an estimated 35% based on the right atrial area index to 7%. The higher mortality in the current cohort may relate to the multiple centers involved and, specifically, the nonuniform selection of patients. Patients without anatomic RV outflow tract obstruction and with adequate RV pressure are likely to be the best candidates for this strategy. Of note, medical attempts at PDA closure were rarely performed in this series but may play an important role. It is noteworthy that all 6 patients without a PDA at the time of the initial study survived to hospital discharge.

Echocardiographic Findings and Mortality

Many neonatal echocardiographic findings were associated with hospital mortality by univariable analysis, including higher right atrial area index, larger TV size, lower TR jet velocity, absence of pulmonary valve leaflets, lack of antegrade pulmonary blood flow, qualitative RV dysfunction, and the presence of effusions or ascites. The LV and its impaired filling also figures prominently in the pathophysiological features of neonates with EA/TVD. Although LV MPI or its subcomponents have been demonstrated to be associated with disease severity in fetuses or neonates with EA/TVD,[35,36] we found a direct association between higher LV MPI and mortality in this disease. The higher MPI reflects shorter LV filling time as the result of RV volume overload with paradoxical septal wall motion and delayed mitral valve opening.[37] More complex ventricular interactions with regard to LV geometry, deformation, dyssynchrony, and torsion, all of which may ultimately impair cardiac output, have also been reported in adult series.[38,39] Of note, LV ejection fraction was not significantly different between survivors and nonsurvivors, similar to other series.[36] Thus, LV MPI may be a more sensitive quantitative measure of LV function in this population.

By multivariable analysis of the neonatal echocardiographic findings alone and with the addition of clinical risk factors, lower TR jet velocity was significantly associated with mortality. This finding is consistent with our previously reported association between lower TR jet velocity and perinatal mortality in the late-gestation fetus[3] and underscores the importance of this measurement both prenatally and postnatally. The TR jet velocity serves as not only a global marker of myocardial function but also of the capacity of the RV to eject antegrade across the pulmonary valve, as previously discussed. If the TR jet is low and the RV is unable to eject antegrade, then more flow is regurgitated to cause elevation of central venous pressure and/or more right to left shunting at the atrial level, leading to decreased cardiac output and/or cyanosis. The TR jet is relatively easy to obtain, in contrast to the right atrial area index, which was not significantly associated with neonatal mortality by multivariable analysis. Although we demonstrated incremental value to higher TR jet velocity with regard to both survival and a biventricular circulation, with or without neonatal intervention, there was no obvious threshold value. That being said, patients with a successful biventricular approach typically had a jet ≥3.0 m/s on their neonatal study, whereas those who were palliated were often ≤2.5 m/s. Those with TR jets between 2.5 and 3.0 m/s appear to represent a “gray zone” where other factors, including variable downstream resistances and nonmeasured indexes of right atrial[40] and/or RV function, may play a larger role.

Lack of antegrade pulmonary blood flow was also significant in the multivariable analysis of neonatal echocardiographic findings and mortality. Multiple studies have identified lack of antegrade pulmonary blood flow as a risk factor for neonatal mortality in this population.[5,12,13,16,17] This finding can be caused by either anatomic or functional pulmonary atresia, both of which present high-risk subgroups, and explains the lack of association between pulmonary valve size and survival. Among patients with anatomic pulmonary atresia, neonatal surgery is required, which may not be well tolerated. As mentioned previously, there was 50% mortality associated with placement of an RV to pulmonary artery conduit. Although neonates with functional pulmonary atresia may not require neonatal surgery, their physiology is unfavorable because of the inability of the RV to eject antegrade. Moreover, a subset of these patients have pulmonary regurgitation and aberrant circular shunt physiology with its attendant low cardiac output and systemic steal.

Echocardiographic Findings and Circulation at Neonatal Discharge

With regard to circulatory outcome at discharge among survivors, lower TR jet velocity and lack of antegrade pulmonary blood flow were associated with a palliated outcome at both the time of the late gestation fetal echocardiogram and neonatal study. Moreover, smaller pulmonary valve measurements at both times (and smaller main pulmonary artery measurement on the neonatal study) were associated with palliation, which likely indicate more significant anatomic RV outflow tract obstruction. These findings have important implications. First, although progressive pathophysiology is known to ensue among second-trimester fetuses with EA/TVD,[41] specific high-risk anatomic and physiologic features do not appear to change substantially from the third trimester to the neonatal period. As a result, late gestation findings may help inform postnatal management strategy, along with critical evaluation of the neonate's ability to transition and assessment of the neonatal echocardiogram. Parental expectations may also be guided accordingly.

Limitations

This study was inherently limited by its retrospective nature. Different institutions likely had distinct biases. It is difficult to understand the complexities of management strategies and the drivers of clinical decision-making. For this reason, we did not group patients by intention to treat as biventricular or palliated, which would involve assumptions about goals of care. Rather, we grouped by discrete events, namely intervention(s), if any, before neonatal hospital discharge. The exclusion from quantitative analyses of neonates who received comfort care or who did not survive >24 hours after birth because of limited data may have led us to underestimate our findings or may have hindered our ability to evaluate previously identified fetal risk factors for mortality, such as pulmonary regurgitation. However, it permits an understanding of those neonates who were prenatally diagnosed and able to be treated. On the other hand, because of the nature of the inception cohort, neonates who were not prenatally diagnosed, likely attributable to milder disease, were not represented. This is underscored by the fact that all neonates with a PDA had right to left shunting on the initial echocardiogram.

