Ebstein’s anomaly: factors associated with death in childhood and adolescence: a multi-centre, long-term study

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Aims The objective of this study is to establish factors associated with death after diagnosis of Ebstein’s anomaly (EA) during childhood and adolescence.

Methods and results This study is a retrospective chart review. All paediatric patients were diagnosed with EA and followed in tertiary-care university hospitals between 1980 and 2005. Factors associated with death were obtained using the Cox regression and log-rank tests. Of the 93 patients with EA, 18 (19%) died and 75 (81%) survived. The median age at EA diagnosis and follow-up was 0 (range 0–162) and 86 months (range 0–216), respectively. After 35 months of diagnosis, the Kaplan–Meier survival probability remains stable at 80%. Young age at presentation (<2 years), hepatomegaly, the need for medication (diuretics and Prostin) and mechanical ventilation at presentation, pulmonary valve defects (defined as moderate-to-severe pulmonary stenosis and pulmonary atresia), patent arterial duct, and ventricular septal defect were significantly associated with death.

Conclusion The overall survival of patients with EA during childhood and adolescence has dramatically improved when compared with earlier reports.

KEYWORDS
Ebstein; Children; Risk factors; Death; Survival

Introduction

Ebstein’s anomaly (EA) is a rare congenital heart malformation; it accounts for <1% of all congenital heart disease.1 Previous reports on the natural history of patients with EA are disappointing and depend on the severity of the malformation. These studies often include a mixed population of foetuses, neonates, young children, adolescents and adults.2–7 Consequently, both the clinical course and the survival time are variables and are often disappointing when compared with the outcome of other congenital heart defects. Although several risk factors have been associated with survival, there is no general consensus.1–16 The objective of this retrospective study was to establish factors associated with death during childhood and adolescence.

Methods

Patients
All six paediatric heart centres were approached with a request to grant access to the medical records of all consecutive live-born patients with EA, diagnosed, and followed by a paediatric cardiologist between 1 January 1980 (when echocardiography was routinely used) and 30 March 2005. An apical or downward displacement of the tricuspid valve from the atrioventricular valve ring <0.8 cm/m² body surface area was set as the criterion for EA. The only patients excluded were those with congenital corrected transposition of the great arteries. Other cardiac associated anomalies were included in the analysis of risk factors.

Methods
A full cohort study was performed on the peri- and neonatal course along with the follow-up period during childhood and adolescence. Demographic and functional parameters, including age, gender, weight, pre-natal diagnosis, duration of pregnancy, and extracardiac pathology, were evaluated. Data on physical examination, echocardiography, chest X-ray, electrophysiology, cardiac catheterization, surgery, post-surgical complication, and necropsy between
1980 and 2005 were collected. Investigations and management decisions were noted as determined by the paediatric cardiologist in each centre.

**Statistical methods**

The Kaplan–Meier survival curve during childhood and adolescence in each centre. intervals and P-values resulting from Wald tests. We checked the assumption of proportional hazards using scaled Schoenfeld residuals. We inspected the linearity assumption for each continuous variable using martingale residuals obtained from fitting the model that contains no covariates. These residuals are then plotted against the values of the covariate together with a Lowess smoother and 95% confidence bands to indicate the functional form that the variable should have in the univariate Cox regression analysis. Univariate analysis was performed on different variables concerning general data, physical examination, additional examination, and surgery. Dichotomous variables, with the factors present in ≤10 or ≥90% of the patients, have been excluded from statistical analysis. The final list of analysed variables is described in Table 1.

For statistical analysis, SAS version 8.0 was used. Statistical significance was assigned at a P-value of ≤0.05 (two-tailed).

### Table 1 Factors used for survival analysis

<table>
<thead>
<tr>
<th>General data</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>X-Thorax</td>
</tr>
<tr>
<td>Gestational age &lt; 37 weeks</td>
<td>Cardiothoracic ratio &gt; 0.65</td>
</tr>
<tr>
<td>Birth weight</td>
<td>Decreased pulmonary vascularity</td>
</tr>
<tr>
<td>Young age at presentation (≤12 months)</td>
<td>Electrocardiogram (ECG)</td>
</tr>
<tr>
<td>Time of diagnosis (measured in months from 1 January 1980)</td>
<td>Peked P-wave (&gt;2.5 mm on lead II)</td>
</tr>
<tr>
<td>Physical examination</td>
<td>Prolonged PR-interval</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>Echocardiography</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>≥0.8 cm²/m² apical displacement</td>
</tr>
<tr>
<td>Heart murmurs</td>
<td>Pulmonary atresia/stenosis</td>
</tr>
<tr>
<td>Need of Medication</td>
<td>Moderate-to-severe tricuspid regurgitation</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>Right atrial dilatation</td>
</tr>
<tr>
<td></td>
<td>Patent arterial duct, shunt</td>
</tr>
<tr>
<td></td>
<td>Patent foramen ovale, atrial and ventricular septal defects</td>
</tr>
</tbody>
</table>

