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Contemporary outcomes and mortality risks of Ebstein anomaly: A single-center experience in Thailand

Varisara Pornprasertchai MD | Chodchanok Vijarnsorn MD | Supaluck Kanjanauthai MD | Paweena Chungsomprasong MD | Prakul Chanthong MD | Kritvikrom Durongpisitkul MD | Jarupim Soongswang MD

Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand

Correspondence
Chodchanok Vijarnsorn, Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, 2 Wanglang Rd., Bangkok 10700, Thailand.
Email: cvijarnsorn@yahoo.com

Abstract

Background: The increasing number of patients with Ebstein anomaly (EA) surviving into adulthood implies improvements in the treatments for the complex lesion. We revisited the clinical outcomes of patients with EA to demonstrate their "real world" survival.

Objectives: To identify the survival and predictors of mortality in patients with EA who underwent medical or surgical management in the present era.

Methods: All patients who had EA with atrioventricular concordance between 1994 and 2016 were retrospectively reviewed. Baseline characteristics, initial echocardiographic findings, treatments, and outcomes were explored. The survival analysis was performed at the end of 2017. A multivariate analysis was used to assess mortality risks.

Results: A total of 153 patients (25.4 ± 20.4 years, 60% female) were analyzed. Of these, 89 patients had been diagnosed with EA in childhood. During the follow-up [median time of 5.2 years (3 days-23.5 years)], 32 patients (20.9%) died due to major cardiac adverse events. The overall survival at 1, 5, and 10 years were 89%, 82.2%, and 79%, respectively. Of the total 153 patients, 64 patients underwent at least one surgical intervention [median age of 17 years (1 day-64.4 years)]. The survival at 1, 5, and 10 years were 87.5%, 82.4%, and 77.7%, respectively, in patients with EA surgery. This survival is comparable to the survival of 89 nonoperated patients with EA: 89.9%, 87.5%, and 81.8%, at 1, 5, and 10 years, respectively. The significant predictors of mortality were: age at diagnosis ≤2 years, tricuspid valve (TV) z-score >3.80, TV displacement >19.5 mm/m^2, presence of severe tricuspid regurgitation, and absence of forward flow across the pulmonic valve at the initial diagnosis.

Conclusion: Patients with EA had a moderately good survival in this era. In this paper, we report five simple predictors of death in this patient population.

KEYWORDS
congenital heart defect, Ebstein anomaly, prognosis, survival

1 | INTRODUCTION

Ebstein anomaly (EA) is a complex congenital heart disease characterized by the delamination and downward displacement of tricuspid valve (TV) leaflets into the right ventricle (RV).[1] A wide array of anatomical variations of TV and RV abnormalities can affect the age-dependent clinical symptoms and outcomes of EA.[1,2] Patients with a mild form of EA can be symptom-free throughout their lives. Conversely, symptoms of severe EA may appear in utero, leading to the demise of the fetus. Cyanosis, congestive heart failure, and arrhythmia are common presentations in children and adults.[1-5] Several grading systems for EA have been described based on pathology and echocardiographic scores.[4,6,7] Nevertheless, limitations in the scoring classifications have made them of little relevance for clinical purposes and have created difficulties in their application to various age groups.

The optimal timing for intervention in EA has been debated, in terms of perioperative risk and the potential need for redo intervention.[1,8-10] The decision for management depends on the individual case. Surgical repairs may include biventricular repair, a one and a half strategy, or univentricular heart palliation based on individual EA morphology.[6,10-15] Usually, operative intervention is indicated in patients who have more than moderate TR and symptoms such as New York Heart Association (NYHA) functional class >II, arrhythmia, progressive cyanosis, paradoxical embolism, or deteriorating exercise capacity measured by cardiopulmonary exercise testing.[8,9,16] In asymptomatic patients; however, surgical repair should be considered when progressive right heart dilation or reduction of RV systolic function and progressive cardiomegaly on chest radiography are present.[8,9] Intermediate term outcomes have been reported for patients with EA, who have had either an operation or a conservative medical treatment.[10,11,13-17] In any case, factors that might predict a poor outcome for patients with EA remain of interest.

In Thailand, surgical techniques and the care of congenital heart defect have developed gradually. Repair of EA is a procedure with a high complexity score index that can only be performed in specialized cardiac centers. Siriraj Hospital is a medical center that provides EA medical and surgical care to patients from neonates to adults. The treatment in our center is based on individual patients and the consensus of the subspecialty team, which includes specialists from cardiovascular surgery, pediatric cardiology, and adult cardiology. In this paper, our aim is to evaluate clinical outcomes and survival, and determine the predictors of mortality for patients with EA who have undergone medical or surgical management. We also aim to reflect the data for this patient population in our developing country.

