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Prediction of Perinatal Mortality in Ebstein's Anomaly Diagnosed in the Second Trimester of Pregnancy

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Keywords
Congenital heart defects · Ebstein's anomaly · Tricuspid valve anomaly · Fetal echocardiography · Prenatal diagnosis

Abstract
Objectives: Firstly, to describe the outcome of a series of fetuses with Ebstein's anomaly (EA) and, secondly, to study the utility of different second-trimester echocardiographic parameters to predict fetal and neonatal mortality. ***Methods:*** 39 fetuses with EA diagnosed between 18 and 28 weeks of gestation were included. Fetal echocardiography included the cardiothoracic ratio (CTR); right atrial (RA) area index; displacement of the tricuspid valve (TV); tricuspid regurgitation; pulmonary artery; and ductus arteriosus flow characteristics. Additionally, 2 novel parameters were obtained: the relative RA area ratio (RA area/cardiac area) and the TV displacement index (TVDI, TV displacement distance/longitudinal diameter of the left ventricle). Correlation between the echocardiographic variables and the primary outcome of perinatal mortality or survival at 1 year of life was evaluated. ***Results:*** From the initial cohort, 8 cases were excluded due to complex congenital heart defects. Termination of pregnancy (TOP) was performed in 15 cases, and fetal death was diagnosed in 3 cases. In the live-born cohort of 13 patients, 4 died in the neonatal period, yielding a perinatal survival rate of 29 and 56%, respectively, after excluding TOP cases. Compared with survivors, nonsurvivors showed a significantly higher CTR (56.7 ± 16.2 vs. 42.6 ± 8.6; $p = 0.04$), relative RA area ratio (0.39 ± 0.13 vs. 0.25 ± 0.05; $p = 0.01$), and TVDI (0.62 ± 0.17 vs. 0.44 ± 0.12; $p = 0.03$) at diagnosis. The best model to predict perinatal mortality was obtained by using a scoring system which included the relative RA area ratio and TVDI (AUC 0.905 [95% CI 0.732–1.000]). ***Conclusions:*** Fetuses with a relative RA area ratio ≥0.29 and TVDI ≥0.65 at the second trimester have the highest risk of dying in the perinatal stage.

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Introduction

Ebstein's anomaly (EA) is a special form of tricuspid valve (TV) dysplasia in which the septal and mural leaflets are displaced into the inlet component of the right ventricle (RV). It affects 1 in 20,000 live births and represents 0.5% of congenital heart defects (CHD) [1, 2]. The abnormal TV location divides the RV into a proximal atrialized and nonfunctional segment and a distal small ventricular chamber, which, combined with a variable degree of valve dysplasia, leads to tricuspid regurgitation (TR) and RV dysfunction. EA encompasses a broad morphologic and functional spectrum, and while it is usually well tolerated when diagnosed in childhood, the identification of this CHD in the fetal or perinatal period usually entails a poor prognosis [3–5].

Studies on perinatal outcome published until the first decade of this century reported fetal and neonatal mortality rates ranging between 50 and 85%, respectively [5–9]. These figures were mainly due to the detection of the most severe forms of EA in the prenatal stage, with most cases being associated with marked cardiomegaly, severe TR, hydrops, and arrhythmias. However, more recent studies have shown improved results [3, 10, 11]. This improvement in EA prognosis may be attributed, firstly, to the advances in prenatal diagnosis, which would allow the identification of milder forms associated with a lower risk of early neonatal complications and, secondly, to the improvement in early neonatal support, surgical techniques, and postsurgical care during the last decades [12], which have managed to decrease early neonatal mortality below 30% [3, 4, 11].

The evolving nature of EA makes parental counseling particularly difficult whenever this condition is diagnosed prenatally, and, especially, when the diagnosis is made in the second trimester of pregnancy. Different fetal echocardiographic parameters, such as increases in the cardiothoracic area [9], right atrial (RA) area index (RAAI) [7–9, 13, 14], RV/left ventricle (LV) ratio [9], TV functional diameter [8], TR [8], and the absence of pulmonary forward flow [7, 8, 10], have been associated with perinatal mortality. However, the results of most of these studies were limited by their small sample size. Recently, larger studies [11], including a multicenter study performed across North America [3], but including fetuses with either EA or TV dysplasia, have identified new prenatal predictors such as the presence of pulmonary regurgitation [3] and the increase in the LV myocardial performance index [15]. Moreover, new prognostic scoring scales [11, 15] have also been proposed. Although these recent data are highly valuable to improve current antenatal advice in EA, information is still scarce regarding these and other potential echocardiographic predictors in the second trimester of pregnancy [4]. Therefore, given that (1) EA is an evolving CHD in fetal life and (2) currently EA is often diagnosed at an earlier gestational age, further studies evaluating prenatal echocardiographic predictors at the second trimester of pregnancy are necessary.

The aims of our study were, firstly, to describe the outcome of a series of fetuses with prenatally diagnosed EA in the second trimester in 2 tertiary-care referral centers in Spain and, secondly, to study the utility of different echocardiographic parameters evaluated at second-trimester pregnancy to predict fetal and neonatal mortality.