All these variables have no missing values, except for birth weight with 25 missings. All these variables are dichotomous, except for the continuous variables birth weight, and time of diagnosis measured in months from 1 January 1980.

### Results

In The Netherlands, between 1980 and 2005, 108 paediatric patients were diagnosed with EA. Fifteen medical records were excluded: four patients had an incomplete record, two patients were misdiagnosed as confirmed on a second echocardiography, eight patients were born before 1980, and one patient was born, diagnosed, and followed in another country. Finally, 93 paediatric patients were included in this large study: 41 males and 52 females. The median age at EA diagnosis was 0 months (range 0–162). Among the total group, 60 (64.5%) patients were diagnosed during the first 2 months of life (only seven were diagnosed with EA during foetal life), 66 (71%) during their first year of life, and only 27 (29%) beyond the first year of age (median age of 49 months, range 15–162). The mean ± SD of gestational age and birth weight of the 93 patients were 39 ± 3 weeks and 3.2 ± 0.6 kg, respectively. Twelve patients were born by caesarean section, only six due to foetal distress. Of the 93 patients, three presented in the period from 1981 to 1985, 16 from 1986 to 1990, 28 from 1991 to 1995, 26 from 1996 to 2000, and 20 from 2001 to 2005 (Table 2).

In all patients, the diagnosis of EA was based on the echocardiographic data using the apical displacement. Both the Celermajer grading and the Carpentier classification were used only once. Supplementary cardiac catheterization had been sporadically performed (5.4%).

On physical examination, 68 (73%) patients presented with a heart murmur, 41 (44%) patients were cyanotic, and 13 (14%) patients were found with clinical hepatomegaly. Eight (8.6%) patients had tachypnoea, six (6.5%) dyspnoea, and five (5.4%) patients presented with a supraventricular arrhythmia. Nine patients had no abnormalities on physical examination. Patients older than 1 year at presentation had significantly more symptoms of fatigue (P < 0.001). Cyanosis was more common in patients younger than 1 year at presentation (P < 0.001).

Nineteen (20.4%) patients were mechanically ventilated at presentation, of whom 12 after receiving Prostin medication. Of the 93 patients, 38 (41%) required medication (e.g. Prostin n = 23, diuretics n = 15, digitals n = 14, and inotropics n = 5) at presentation. Patients receiving Prostin were all in the neonatal period. Patients who were diagnosed during the first year of life received significantly more medication in comparison with those patients diagnosed later in life (P < 0.001).

Extracardiac and genetic abnormalities were rare; only three patients underwent chromosomal investigation (all normal). Extracardiac morbidity was present in 35% of the patients: most common were asthma (n = 5) and mental retardation (n = 6).

Thirty (32%) patients with EA underwent at least one surgical treatment during childhood and adolescence. The indications for operation were overt heart failure, cyanosis, and acidosis associated with tricuspid regurgitation, depressed right ventricular function, and severe cardiomegaly. The median age at the first operation was 38 months (range 0–185). The first operation took place between 1989 and 2005. Both univentricular and biventricular procedures were common, with or without valve repair. Seventy-five (81%) patients were alive at the end of the study with a median age of 124 months (~10 years, range 3–216 months, Table 2). The median follow-up after diagnosis
The mean body mass index standard deviation score was also slightly decreased (mean BMI-SDS $2 \pm 0.27$). Information on the parents height and BMI was not available. During the follow-up period, 11 (12% of the whole paediatric EA population) patients presented with, most commonly, supraventricular rhythm disorders requiring hospitalization and, in 6 patients, catheter ablation. At the end of the study, only two patients were on beta-blocker therapy continuously because of rhythm disturbances. Furthermore, 18 (19%) patients had complaints of slight fatigue (defined as New York Heart Association class II), with little use of one (or combination of) medication, for example, diuretics $n = 1$, angiotensin-converting enzyme blocker $n = 1$, digitalis $n = 1$, beta-blocker $n = 4$ and aspirin $n = 2$. The other 58 alive patients had no significant functional impairment and were all in New York Heart Association class I at the end of the study.