2 | METHODS

The hospital-based, single-center observational study was conducted using a database from a large referral tertiary center in Thailand. Following the approval of the institution's ethics committee, all patients who were diagnosed with EA by

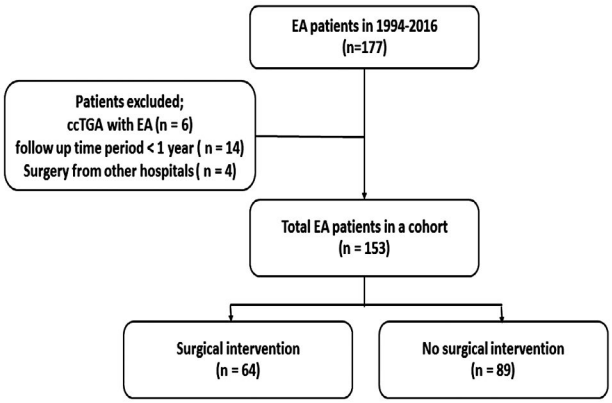


FIGURE 1 Flow of study (*n* = 153). Abbreviations: EA, Ebstein anomaly; ccTGA, congenital corrected transposition of great arteries

2D-tranthoracic echocardiography (2D-TTE) between January 1, 1994 and December 31, 2016 in Siriraj Hospital, Mahidol University, were retrospectively reviewed. The flow of the study is shown in Figure 1. Demographic data were collected for age at diagnosis, gender, oxygen saturation, presenting symptoms and NYHA Functional class, electrocardiography (ECG), and echocardiographic findings at the initial presentation. Treatment and clinical outcomes were recorded with regards to type of surgical intervention, functional class, oxygen saturation, presence of cardiac arrhythmia, right heart failure, and mortality following diagnosis at the most recent follow-up at the end of 2017.

2.1 | Echocardiographic measurement

2D-TTE has been long used as the initial diagnostic tool for EA. Diagnostic criteria have been defined as apical displacement of the septal leaflet of TV greater than 8 mm/m^2 from the AV valve ring, measured in the apical four-chamber view.[1] Tricuspid regurgitation (TR) was assessed subjectively by color Doppler using a subjective scale of 0 (none) to 4 (severe). None of the neonatal EA cases in our institution were assessed with the GOSE score. TV annulus and its *z*-score, right ventricular systolic pressure, presence of forward flow across pulmonary valve (PV), presence of right ventricular outflow tract obstruction, left ventricular ejection fraction, size of pulmonary arteries (PA), and additional associated cardiac defects were retrospectively reviewed from the institution's echocardiographic database.

2.2 | Electrocardiogram analysis

Twelve-lead ECGs were acquired using standard lead positions, with a commercially available digital recorder, and then collected and analyzed. The onset and the termination of pertinent ECG complexes were manually detected, and the QRS duration was measured in each precordial lead. Averaged values were used for the analysis. The PR interval and PQ interval were measured in leads I, II, V^1, and V^6. The P wave height and width were measured in lead II. Two

additional depolarization parameters were included: the "S wave upstroke time," which was measured as the longest interval from the nadir of the S wave to the point of intersection of the upstroke portion of the S wave with the isoelectric line, and the "QRS fractionation," which was defined as the presence of a distinct, low-voltage wave (<0.5 mV) in the terminal portion of the QRS complex or the early ST-segment. Specifically, the S wave upstroke time was measured in lead I as right bundle branch block in most patients obscured this time duration when measured in the right chest lead. The QRS fractionation was measured in V^1-V^3 as mentioned in a previous publication.[18]

2.3 | Statistical analysis

The patients' baseline characteristics and outcomes were summarized using descriptive statistics. Normally distributed data were presented as the mean ±SD, or in cases where the distribution was not normal, as median with range. Categorical data were represented as a number and a percentage (%). Differences between the categorical data were assessed using a chi-square. Cumulative survival, from date of diagnosis to the mortality endpoint, was calculated using the Kaplan-Meier method. The relation between baseline characteristics and mortality was evaluated with Cox regression and multivariate analysis. A *P* value <.05 was considered to be statistically significant. The statistical analyses were performed with SPSS 20.0 for Windows (SPSS Inc, Chicago, Illinois).