Methods

Study Population

Fetuses with EA diagnosed between 18 and 28 weeks of pregnancy were retrospectively recruited from a cohort of fetal CHD evaluated from January 2002 to November 2018 at BCNatal, Hospital Clínic and Hospital Sant Joan de Déu, in Barcelona and the Hospital Universitario 12 de Octubre in Madrid, 2 tertiary referral centers for prenatal diagnosis and management of CHD in Spain. EA was defined as a displacement of the septal and/or posterior leaflets of the TV into the inlet component of the RV, which determined a variable degree of tricuspid dysplasia with TR (Fig. 1). Baseline, echocardiographic, and perinatal characteristics were collected from medical registers, recorded videos, and databases of the fetal cardiology units. Fetal ultrasound examination, including a detailed extracardiac structural survey and complete echocardiography, was performed by fetal medicine specialists together with pediatric cardiologists, and following the standardized guidelines of the International Society of Ultrasound in Obstetrics and Gynecology and other expert guidelines [16, 17]. Gestational age (GA) was calculated based on the crown-rump length obtained at first-trimester ultrasound [18] or biparietal diameter [19] if the first was not available. An invasive procedure was offered in all cases in which the karyotype was unknown at the time of diagnosis. In the last 3 years of the study period, microarray comparative genomic hybridization was offered. The study was approved by the institutional ethics committees of both centers.

Baseline and Perinatal Characteristics

Reason for referral, GA at diagnosis, associated cardiac or extracardiac abnormalities, presence of chromosomal anomalies, pregnancy outcome, including termination of pregnancy (TOP), intrauterine fetal death (IFD), and neonatal death, GA at delivery, birth weight, Apgar score at 5 min, and umbilical artery gasometry at delivery, as well as necessity for and the type of surgery were recorded.

All fetuses underwent serial follow-up evaluations from diagnosis until delivery in order to monitor cardiac function, fetal growth, and the presence of hydrops. The reliability of the diagnosis was confirmed by postnatal pediatric cardiologist examination

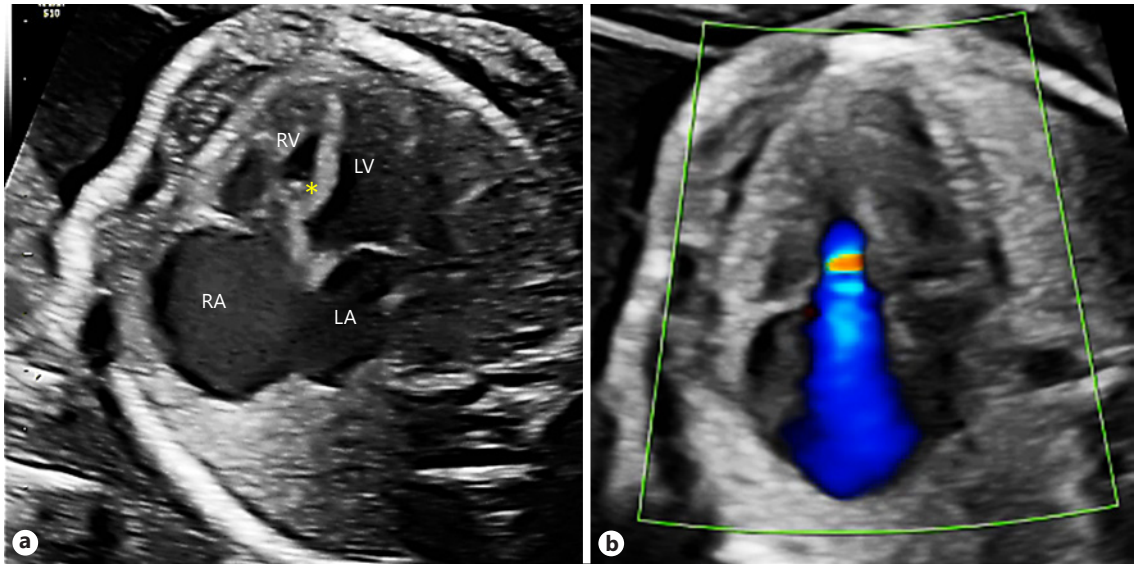

Fig. 1. Ebstein's anomaly diagnosed at 22 weeks of gestation. **a** End-diastolic 4-chamber view showing the displacement of the tricuspid septal and posterior leaflets into the inlet portion of the right ventricle (RV; yellow asterisk). **b** Same case at end-systolic phase illustrating the significant tricuspid regurgitation, which reached the posterior wall of the right atrium (RA; blue color Doppler signal). LA, left atrium; LV, left ventricle.

or by autopsy in cases of TOP or perinatal death. Presence of chromosomal anomalies was also excluded by postnatal clinical examination in the cases in which a genetic study was not carried out during pregnancy.

Postnatal Outcomes

Postnatal management was uniform in both centers. Our standard practice was to perform an echocardiography on the first day of life. Prostaglandin E1 infusion was started if oxygen saturation in the neonate was <85% or if anterograde pulmonary flow was absent. Serial echocardiographic and clinical evaluations were performed in order to assess RV adaptation to the drop in pulmonary vascular resistance within the first days of life. Prostaglandin E1 infusion was stopped if RV performance was good enough to maintain oxygen saturation >85%. Thereafter, patients were discharged with close ambulatory control during the first year of life. On the other hand, patients with severe EA and need of ductal patency were treated in the single ventricle pathway with a systemic-pulmonary shunt or a ductal stent in the neonatal period, and then a Starnes procedure and cavopulmonary anastomosis [12]. Postnatal follow-up for at least 12 months was available for all surviving patients.