Fourteen patients died during the neonatal period ($\leq 1$ month), one patient died before the age of 1 year, and three patients died after infancy. The cause of death is shown in Table 3. Of the 18 deceased patients, six had surgery. Four operated patients died after their first procedure and two after their second procedure: univentricular approach (Starnes procedure) $n = 1$, palliative systemic pulmonary Blalock Taussig (BT) shunt $n = 2$, miscellaneous [aortic arch reconstruction with closure of ventricular-VSD and atrial septal defects] $n = 1$, BT shunt followed by tricuspid valve repair during the second procedure $n = 1$, and univentricular approach (Starnes procedure) followed by BT shunt during the second procedure $n = 1$; all six died during the early post-operative period (within 30 days of last surgery), with cardiogenic shock, the most frequent cause of death ($n = 5$). Of the 75 patients alive at last follow-up, 15 patients had already been referred to an adult cardiologist.

Survival after Ebstein's anomaly diagnosis in the whole population

Survival after EA diagnosis was estimated using the Kaplan–Meier method (Figure 1). At the first month after diagnosis, 12 patients had died resulting in a probability of survival of 0.87 (95% CI: 0.80–0.94). At 12 months after diagnosis, 16 patients had died and five censored resulting in a survival probability of 0.83 (95% CI: 0.75–0.90). Two other patients died at 15 and 35 months after EA diagnosis. After 35 months of diagnosis, the Kaplan–Meier survival probability remains stable at 80% (95% CI: 0.72–0.89).

Factors associated with death in childhood and adolescence

Using univariate Cox regression analysis, the following factors were negatively associated with time from diagnosis until death (see also Table 4):

Young age at presentation ($\leq 12$ months) was significantly associated with death (hazard ratio 7.9, 95% CI: 1.05–59.2), which means that the estimated short-term mortality risk among patients diagnosed before the age of 1 year was 7.9 times the risk in the group of patients diagnosed after 1 year of age.

Male sex, gestational age, and birth weight were not significantly associated with the outcome in this study population.

Hepatomegaly at the time of EA diagnosis was significantly associated with death (HR 3.4, 95% CI: 1.3–9.1).
The need of mechanical ventilation at presentation was also associated with shorter survival time (HR 6.8, 95% CI: 2.7–17.3). The need of medication at presentation (HR 8.3, 95% CI: 2.4–28.7), for example, diuretics and Prostin, was significantly associated with death. The findings on the chest X-ray and ECG did not reach a significant level. In the current study, very few patients had arrhythmias as a presenting feature.

On echocardiography, cardiac defects that were significantly associated with death were patent arterial duct (HR 3.1, 95% CI: 1.2–8.4) and VSD (HR 4.7, 95% CI: 1.8–12.5). Pulmonary valve defects, defined as moderate-to-severe pulmonary stenosis and pulmonary atresia, were significantly related to an adverse outcome (HR 5.8, 95% CI: 2.3–14.7). Moderate-to-severe tricuspid regurgitation did not reach significance at the 5% level (HR 2.6, 95% CI: 0.9–7.2, \( P = 0.07 \)).

No association was found between the need for operation and survival.


**Discussion**

Neonatal presentation of EA of the tricuspid valve is a rare cardiac condition with poor prognosis. Most studies identifying predictors of a long-term outcome involve mixed populations from foetal to late adult life. Previous reports have shown that foetuses and symptomatic newborns have a significantly more adverse outcome than older children.\(^2\)\(^7\) Diagnosis and death in utero are often related to patients at the severe end of the spectrum.\(^20\) The inference from the Kaplan–Meier survival analysis in a cohort of subjects of various ages may be misleading. This current study constrains itself to live-born patients seen by paediatric cardiologists and identifies factors associated with death in childhood and adolescence. It does not include patients diagnosed beyond adolescence. Furthermore, the cohort includes EA patients from recent era (after 1980), which has seen an improvement in neonatal and post-operative cardiac management that influenced the morbidity and mortality in this group of patients.

Eighteen of the 93 patients died, 14 during the neonatal period. After 35 months of diagnosis, the Kaplan–Meier survival probability remains stable at 80% (95% CI: 0.72–0.89). Seventy-five (81%) patients were alive at the end of the study with a median age of 124 months (~10 years).