3 | RESULTS

3.1 | Patients' baseline characteristics

A total of 153 patients with EA (current age 25.4 ± 20.4 years, 60% female) were included in the study cohort. Median age at diagnosis was 11.7 years (range 1 day-72.7 years). Of the patients, 89 were diagnosed at under 18 years of age and 64 patients were diagnosed at an age of ≥18 years. Of the total, 43 patients were initially diagnosed in infancy (age <1 year). Clinical presentations of the patients in the cohort included cyanosis (39.9%), heart failure (22.2%), audible murmur that was relatively asymptomatic (13.7%), palpitation (12.4%), abnormal chest radiography, cardiomegaly (3.3%), prenatal diagnosis of EA (2.6%), syncope (1.9%), and neurological deficit (1.9%). The median follow-up time was 5.2 years (3 days-23.5 years), and 64 patients (41.8%) underwent at least one surgical intervention. The baseline characteristics of the study population are summarized in Table 1.

3.2 | Electrocardiographic and arrhythmic findings

Of the 153 patients, 140 ECG tracings prior to any interventions being performed were retrieved from the database and all ECG parameters were reviewed. QRS axis was 78° ± 75° degree. The AV conduction time (PR interval in lead II) ranged from 80 to 280 milliseconds. Prolongation of the PR interval >95th percentile for age was found in 72 patients (47%). The P wave amplitude was 2.2 ± 1.4 mm and width was 100 ± 26 milliseconds in lead II. Right bundle branch block was identified in 90 patients (58.8%). Fourteen patients (9.2%) had preexcitation. The QRS duration ranged from 59 to 204 milliseconds. Abnormal prolonged QRS duration (>95th percentile for age) was documented in 88 (57%) of the patients. The S wave upstroke time was 70 ± 36 milliseconds and it ranged from 10 to 180 milliseconds. QRS fractionation was presented in 39 patients (25.5%). Of the patients, 49 (32%) had arrhythmic events during a follow-up, which included 26 supraventricular tachycardia (17%), 10 atrial flutter (6.5%), 5 atrial fibrillation (3.2%), 6 ventricular tachycardia (4%), and 2 sinus node dysfunction (1.3%).

3.3 | Surgical intervention

In our cohort, 64 patients (41.8%) underwent 85 operations. The median age at first surgical operation was 17 years (1 day-64.4 years). Fifteen patients (23.4%) had operations in infancy (age less than 1 year). At the time of their surgery, 42 patients were under 18 years of age. In 52 patients (81.3%), the intended strategy of surgery was biventricular repair; in 9 patients (14%), the intended strategy was one and a half ventricle repair; and in 3 patients (4.7%), the intended strategy was univentricular palliation. Nevertheless, three patients had operations that crossed over from biventricular repair to one and a half ventricular repair (n = 1), and to univentricular palliation (n = 2). In patients who underwent biventricular repair, TV replacement was the final surgery in seven patients. Several techniques of TV repair were performed in the center, such as cone reconstruction (n = 7), the Danielson technique (n = 3), the Carpentier technique (n = 2), among others (n = 30). The overall early postoperative mortality rate was 14%. Six patients died in the early postoperative period after biventricular repair and three patients died after one and a half ventricular repair and univentricular palliation. Details of the surgical interventions are illustrated in Figure 2.

3.4 | Survival

At the median follow-up of 5.2 years (0-23.5 years), 32 patients had died from major cardiac adverse events, which accounts for a mortality rate of 19.9%. Overall, the survival of patients with EA following diagnosis at 1, 5, and 10 years was 88.9%, 82.2%, and 78%, respectively (Figure 3, left panel).

At the time of follow-up, 15 patients who had undergone EA surgery died (9 deaths were related to early postoperative surgery and 6 deaths occurred late after surgery due to heart failure). The 1, 5, and 10 year survival rates following surgery were 85.9%, 82.3%, and 74.2%, respectively. The survival rates in the surgery group after diagnosis were 87.5%, 82.4%, and 77.7% at 1, 5, and 10 years, respectively. In the 89 patients who did not undergo EA surgery, 17 patients died due to heart failure (n = 13), ventricular tachycardia (n = 1), atrial flutter and complete atrioventricular block (n = 1), and sepsis, related to heart failure (n = 2). The survival of the nonsurgery group was 89.9%, 87.5%, and 81.8%, at 1, 5, and 10 years. The Kaplan-Meier estimated survival curves showed no statistical

TABLE 1 Patients' characteristics (n = 153)