Fetal Echocardiography

The following echocardiographic data were systematically obtained at the time of diagnosis:

1 Cardiac size and cardiothoracic ratio (CTR), defined as cardiac area/thoracic area; severe cardiomegaly was defined as CTR >50%.
2 RAAI [13], defined as the ratio between the combined area of the RA and the atrialized RV to that of the functional RV and left heart in a 4-chamber view at end-systole.
3 Displacement of the septal and/or posterior leaflets from the tricuspid annulus; we classified it as severe when it was barely visible due to a very apical insertion below the moderator band; we also measured the functional tricuspid ring (Fig. 2).
4 Maximum TR velocity; TR severity was also graded qualitatively as mild (narrow jet), moderate (broad jet not reaching the RA posterior wall), and severe (broad jet reaching the RA posterior wall or severe RA dilatation) [11].
5 Pulmonary trunk filling was categorized as anterograde or ductus-dependent retrograde flow; presence of pulmonary insufficiency was also qualitatively evaluated.
6 Maximum systolic peak velocity in the aorta and pulmonary artery (if anterograde flow was present).
7 Umbilical artery diastolic flow was qualitatively classified as anterograde, absent, or reversed.
8 Ductus venous flow was classified as normal or absent/retrograde during the atrial contraction.

In addition to the above-detailed parameters, we retrospectively calculated the SickKids score for all cases (as shown in online suppl. Table 1; for all online supplementary material, see www.karger.com/doi/10.1159/000504979) [11], and we also measured 2 novel parameters (Fig. 2):

1 TV displacement index (TVDI), defined as the ratio between the distance of the TV displacement from the tricuspid annulus and the longitudinal diameter of the LV at end-diastole.
2 Relative RA area ratio, defined as the ratio between RA area and total cardiac area at end-systole.

For these indices, we re-analyzed all our cases using the frame-by-frame cine-loop function. As shown in Figure 2, end-diastole was defined as the frame at which the mitral valve closes, and, thus, the LV reaches it largest size. LV longitudinal diameter was measured from the mitral valve ring to the apex including the endocardium.

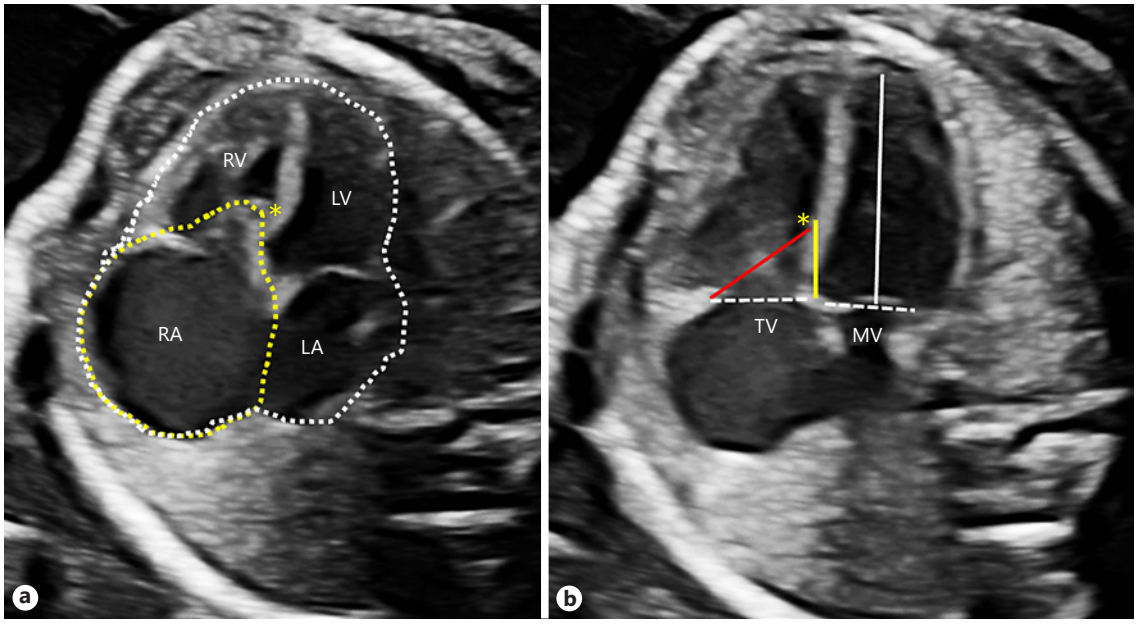

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Fig. 2. a Calculation of relative right atrium (RA) area ratio in 4-chamber view at end-diastole. The yellow asterisk marks the tricuspid displacement into the right ventricle. The relative RA area ratio was obtained as the ratio between the combined area of the RA and the atrialized RV (yellow dotted line) to cardiac area (white dotted line). **b** Measurement of the functional tricuspid ring (red line) and the displacement of the tricuspid valve from the tricuspid annulus (yellow line). The image also illustrates the measurement of left ventricular length (white line). The tricuspid displacement to left ventricular length ratio (TVDI) was calculated by dividing these 2 last measurements.

Statistical Analysis

Continuous variables were expressed as means ± SD and qualitative variables as numbers (%). Categorical variables were compared between outcome groups (survival vs. mortality) using Pearson's χ^2 or Fisher's exact nonparametric test. Sensitivity, specificity, positive and negative predictive values, and false-positive and false-negative rates of the SickKids score for mortality and survival prediction were calculated considering the high-risk cutoff of >8 and the low-risk cutoff <3 proposed by the authors [11].