All of the neonatal echocardiograms were read by a core laboratory to ensure consistency. Only the first study was reviewed, and we acknowledge that the physiology may change significantly over the first few days of life, including the evolution of pulmonary stenosis as the pulmonary vascular resistance falls. In addition, echocardiograms following intervention and outcomes beyond neonatal hospital discharge were not reviewed, but they would provide valuable information in the future, particularly on eventual single versus 1.5 ventricle palliation. Finally, the retrospective nature of the study precluded more advanced measurements of right atrial or ventricular function, such as deformation analysis or 3-dimensional volume or ejection fraction, which may be avenues for future research. Such evaluation may provide insight beyond the TR jet velocity as to the fate of the RV in this disease.

Future Directions

Given the heterogeneity in management of neonates with severe EA/TVD and the persistently poor outcomes across multiple institutions, a prospective approach is warranted to improve care for this high-risk population. The comprehensive identification of patient factors and outcomes may be used to inform treatment algorithms, and both conventional and novel echocardiographic indexes may refine various treatment pathways. Ultimately, a multidisciplinary approach that transcends individual institutions' walls will be necessary to lead to improved outcomes.

CONCLUSIONS

Among prenatally diagnosed neonates with severe EA/TVD who survived >24 hours and were intended to be treated, mortality remained high at 25%. Notable risk factors for neonatal mortality included lower birth weight, lower TR jet velocity, and lack of antegrade pulmonary blood flow. The echocardiographic risk factors for a palliated outcome also included lower TR jet velocity and lack of antegrade pulmonary blood flow, along with smaller pulmonary valve dimension, at both the time of the neonatal and the late gestation fetal study. Patients with adequate RV pressure (≥3.0 m/s) and antegrade pulmonary blood flow suggestive of a competent RV may be managed medically as the pulmonary vascular resistance falls and the PDA closes, or with isolated PDA ligation, to attain a biventricular circulation. On the other hand, for patients with low RV pressure who are unlikely to eject antegrade, palliation with RVE may be the best strategy to achieve survival beyond the tenuous neonatal period. Other strategies, such as TV repair or ductal stenting or shunt placement, were associated with substantial mortality in our series. Prospective exploration and evaluation of management practices of this complex and challenging group of patients is necessary going forward.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Figure S1

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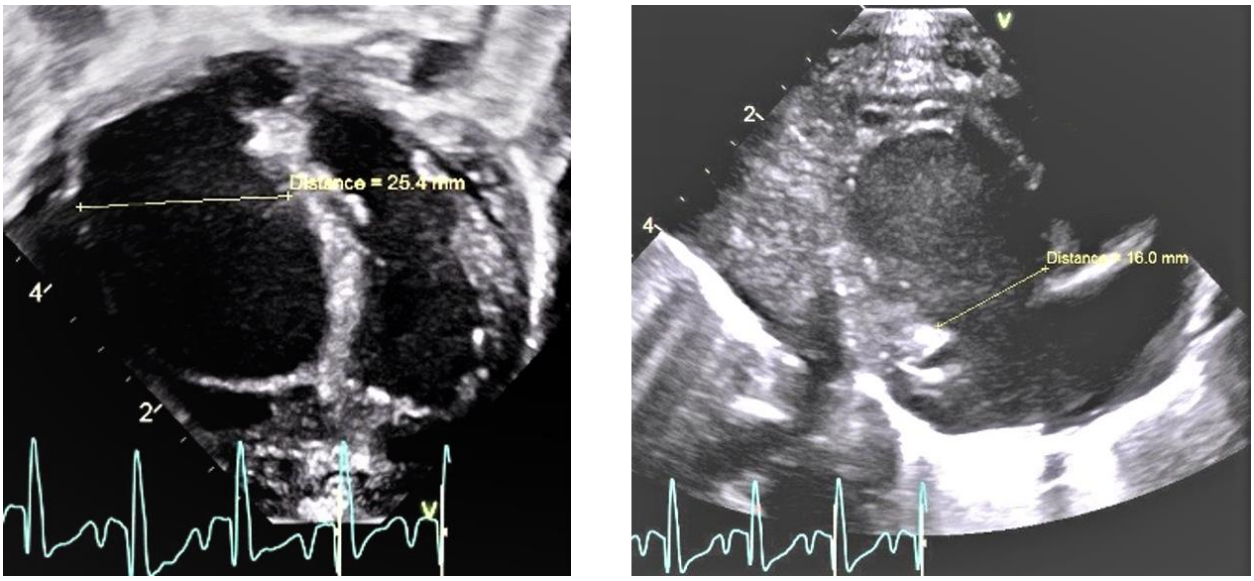
SUPPLEMENTAL MATERIAL

Figure S1. Transthoracic echocardiographic images of the measurements used to obtain the tricuspid valve (TV) area.



The lateral and anteroposterior hinge points of the TV are measured in the apical four chamber and parasternal long axis views, respectively.