	Total (n = 153)	Surgical intervention (n = 64)	No surgical intervention (n = 89)	P value
Age at diagnosis (years)	18.6 ± 19.4	15.6 ± 16.2	20.8 ± 21.4	.103
Male gender	60 (39.2)	32 (50)	28 (31.5)	.029*
NYHA functional class				.168
I	66 (43.1)	21 (32.8)	45 (50.6)	
II	67 (43.8)	33 (51.6)	34 (38.2)	
III	15 (9.8)	8 (12.5)	7 (7.9)	
IV	5 (3.3)	2 (3.1)	3 (3.4)	
Presence of syndrome	7 (4.6)	3 (4.7)	4 (4.5)	1.000
Stroke at presentation	7 (4.6)	3 (4.7)	4 (4.5)	1.000
Presence of arrhythmia	49 (32.0)	19 (29.7)	30 (33.7)	.364
SpO_2 ≤ 90%	70 (45.8)	34 (53.0)	36 (40.4)	.073
Hct >45%	55 (35.9)	25 (39.1)	30 (33.7)	.502
CT ratio >0.7	52 (34.0)	28 (43.8)	24 (27.0)	.024*
TV displacement index (mm/m^2)	29.80 (23.5)	29.39 (18.6)	30.08 (26.4)	.867
TV z-score	2.96 (1.7)	3.51 (1.6)	2.52 (1.6)	.001*
TR severity				.095
no	7 (4.6)	4 (6.3)	2 (2.2)	
trivial and mild-moderate	33 (21.6) 45	14 (21.8) 12	19 (21.4) 33	
severe	(28.8)	(18.8)	(37.1)	
RVOT obstruction	69 (45.1)	34 (53.1)	35 (39.3)	
PS				.036*
PA	14 (9.2)	7 (10.9)	7 (7.9)	
LVEF (%)	12 (7.8)	9 (14.0)	3 (3.4)	.173
	66.13 (10.5)	64.70 (10.6)	67.12 (10.4)	

Abbreviations: CT ratio, cardiothoracic ratio; Hct, hematocrit; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PA, pulmonary atresia; PS, pulmonary stenosis; PV, pulmonary valve; RVOT, right ventricular outflow tract; SpO_2, percutaneous oxygen saturation; TR, tricuspid valve regurgitation; TV, tricuspid valve.
Data represented by mean ±SD, median (range) and n (% within column).
*Statistically significance at P value <.05.

difference between the two groups (log rank P = .89) (Figure 3, right panel).

3.5 | Mortality risk factors

Demographic factors were reviewed for the overall mortality risk analysis. The TV annulus was adjusted with a z-score and modified for the categorical data using a receiver operating characteristic (ROC) curve. The cutoff value that was significant for the highest sensitivity and specificity for the TV annulus z-score was above 3.8. Similar to the indexed TV displacement, the cutoff value for ROC was a TV displacement index >19.5 mm/m^2. Univariate analysis showed that 10 factors were associated with mortality, such as: age ≤2 years, NYHA III-IV, oxygen saturation ≤90%, Hct at diagnosis >45%, CT ratio >0.7 on chest radiography, TV annulus z-score >3.80, TV displacement index >19.5 mm/m^2, presence of severe TR, absence of forward flow across PV at diagnosis, and P wave width >90 millisecond. Following the multivariate analysis, only 5 independent predictors of mortality were found in patients with EA, including age at diagnosis ≤2 years (hazard ratio 3.36, 95% CI: 1.02-10.88, P = .04), TV annulus z-score >3.80 (hazard ratio 4.77, 95% CI: 1.69-13.42, P = .003), TV displacement index >19.5 mm/m^2 (hazard ratio 9.39, 95% CI: 1.2-72.9, P = .03), presence of severe TR at diagnosis (hazard ratio 3.62, 95% CI: 1.25-10.67, P = .018), and absence of forward flow across the PV (hazard ratio 5.57, 95% CI: 1.64-18.93, P = .006) (Table 2).

In the surgery group (n = 64), the univariate analysis demonstrated 4 factors that may be associated with mortality, including surgery in neonate and infants (age <1 year), TV displacement index >19.5 mm/m^2, presence of severe TR, and absence of forward flow across PV at diagnosis. Following the multivariate analysis, the only strong predictor related to death in this group was surgery in neonates and infants (hazard ratio 43.5, 95% CI: 2.21-859.9, P = .013) (Table 3).