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**Table 4** Factors associated with survival time after diagnosis of Ebstein’s anomaly

<table>
<thead>
<tr>
<th>Feature</th>
<th>HR</th>
<th>95% CI</th>
<th>( P )-value</th>
<th>Wald</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young age at presentation (&lt;12 months)</td>
<td>7.9</td>
<td>1.05–59.2</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Gestational age≤37 weeks</td>
<td>1.6</td>
<td>0.45–5.4</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>3.4</td>
<td>1.3–9.1</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>6.8</td>
<td>2.7–17.3</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td>8.3</td>
<td>2.4–28.7</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Patent arterial duct</td>
<td>3.1</td>
<td>1.2–8.4</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>4.7</td>
<td>1.8–12.5</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Pulmonary valve defects</td>
<td>5.8</td>
<td>2.3–14.7</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Moderate and severe tricuspid regurgitation</td>
<td>2.6</td>
<td>0.9–7.2</td>
<td>0.07</td>
<td></td>
</tr>
</tbody>
</table>

Cox proportional hazards models. HR, hazard ratio.
study of Celermajer et al.\textsuperscript{3} reported an actuarial survival for all live-born patients of 67\% at 1 year and 59\% at 10 years. When limiting the population studied to the neonates diagnosed at birth, we find more optimistic numbers: Kaplan–Meier survival 76\% (95\% CI: 63–88) at 1 year and 73\% (95\% CI: 61–86) at 10 years. This might be due to the era in which the study population was diagnosed: 1958–1991 in the Celermajer study vs. 1980–2005 in the present study. This is also applicable to the study of Hong and Möller,\textsuperscript{12} with their patients evaluated between 1947 and 1990. They found that nearly half of the infants died during the first year of life. The authors believe that the improvement of the diagnostic methods, current neonatal care, and the substantial improvements of new surgical approaches during infancy and childhood might have dramatically improved the survival rate in the current study.

In this study, emerging factors for death were young age at presentation (≤12 months), hepatomegaly, requiring mechanical ventilation and medication, pulmonary valve defects, patent arterial duct, and VSD.

Diagnosis made during foetal life (only seven of the 93 patients) could not be analysed as a risk factor in this study (n < 10). The predictive value of the latter could have been underestimated even when fully reported, as foetuses with the worst spectrum of EA might die already in early pregnancy, before referral to pre-natal diagnosis could take place. Early post-natal presentation has emerged as a predictor of death. This is similar to some of the previous studies.\textsuperscript{2,3,7,8,11,12} Gentles et al.\textsuperscript{4} found male sex to be a predictor of death. However, gender does not play a role as a predictor of death in the current study, nor did it in another previous study performed by Attie et al.\textsuperscript{2}

Celermajer et al.\textsuperscript{11} found that patients who were symptomatic or had significant cardiac enlargement during the neonatal period had poor prognosis. As hepatomegaly and the need of mechanical ventilation are indicators of heart failure, it is not surprising that they are significant predictors of death during early childhood. In addition, the need for medication, e.g. diuretics and Prostin, as risk factors for a poor outcome was not unexpected.

Cyansis and arrhythmias were not found to be risk factors for death in the current study, nor in the study of Celermajer et al.\textsuperscript{11} Other authors (Attie et al.\textsuperscript{2} and Giuliani et al.\textsuperscript{8}) did find cyanosis to be a risk factor. The difference between their studies and the present one is the population studied: adults vs. children. If an adult with EA develops cyanosis later in life, with the cyanosis as the presenting feature, it indicates deterioration in heart function. The older age of Attie’s population could also explain why arrhythmias were a frequent presenting feature in contrast to our patient group. Yetman et al.\textsuperscript{13} had studied neonates. They did find a significant difference between the cyanotic neonates and those without cyanosis. If this current study would only limit itself to neonates, the clinical symptom of cyanosis still does not reach significance. A possible explanation is the time span of the studied population. Yetman et al.\textsuperscript{13} had a time span between 1954 and 1996. Before 1980, echocardiography for diagnosis was not available and surgical techniques were not optimal. Therefore, there could be several biases: (i) not all neonates had EA, (ii) neonates with EA were not diagnosed, because of the absence of cyanosis, and (iii) the treatment was not up to the current standards.