Collected echocardiographic variables were analyzed to evaluate their correlation with the primary outcome of mortality or survival at 1 year of life. Those variables with values of $p < 0.1$ in the univariate analysis were entered as covariates in a multivariate model with stepwise forward selection using entry criteria of $p < 0.05$. Receiver-operating characteristic (ROC) curves were constructed to select cutoff points related to outcome for those continuous variables that failed to be included in the regression model. Optimal cutoff points of those ROC curves with acceptable areas under the curve (AUC >0.700) were then used to create categorical variables that were introduced in the multivariate model. Scoring systems with different combinations of variables were also assessed. Finally, the resulting model was compared to the SickKids score in terms of outcome prediction by means of ROC curve analysis. p values for all tests were two sided, and the criterion for statistical significance was $p < 0.05$. Data were analyzed using IBM SPSS statistical software, version 23 (IBM, Armonk, NY, USA).

Results

Baseline and Perinatal Characteristics

During the study period, 50 fetuses with EA were diagnosed in the 2 centers. Indications for echocardiographic examination were: suspicion of CHD in 42 cases (84%), other fetal anomaly in 3 (6%), increased nuchal translucency in 2 (4%), abnormal flow in ductus venous at first-trimester ultrasound in 2 (4%), and difficulty in fetal heart assessment during the second-trimester ultrasound in 1 (2%).

The median GA at diagnosis was 22.1 (range 13.5–39.0) weeks. According to the purpose of our study and as shown in Figure 3, we excluded 11 EA cases, 3 cases diagnosed before 18 weeks underwent TOP, and 8 cases diagnosed beyond 28 weeks, resulting in 39 cases diagnosed at the second trimester (18–28 weeks). Only 1 case corresponded to a multiple gestation in our series. This was a monochorionic diamniotic pregnancy, complicated by selective fetal growth restriction with absent diastolic flow in the umbilical artery. The parents requested TOP, which was performed at 16 weeks of gestation by

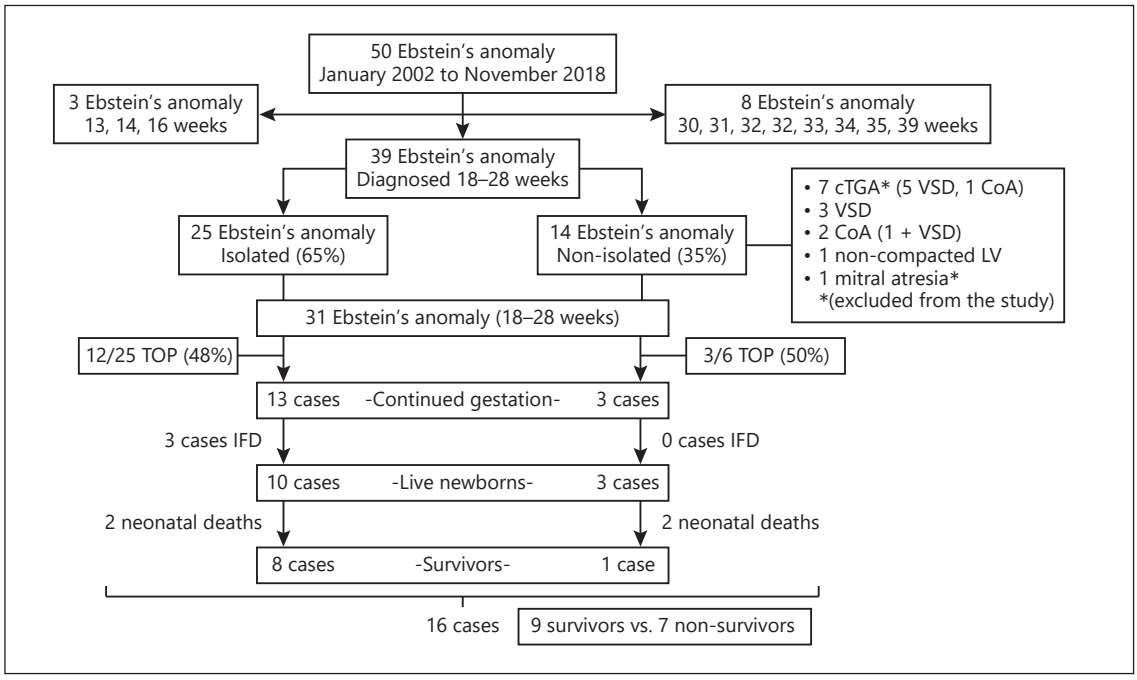

Fig. 3. Study population flowchart. cTGA, corrected transposition of great arteries; VSD, ventricular septal defect; CoA, coarctation of the aorta; LV, left ventricle; TOP, termination of pregnancy; IFD, intrauterine fetal death.

fetoscopy. The surviving fetus was diagnosed with an EA at 20 weeks of gestation.

Fourteen of the 39 cases (36%) were associated with another CHD. The details of these cases are summarized in online supplementary Table 2. The 7 cases of EA associated with congenitally corrected transposition of the great arteries were excluded from the study since many of the previously described echocardiographic predictors cannot be applied to this complex CHD. One case of EA was associated with mitral atresia and hypoplastic left-heart syndrome. This last case was also excluded in order to include only those CHD in which the outcome would depend mainly on the EA component. Thus, the final population of our study included 31 cases (Fig. 3).