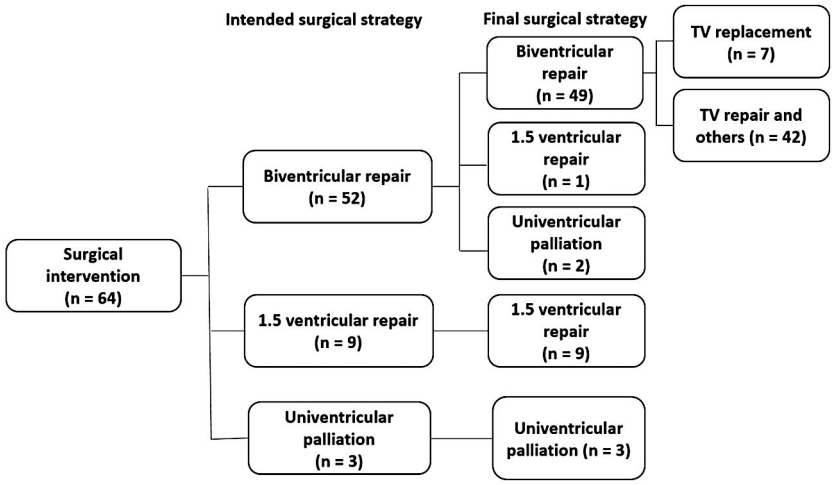
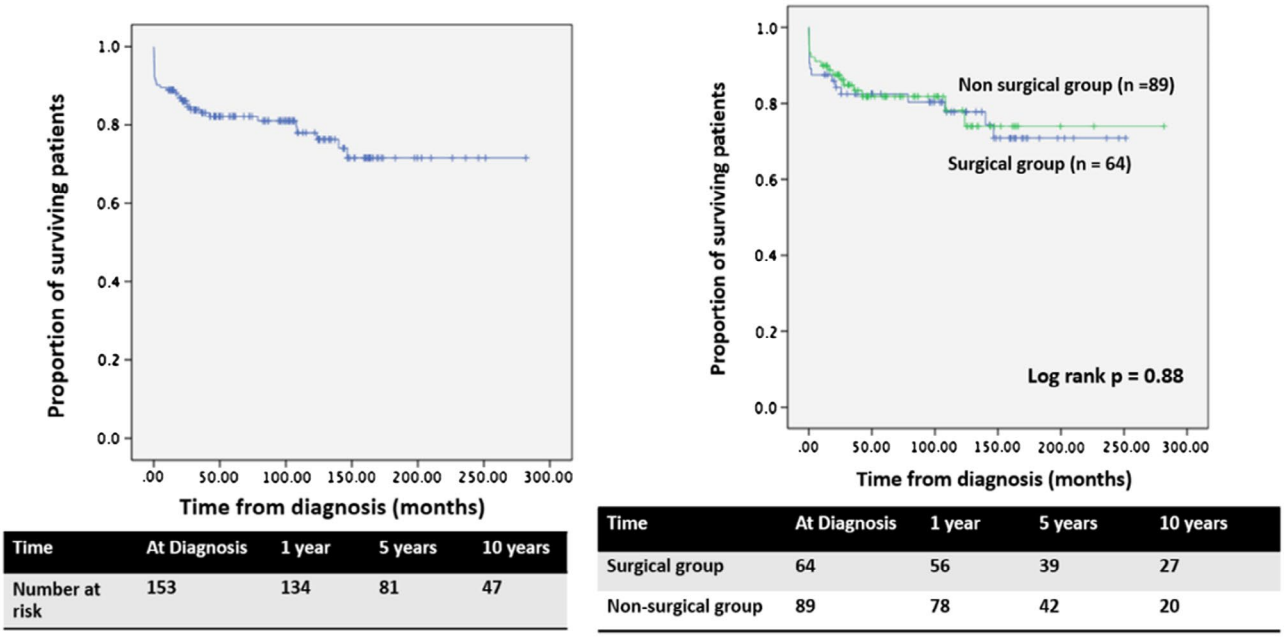


FIGURE 2 Surgical intervention in patients with Ebstein anomaly (*n* = 64)



Time	At Diagnosis	1 year	5 years	10 years
Number at risk	153	134	81	47

Time	At Diagnosis	1 year	5 years	10 years
Surgical group	64	56	39	27
Non-surgical group	89	78	42	20

FIGURE 3 Left panel: cumulative survival of all patients with Ebstein anomaly (*n* = 153), and right panel: cumulative survival of patients who underwent Ebstein anomaly surgery and patients who did not undergo Ebstein anomaly surgery in a cohort (surgical group; blue line and nonsurgical group; green line)

Looking at the 89 patients who had no surgical intervention, 3 significant predictors were found for mortality in the multivariate model, including cardiothoracic ration >0.7 on chest radiography (hazard ratio 2.38, 95% CI: 1.17-100.11, *P* = .03), TV annulus *z*-score >3.80 (hazard ratio 1.78, 95% CI: 1.1-31.9, *P* = .03), and TV displacement index > 19.5 mm/m^2 (hazard ratio 1.99, 95% CI: 1.0-57.9, *P* = .05) (Table 4).