Severe tricuspid regurgitation has already emerged as a risk factor in the studies done by Yetman et al.\textsuperscript{13} and Attie et al.\textsuperscript{2} Although one would consider a certain tricuspid regurgitation as moderate, another might consider it as severe and vice versa. In the current study, the majority of the patients were assessed with tricuspid regurgitation. The severity of tricuspid regurgitation (moderate and severe vs. mild and none) was not associated with death.

Patent arterial duct and VSD were significantly associated with death. In neonates with EA, prolonged patency of the arterial duct in patients without anatomic right ventricular outflow tract obstruction was recently reported to be deleterious.\textsuperscript{21} We postulate that these types of ‘circular shunts’ may develop in patients with pulmonary and tricuspid insufficiency in combination with VSD as well.

It is not surprising that pulmonary valve defects were found to be predictors of death in our study. Associated cardiac abnormalities, pulmonary stenosis, and pulmonary atresia were common in other reports.\textsuperscript{3,7,11} Structural pulmonary valve abnormalities are most likely secondary to the tricuspid valve anomaly, resulting from the low anterograde flow during tract development.\textsuperscript{3} Coexisting pulmonary atresia, be it structural or functional, is already recognized as a predictor of poor outcome.\textsuperscript{2,22}

Earlier published studies, e.g. Watson,\textsuperscript{5} suggested that surgery should not be performed during childhood. As mentioned by Attenhofer et al.\textsuperscript{1} this was before the echocardiographic era, implicating that this does not reflect the population studied in the current study. Others, e.g. Knott-Craig et al.\textsuperscript{23} Starnes et al.\textsuperscript{24} Pflaumer et al.\textsuperscript{16} and Arizmendi et al.\textsuperscript{7} conclude that univentricular and biventricular repairs of EA in the critically ill neonates are feasible and the repair seems durable. In the present study, biventricular and univentricular procedures were carried out successfully. However, it is not possible to conclude that (specific type of) surgery is a risk factor for death or a treatment that improves outcome by means of survival, because no randomization took place, and different types of operations were performed in a small number of patients by several surgeons. The latter was also confirmed by Saris et al.\textsuperscript{25}

Statistical model
An attempt to set up a preliminary survival prediction model was made. The multivariable Cox proportional hazard regression analysis resulted in a combination of three variables (requiring mechanical ventilation, pulmonary valve defects, and VSD) that could predict death after diagnosis of EA was made. However, from statistical point of view, the low number of death (n = 18) is a strong contraindication to perform multivariable regression analysis with more than two predictors. Therefore, we limited our results to the univariate analysis.

Study limitations
This is a retrospective study of all consecutive live-born EA patients referred to six paediatric heart centres over a 25-year period. Some variables, e.g. pre-natal diagnosis, were not yet available. Recent studies on EA use the Celermajer severity score,\textsuperscript{2,13,15,23} Carpentier’s classification,\textsuperscript{26} or septal leaflet attachment ratio.\textsuperscript{4} However, even in these...
studies, the Celermajer severity score was not always assessed at presentation. It was done later in life or retrospectively on ‘available echocardiographic data’, as this score was introduced only in the 1990s. As no grading like this occurred in The Netherlands, this factor was not studied in the analyses.

As mentioned by Celermajer et al., a consequence of a retrospective study is the individualization of the timing and type of investigations and treatment. Some of the echocardiographic data were no longer available for review. The quality of both the echocardiographic equipment and type of investigations and treatment. Some of the important variables rather than just echocardiography. The EA diagnoses were made by a selected group of (experienced) paediatric cardiologists working in all the six tertiary centres. The participation of all paediatric heart centres was crucial for the inclusion of such a large paediatric population.

Conclusions

This study has investigated the factors that were associated with death after the diagnosis of EA in childhood and adolescence. There was no death registered after the age of 49 months. On the basis of this large paediatric cohort of patients, the factors associated with death were already assessed at diagnosis. Age at presentation (<12 months), hepatomegaly, need for mechanical ventilation and medication, and associated cardiac abnormalities were strongly associated with death early in childhood.

In the present review, the survival of patients with EA during childhood and adolescence has improved dramatically: after 35 months of diagnosis, the Kaplan–Meier survival probability remains stable at 80% (95% CI: 0.72–0.89). We strongly believe that the improvement of diagnostic methods, current neonatal care, and the new catheter and surgical interventions will further improve their outcome.

Acknowledgement

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Conflict of interest: none declared.

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