No chromosomal anomalies were identified in our series, neither among the 22 cases (71%) in which an amniocentesis was performed nor in the 9 cases in which the information was confirmed by the postnatal clinical exam. One isolated EA case presented with fetal growth restriction, but no other associated extracardiac malformations were identified in our series.

After prenatal counselling, 15 parents (48%) opted for TOP at a median GA of 22.0 weeks (range 20.2–27.6) weeks. Online supplementary Table 3 shows the clinical characteristics of these patients. One case presented with a severe RA enlargement associated with paroxysmal supraventricular tachycardia. Eleven cases corresponded with isolated EA forms, all of them presenting with moderate or severe cardiomegaly or reverse flow in the ductus arteriosus, while the remaining 3 EA cases were associated with another CHD.

Among those 16 patients who decided to continue pregnancy, spontaneous IFD occurred in 3 cases (19%). All of them corresponded to isolated EA cases, showing severe TR and cardiomegaly at diagnosis: 1 case developed hydrops at 29 weeks and 2 other cases were diagnosed with IFD at 32 weeks. The remaining 13 cases reached term pregnancy. Nine cases (69%) were delivered vaginally, and 4 cases (31%) required cesarean section (2 for breech presentation and 2 for other obstetrical reasons). Median GA at delivery was 39.0 weeks (range 37.6–40.6). Mean birth weight was 3,287 ± 543 g. Four cases (31%) presented birth weight <10th percentile. No case had an Apgar scores <7 at 5 min or umbilical artery pH <7.10 in our series.

Postnatal Outcome

There were 4 deaths in the neonatal period. Online supplementary Table 4 details their clinical characteristics. As shown, 2 newborns had isolated EA with refractory hypox-

Table 1. Echocardiographic findings at the time Ebstein's anomaly (EA) was diagnosed: comparison between neonatal survivors and nonsurvivors (intrauterine fetal and neonatal death)

	Survivors (n = 9)	Nonsurvivors (n = 7)	p value
Gestational age at diagnosis, weeks	23.0±1.97	24.6±3.24	0.24
Isolated EA, *n* (%)	7 (77.7)	5 (71.4)	1.00
Cardiothoracic ratio (CTR)	42.56±8.56	56.71±16.22	*0.04*
Severe cardiomegaly, *n* (%)	3 (33.3)	5 (71.4)	0.33
Right atrium (RA) area index	0.58±0.16	0.73±0.38	0.30
Relative RA area ratio	0.25±0.05	0.39±0.13	*0.01*
Tricuspid displacement, mm	8.61±4.21	11.48±4.19	0.19
Severe TV displacement (%)	4 (44.4)	5 (71.4)	0.35
LV length, mm	19.48±7.73	18.05±3.37	0.65
TV displacement index	0.44±0.12	0.62±0.17	0.03
Functional tricuspid ring, mm	12.43±3.05	12.88±4.34	0.81
Functional tricuspid ring, *z*-score	3.77±1.42	4.28±1.77	0.53
Tricuspid regurgitation (TR)			
Maximum velocity, cm/s	157.11±72.59	190.43±88.41	0.42
Gradient, mm Hg	11.74±9.39	17.18±12.76	0.34
Severe TR, *n* (%)	3 (40)	4 (62.5)	0.33
Aortic maximum velocity, cm/s	75.33±12.28	71.00±11.10	0.48
Pulmonary maximum velocity, cm/s	58.13±15.15	57.40±15.58	0.93
Reversal PA flow, *n* (%)	2 (22.2)	4 (28.6)	1.00
Pulmonary insufficiency, *n* (%)	2 (20)	2 (25)	0.60
Abnormal DV flow, *n* (%)	0 (0)	2 (28.6)	0.52
Absent/reversal UA flow, *n* (%)	0 (0)	0 (0)	1.00
UA pulsatility index	1.05±0.25	1.15±0.35	0.42
SickKids score	5.44±1.42	7.43±2.44	0.06

TV, tricuspid valve; LV, left ventricle; PA, pulmonary artery; DV, ductus venosus; UA, umbilical artery. Severe cardiomegaly was defined as CTR >50%. Severe TR was considered when it was holosystolic with broad jet extending to the posterior RA wall. Mean ± SD or *n* (%). Student's *t* test for independent samples, Pearson's χ^2 test, or Fisher's exact test was employed, as appropriate.

emia and pulmonary hypertension in the context of severe cardiomegaly and functional pulmonary atresia, and 2 newborns presented with non-isolated EA and complications after performing palliative surgery during the first days of life. Therefore, the overall survival rate was 29% (9/31) and 56% (9/16) after excluding the cases that underwent TOP.

Among the remaining 9 alive children, only 3 cases required surgery during the first year of life. One infant underwent pulmonary valvuloplasty and closure of the atrial septal defect, and 2 cases, both with marked RV hypoplasia, required ductal stent placement during the postnatal period and subsequent Glenn's surgery at 4 and 6 months of life, respectively. The median follow-up for surviving children was 6 years (range 2–13).