4 | DISCUSSION

The present study used a 20-year congenital heart clinic database from a large, tertiary center in Thailand. Of 153 patients who had been diagnosed with EA (89 < 18 years of age; 64 ≥ 18 years of age), 41% had EA surgery. In this cohort, survival of patients with EA following diagnosis at 1, 5, and 10 years was 88.9%, 82.2%, and 78%, respectively, which was moderately good. Independent risks of overall mortality in patients with EA included age at diagnosis ≤2 years, TV annulus *z*-score >3.80, TV displacement index >19.5 mm/m^2, presence of severe TR at diagnosis, and absence of forward flow across the PV. In particular, cardiothoracic ratio >0.7 on chest radiography, TV annulus *z*-score >3.80, and TV displacement index >19.5 mm/m^2 remained significant predictors of mortality for patients who did not undergo EA surgery based on the multivariate model. These findings suggest new, simple cutoff values for echocardiography that can aid

TABLE 2 Predictors of overall mortality (n = 153)

Variable	Crude hazard ratio (95% CI)	*P* value	Adjusted hazard ratio (95% CI)	*P* value
Female gender	1.35 (0.65-2.81)	.421		
Age at diagnosis ≤2 years	4.60 (2.24-9.42)	<.001*	3.36 (1.02-10.88)	.046*
NYHA functional class III-IV at diagnosis	2.63 (1.18-5.88)	.018*		
SpO_2 at presentation ≤90%	5.51 (2.26-13.44)	<.001*		
CT ratio >0.7	10.85 (4.36-26.99)	<.001*		
Hct at diagnosis >45%	2.57 (1.22-5.41)	0.013*		
Arrhythmia at presentation	0.87 (0.48-1.80)	.699		
TV annulus *z*-score >3.80	2.49 (1.11-5.61)	.028*	4.77 (1.69-13.42)	.003*
TV displacement index >19.5 mm/m^2	21.67 (2.93-150.53)	.003*	9.39 (1.20-72.90)	.032*
Presence of severe TR at diagnosis	3.36 (1.59-7.12)	.002*	3.62 (1.25-10.67)	.018*
Absence of forward flow across PV	8.74 (4.18-18.27)	<.001*	5.57 (1.64-18.93)	.006*
Wide QRS complex at diagnosis	0.91 (0.413-2.00)	.815		
P wave width >90 msec	0.24 (0.10-0.52)	<.001*		
R in V^1 + S in V^6 >6.5 mm	3.10 (1.42-6.77)	.005*		
Surgical treatment	0.95 (0.47-1.91)	.878		

Abbreviations: CT ratio, cardiothoracic ratio; Hct, hematocrit; NYHA, New York Heart Association; PA, pulmonary atresia; PS, pulmonary stenosis; PV, pulmonary valve; RVOT, right ventricular outflow tract; SpO_2, percutaneous oxygen saturation; TR, tricuspid valve regurgitation; TV, tricuspid valve. Univariate and multivariate analysis by Cox regression method.
*Statistically significant at P <.05.

TABLE 3 Predictors of mortality in surgery group (n = 64)

Variable	Crude hazard ratio (95% CI)	*P* value	Adjusted hazard ratio (95% CI)	*P* value
Female gender	0.817 (0.77-6.67)	.126		
Age at surgery <1 year (neonatal and infancy period)	3.31 (1.64-6.79)	<.001*	43.5 (2.21-859.9)	.013*
NYHA functional class III-IV at diagnosis	0.908 (0.78-7.88)	.153		
SpO_2 at presentation ≤90%	0.925 (0.13-1.24)	.090		
CT ratio >0.7	2.072 (2.14-29.39)	<.001*		
Hct at diagnosis >45 g/dL	0.627 (0.64-5.36)	.248		
TV annulus *z*-score >3.80	0.796 (0.75-6.25)	.135		
TV displacement index >19.5 mm/m^2	3.807 (0.23-8.72)	.020*		
Presence of severe TR at diagnosis	0.796 (0.75-6.52)	.002*		
Absence of forward flow across PV	1.944 (2.50-19.46)	.001*		

Abbreviations: CT ratio, cardiothoracic ratio; Hct, hematocrit; NYHA, New York Heart Association; PA, pulmonary atresia; PS, pulmonary stenosis; PV, pulmonary valve; RVOT, right ventricular outflow tract; SpO_2, percutaneous oxygen saturation; TR, tricuspid valve regurgitation; TV, tricuspid valve. Univariate and multivariate analysis by Cox regression method.
*Statistically significant at P <.05.

physicians in judging the timing of an operation in some patients with EA, even though they are relatively asymptomatic.