Fetal Echocardiography

Table 1 details and compares echocardiographic variables at EA diagnosis between the survivors and nonsurvivors (IFD and neonatal death). The mean GA at evaluation did not significantly differ between both groups, and 11 cases (69%) were evaluated <25 weeks of gestation. Half of the cases presented severe cardiomegaly at diagnosis, and 9 cases (56%) were classified as EA with severe TV displacement, all of them presenting severe TR. On the contrary, the presence of reversed flow in the pulmonary artery and pulmonary insufficiency was less frequent at diagnosis: 6 (37%) and 4 (25%) cases, respectively. Compared with survivors, nonsurvivors showed a significantly higher CTR, relative RA area ratio, and TV displacement as demonstrated by a higher TVDI at the time of diagnosis. No significant differences were found in the other parameters evaluated, including the variables assessed to calculate the SickKids score. Only 3 cases (18%) presented a SickKids high-risk score ≥8 at diagnosis, while the rest scored between 4 and 8 (Fig. 4a). Therefore, the SickKids score allowed us to identify 43% (3/7)

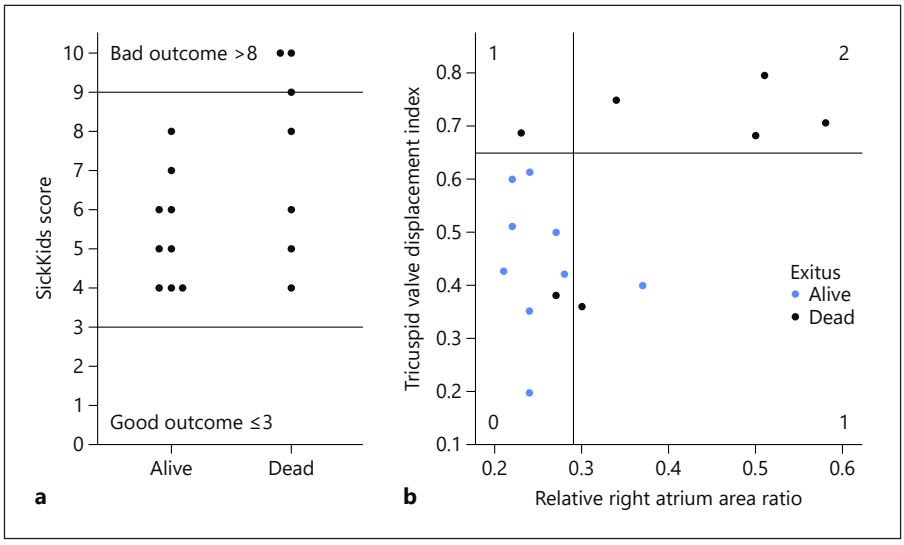

Fig. 4. a Graph illustrating the SickKids scores of the 16 patients with Ebstein's anomaly (EA) in our cohort. **b** Graph showing the application of the tricuspid valve displacement index and the relative right atrium area ratio of our cases.

Table 2. Sensitivity, specificity, and positive (PPV) and negative (NPV) predictive values for the SickKids score applied to our cohort and our second-trimester Ebstein's anomaly score for mortality

Scoring system	Sensitivity	Specificity	PPV	NPV
SickKids score				
≤3: low risk	0 (0–34)	100 (59–100)	0	44 (44–44)
>8: high risk	43 (10–82)	100 (66–100)	100	69 (54–81)
Our score				
0/2: low risk	88.9 (52–99)	86 (42–99)	89 (56–98)	86 (48–98)
≥1: high risk	86 (42–99)	89 (52–99)	86 (48–98)	89 (56–98)
2/2: high risk	57 (18–90)	100 (66–100)	100	75 (56–88)

Data are percentages (95% CI).

of the cases that ended with a perinatal death (Table 2). In contrast and as shown in Figure 4a, none of the cases in the survival group showed a low-risk score ≤3. The following variables were entered in the logistic regression analysis: CTR, RAAI, pulmonary forward flow, TR, pulmonary regurgitation, end-diastolic umbilical artery flow, *z*-score of the functional tricuspid ring, relative RA area ratio, TVDI, and arterial duct flow. High-risk cutoff points were defined after analysis of ROC curves for the continuous variables with acceptable AUC: CTR (cutoff ≥50.5; AUC 0.754; 95% CI, 0.494–1.000); relative RA area ratio (cutoff ≥0.29; AUC 0.833; 95% CI, 0.624–1.000), and TVDI (cutoff ≥0.6472; AUC 0.778; 95% CI, 0.502–1.000). Multiple scoring systems including a combination of variables were also tested.

None of the variables associated with a poor outcome in previous studies remained in the regression model. In fact, the best model to predict perinatal mortality in our series was obtained using a scoring system which included the relative RA area ratio and TVDI, with 1 point for each if present and 0 if absent (Fig. 4b; online suppl. Fig. 1). In Table 2, the sensitivity, specificity, and positive and negative predictive values for both low-risk (0/2) and high-risk (2/2) *EA second-trimester scores* are reported. Our novel second-trimester EA scoring system performed better than the SickKids score in our cohort (SickKids: AUC 0.746 [95% CI, 0.484–1.000] vs. our scoring system: AUC 0.905 [95% CI, 0.732–1.000]; Fig. 5).

Discussion

Our data confirm that EA is a complex CHD with a global perinatal survival of 56% after excluding TOP cases, which is substantially lower than that of other forms of CHD but similar to contemporary series. We also demonstrate that since EA is an evolving CHD, some of the prognostic echocardiographic parameters and predictive scores described in recent studies do not fully apply at an earlier GA. Finally, we propose 2 new parameters to

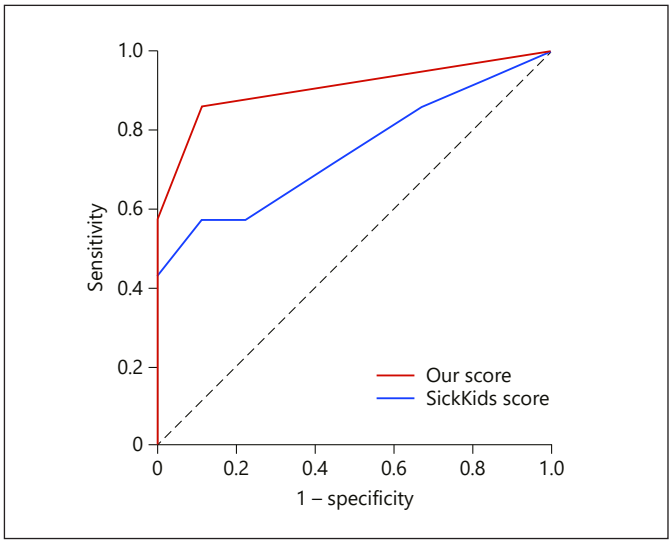

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Fig. 5. Receiver-operating characteristic curves for the SickKids score and our second-trimester score. Area under the curve (AUC) SickKids 0.746 (95% CI 0.484–1.000) versus AUC of our scoring system 0.905 (95% CI 0.732–1.000).

quantify both the RA dilatation and the tricuspid valve displacement in relation to other biometric parameters of the heart, which are easily applicable in clinical practice and are associated with perinatal mortality even from the second trimester of pregnancy.

Table 3 summarizes relevant data from the most recent studies focusing on the prognostic evaluation of EA in fetal life. Although our data on intrauterine and neonatal deaths are comparable with those reported in the Table 3, our series differs from these studies in some aspects that deserve to be highlighted. First, we did not exclude all CHD associated with EA, in fact in 6 cases (19%) EA was accompanied by other CHD, but in these cases the associated defect had less prognostic relevance than EA (online suppl. Table 2). However, we did not include cases of TV dysplasia without TV displacement into the inlet component of the RV, and, therefore, our series was purely composed of EA fetuses. Additionally, in our series, we did not identify extracardiac malformations or associated genetic syndromes that could also affect prognosis, as do most of the studies summarized in Table 3 [3, 4, 11, 14]. Second, in our study, the GA at diagnosis was lower than in the majority of studies, with 84% of our cases being evaluated <25 weeks of gestation. Third, all our cases were born at term, and, thus, we do not have the adverse effect of prematurity as a confounding factor on EA prognosis. Finally, our TOP rate was higher than previously reported, which could partly be explained by the lower GA at diagnosis, as almost all pregnancies resulting in TOP were <24 weeks. As shown in online supplementary Table 3, 3 TOP cases were associated with other CHD, and the remaining cases were associated with severe cardiomegaly or reverse flow in the ductus arteriosus and, therefore, corresponded to cases in the more severe EA spectrum. This was further confirmed applying retrospectively our second-trimester score, since the majority of these fetuses scored 2 ($n = 7$) or 1 ($n = 5$), and none scored 0. Our data reflect the difficulty of antenatal counseling in this complex CHD in the second trimester of pregnancy, which will not only be determined by the high risk of disease progression in cases of severe EA throughout pregnancy but also by the legal limitations of third-trimester TOP in some countries.

Different echocardiographic parameters have been correlated with perinatal mortality in EA, such as reverse flow in the ductus arteriosus and pulmonary insufficiency [3, 15]. However, the results of the largest available multicenter study [3] do not fully correspond to our series (Table 2). This might be explained by the lower GA of our cohort, since most cases included by Freud et al. [3] were diagnosed in the third trimester of pregnancy, with only 65/215 (30%) cases being evaluated <24 weeks (Table 3). Another factor might be our high rate of TOP, especially of the most severe forms of EA with reverse ductal flow and pulmonary insufficiency, some of which would probably have had a poor outcome. Nonetheless, in our series, only 4 (25%) of the continuing pregnancies presented pulmonary insufficiency at diagnosis and <30% presented reverse flow in the ductus arteriosus (with no differences between survivors and nonsurvivors). Finally, an additional explanation might be that this study included fetuses either having EA or TV dysplasia.

To our knowledge, only 2 recent studies have focused on the prognostic evaluation of EA at an earlier GA [4, 11]. As shown in Table 3, Selamet Tierney et al. [4] studied 51 fetuses with either EA or TV dysplasia diagnosed between 18 and 24 weeks of gestation and showed that 21% of the cases developed new pathophysiological findings between diagnosis and follow-up despite an initially favorable appearing status [4]. Based on these results, the authors proposed a new severity score, which included the CTR, the TV annulus diameter z-score, and the presence of pulmonary regurgitation, none of which achieved the necessary significance to remain in our logistic regression model. Additionally, 2 new scoring systems have also been proposed recently: the TRIPP score (TRIcuspid malformation Prognosis Prediction score) [15] and the

Table 3. Summary of the more recent literature on the prediction of perinatal mortality in Ebstein's anomaly (EA)