The extreme variability and complexity of this rare congenital heart defect, reported in this cohort, are consistent with prior studies.[1,2] The most common presenting symptom was cyanosis in 39.9% of all patients, similar to the study by Celermajer and colleagues who reported cyanosis in 38% of their patients.[4] Abnormal electrocardiographic findings on initial ECG, including prolonged PR

TABLE 4 Predictors of mortality in patients who did not undergo EA surgery (n = 89)

Variable	Crude hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Female gender	−0.169 (0.31-2.30)	.74		
Age at diagnosis ≤2 years	1.248 (1.32-2.30)	.011*		
NYHA functional class III-IV at diagnosis	1.049 (0.93-8.80)	.098		
Oxygen saturation at presentation ≤90%	2.548 (2.9-56.38)	<.001*		
CXR at diagnosis CT ratio >0.7	2.621 (3.86-49.0)	<.001*	2.38 (1.17-100.11)	.036*
Hct at diagnosis >45 g/dL	1.283 (1.25-10.45)	.013*		
TV annulus *z*-score >3.80	2.293 (3.08-31.82)	<.001*	1.780 (1.10-31.93)	.039*
TV displacement index >19.5 mm/m^2	2.84 (2.2-130.60)	<.001*	1.99 (1.00-57.90)	.050*
Presence of severe TR at diagnosis	1.587 (1.70-14.01)	.002*		
Absence of forward flow across PV	3.412 (8.27-111.26)	<.001*		

Abbreviations: CT ratio, cardiothoracic ratio; CXR, chest radiography; Hct, hematocrit; NYHA, New York Heart Association; PA, pulmonary atresia; PS, pulmonary stenosis; RVOT, right ventricular outflow tract; TR, tricuspid valve regurgitation; TV, tricuspid valve.
Univariate and multivariate analysis by Cox regression method.
*Statistically significant at P <.05.

interval, RBBB pattern, preexcitation, wide QRS complex, and QRS fractionation, were documented in our cohort, as previously reported in anecdotal publications.[1,3,18] The possible substrate for the accessory pathway and preexcitation, in relation to the anatomically displaced TV leaflet, which leads to a discontinuity of the central fibrous body and septal atrioventricular ring with direct muscular connections, has been described in previous reports.[1,18] Approximately 6%-36% of the patients with EA in previous studies had at least 1 accessory pathway (AP).[2,19,20] In our study, 14 patients (10%) had preexcitation in their initial ECG. Moreover, 26 patients in the cohort (14%) experienced supraventricular tachycardia. Presence of QRS fractionation has been mentioned to be associated with a large atrialized portion of the right ventricle and a prolonged S wave upstroke time was found to be correlated with indexed right ventricular end diastolic volume in cardiac magnetic resonance imaging.[18] In our study, a prolonged S wave upstroke time of 70 ± 36 msec was reported in patients' baseline ECG. One-fourth of the patients also had QRS fractionation. Nonetheless, neither prolonged S wave upstroke time nor presence of QRS fractionation on baseline ECG was associated with mortality or arrhythmic events in the study cohort.

Several series of EA have been reported in terms of their midterm results for management in EA, with either operations or conservative medical treatments.[5,11,13,15,17] The indications for surgery in patients with EA have been recently published in a guideline for adults.[8,9] Nonetheless, certain criteria in asymptomatic patients have been long debated, because of the remarkable variation in anatomy and hemodynamics of these patients. In our cohort, 64 patients with EA (41.8%) underwent surgical intervention. With regard to their demographics, operated and unoperated patients had clinically different TV *z*-scores and the presence of RVOT obstruction. Of the 64 patients who had operations, 49 patients had biventricular repair, 10 had one and a half ventricular repair, and 5 had univentricular palliation in their final surgical strategy. In our series, 15 patients underwent their first EA surgery during the neonatal period and infancy. The perioperative mortality rate (30-day mortality postoperatively) in our center was 14%, which is comparable to the multicenter study from a Dutch pediatric heart center.[14] This rate appears to be higher than that of the large-scale study from the Mayo clinic[11] and the Society of Thoracic Surgeons Congenital Heart Surgery Database (STS-CHSD),[15] which reported perioperative mortality of 5.9%. The latter study also reported that in-hospital mortality was high in neonatal patients (23.4%), in comparison to infants (4.1%), children (0.7%), and adults (1.1%). Late death due to major adverse cardiac events occurred in another 6 patients in our cohort, accounting for an overall mortality in the surgery group of 23%. The 1, 5, and 10 year survival in our patients who had EA surgery after operation was 85.9%, 82.3%, and 74.2%, respectively, which was less than that of the Mayo clinic group that reported survival of 92%, 88%, and 85% at 1, 5, and 10 years, respectively, in adults with EA surgery.[11] Age at surgery is hypothesized to affect mortality outcomes since two-thirds of our EA surgeries were performed in pediatrics. We, therefore, explored age group–relevant deaths in the 64 patients who had EA surgery. The association between surgery in pediatrics (age under 18 years, n = 42) and mortality was not statistically significant (P = .15). Nevertheless, EA surgery in neonates and infants is only one of the independent mortality risks, as reported previously.[15,16]

Of the 89 unoperated patients with EA in the cohort, survival at 1, 5, and 10 years after diagnosis were 89.9%, 87.5%, and 81.8%, respectively. In a previous study of 72 unoperated adult patients between 1972 and 1997, the authors found that the predictors of cardiac-related death in severe forms of EA, were male sex, cyanosis, worse functional class, severe TR, and early age at diagnosis.[5] In the present study, the significant mortality risks in the multivariate model were cardiothoracic ratio >0.7 on chest radiography (hazard ratio 2.38, 95% CI: 1.17-100.11, $P = .03$), TV annulus z-score >3.80 (hazard ratio 1.78, 95% CI: 1.1-31.9, $P = .03$), and TV displacement index >19.5 mm/m^2 (hazard ratio 1.99, 95% CI: 1.0-57.9, $P = .05$). The variables that were indicated in a prior publication,[5] such as age at diagnosis <2 years, cyanosis, elevated hematocrit, severe TR, and RVOT obstruction were only dependent risks in the univariate analysis. These findings suggest that patients who are relatively asymptomatic or are receiving a conservative treatment for EA and have a larger CT ratio (>0.7), a TV annulus dilation to z-score >3.8, or a marked TV displacement index >19.5 mm/m^2 should be cautiously managed and be especially aware of adverse cardiac events. These simple and feasible measurements may aid physicians in the treatment and follow-up of unoperated patients. Further research should be conducted using aggregate data.

5 | STUDY LIMITATIONS

We acknowledge several limitations in this retrospective study of the rare EA disease. Over the 20-year period covered by the research, bias cannot always be excluded due to the retrospective nature. We included only patients with EA who were newly diagnosed and confirmed with 2D-TTE by a cardiologist in the center. We excluded patients who had been diagnosed with EA but had a repaired EA from other hospitals. All ECG and echocardiographic measurements were retrieved and reviewed carefully. Our retrospective data lacked some of the variables that could have been prognostic factors, such as GOSE score, RV volume, magnetic resonance data, and brain natriuretic peptide level. In echocardiographic measurement, TV displacement index was limited in six patients who had severely displaced TV insertion to right ventricular outflow tract. The authors decided not to interpret their TV displacement value. To deal with the immortal time bias, the age of patients was explored first and we found that patients who had died or had survived in the study were not statistically different, using the survival endpoint as the date of mortality. In the survival analysis, time of diagnosis was counted as time 0. In the EA surgery group, we also analyzed survival after operation using time 0 as the date of operation. All 153 patients were contacted in 2017 to confirm their functional class and their status as either dead or alive. We are aware that the techniques of surgical repair for EA and its management have changed over time. Nevertheless, the decision making for EA, especially from a surgical perspective, and in our center, is done by surgeons and cardiologists. The technique of repair, however, is not the aim or scope of this study. Lastly, this study includes a small number of patients and a mixed patient population of adults and pediatrics since EA is a rare congenital heart defect. A mixed population would provide more information regarding the natural history and predictors. Some predictors were chosen to use indexed values and z-scores.

6 | CONCLUSIONS

We report a moderately good long-term survival of patients with EA, based on data from a large, single-center cohort in Thailand. At the median time of 5.2 years, the 1-, 5-, and 10-year survival rates were 88.9%, 82.2%, and 78%, respectively. Important predictors of death for overall EA include age at diagnosis ≤2 years, TV annulus z-score >3.80, TV displacement index >19.5 mm/m^2, presence of severe TR at diagnosis, and absence of forward flow across the PV. For patients who undergo surgery, the mortality risk is highest among those undergoing surgery as neonates and infants. In unoperated patients with EA, predictors of mortality are cardiothoracic ratio >0.7 on chest radiography, TV annulus z-score >3.80, and TV displacement index >19.5 mm/m^2. These simple variables may help physicians in making decisions for the care of patients with EA.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest with the contents of this article.

AUTHOR CONTRIBUTIONS

Concept/design: Vijarnsorn.
Data analysis/interpretation: Vijarnsorn, Pornprasertchai.
Data collection: Pornprasertchai.
Drafting article: Vijarnsorn, Pornprasertchai.
Critical revision of article: Vijarnsorn, Kanjanauthai, Durongpisitkul, Soongswang.
Approval of article: Vijarnsorn, Pornprasertchai, Kanjanauthi, Chungsomprasong, Chanthong, Durongpisitkul, Soongswang.
All authors read and approved the final version of the manuscript.

ORCID

Chodchanok Vijarnsorn https://orcid.org/0000-0001-7124-2064

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