Authors, year	Study population	Perinatal outcome	Prognostic predictors
Lasa et al. [14], 2012	EA/TVD (complex CHD excluded) Period 2000–2008 *n* = 21 fetuses (mean GA = 25 weeks; range 17–37) [*5 cases LTFU]	TOP: 2/16 (13%) IFD: 2/16 (13%) Hydrops: (6%) Perinatal survival: 57%* *[excluding TOP]	Increased RA area index Shorter combined LV isovolumic contraction and relaxation time
Freud et al. [3], 2015	EA/TVD (complex CHD excluded) Period 2005–2011 (23 centers/North America) *n* = 243 fetuses (mean GA ± SD = 27±5.9 weeks) [*11 cases LTFU] (diagnosed <24 weeks = 30% = 65/215 cases)	TOP: 15/243 (6%) IFD: 41/243 (17%) Hydrops: 6% Perinatal survival: 55%* *[excluding LTFU + TOP] Neonatal survival: 70%* *[excluding LTFU + TOP + IFD]	GA at dx <32 weeks Increased TV annulus diameter *z*-score Pulmonary regurgitation Pericardial effusion
Wertaschnigg et al. [11], 2016	EA/TVD (complex CHD excluded) Period 2000–2014 *n* = 52 fetuses (mean GA = 23 weeks; range 18–40) *n* = 27 newborns (mean age = 6 days; range 0–28) [*11 cases LTFU]	TOP: 5/52 (12%) IFD: 8/47 (17%) Neonatal death: 10/47 (21%) Perinatal survival: 62%* *[excluding TOP] Neonatal survival: 1 month: 86% *[excluding IFD]	Lower GA, lower birth weight Increased CTR Increased RA area index Severe TR Retrograde flow at arterial duct Pulmonary regurgitation High SickKids score
Selamet Tierney et al. [4], 2017	EA/TVD (complex CHD excluded) Period 2005–2013 *n* = 51 fetuses (mean GA = 21 weeks; range 18–24) [*all cases with a second echo 4 weeks apart]	Severe EA criteria*: (1) <24 weeks: 33/51 (65%) (2) >24 weeks: 44/51 (86%) [*pulmonary regurgitation or CTR >0.48 or TV annulus *z*-score >5.6]	Severe EA score TV annulus diameter *z*-score
Torigoe et al. [15], 2019	EA/TVD (complex CHD excluded) Period 2000–2015 *n* = 36 fetuses (mean GA = 33 weeks; range 18–37) (diagnosed <24 weeks = 22% = 8/36 cases) [*1 case LTFU]	TOP: 2/35 (6%) IFD <22 weeks: 2/35 (6%) IFD >22 weeks: 4/31 (13%) Neonatal death: 6/31 (19%) Perinatal survival: 68%* *[excluding TOP/IFD <22 weeks]	TRIPP score: TR peak velocity LV myocardial performance index Pulmonary artery flow Ductus arteriosus flow
Current study	EA (complex CHD excluded for prediction analysis)* Period 2002–2018 *n* = 31 fetuses (mean GA = 22.5 weeks; range 18–27.6) [*6/31 cases associated with other CHD]	TOP: 15/31 (48%) IFD: 3/16 (19%) Neonatal death: 4/13 (31%) Perinatal survival: 56%* *[excluding TOP]	CTR Relative RA area ratio TV displacement index

TVD, tricuspid valve (TV) dysplasia; CHD, congenital heart disease; GA, gestational age; LTFU, lost to follow-up; TOP, termination of pregnancy; IFD, intrauterine fetal death; RA, right atrium; LV, left ventricle; CTR, cardiothoracic ratio; TR, tricuspid regurgitation.

SickKids score [11]. Since the TRIPP score included the LV Tei-index, combined with the presence of TR and the flow characteristics in the pulmonary artery and ductus arteriosus, we could not validate it in our series. Nevertheless, LV functional parameters seem to have potential as prospective markers in the future. However, applying the SickKids score to our cohort, we found that although a score >8 was highly predictive of a poor outcome, most of the fetuses in our cohort (13/16, 81%) had an intermediate score (between 4 and 8), which has poor predictability [11].

Our data on the 2 novel proposed echocardiographic predictors are noteworthy since both parameters can be measured easily in 4-chamber view and seem to be good predictors of mortality and survival. Both indices were designed to better reflect the magnitude of RA dilatation and TV displacement. We chose the cardiac area to normalize RA area, as this relation is easier to understand than the RAAI described and the LV longitudinal diameter to normalize the TV displacement, since it can be difficult to assess the apex of the RV in EA, especially in cases where the TV is inserted below the moderator band. Since RA dilatation is progressive in EA, we believe that the relative RA ratio could better reflect the initial phase of RA enlargement than the RAAI, which was described in neonates and does not include the RA area in the denominator. Moreover, adjusting both, the size of the RA and the displacement of the TV by another biometric parameter of the heart offers the advantage of obtaining a ratio or index that can be easier to interpret from a clinical point of view throughout the entire pregnancy. In fact, in our series, a relative RA area ratio <0.29 plus a TVDI <0.65 (score 0/2), allowed us to identify 89% of surviving fetuses with a specificity of 86% and a false-negative rate of 11% (Table 2). On the contrary, when both parameters were abnormal (score 2/2), no fetus survived, and there were no false-positive results (specificity 100%, positive predictive value 100%). Additionally, our score seems to be more sensitive than the SickKids score (57 vs. 42%) for poor outcome prediction, and it has a reduced number of fetuses classified at intermediate risk.

We acknowledge that prenatal counseling in EA is complex, especially in the previability stage, and our data should be interpreted with caution. As the models proposed in the literature, most of which have not been yet validated externally, our scoring system should be evaluated in a different population, either retrospectively or ideally in a prospective manner. For the moment and based on the available data, serial echocardiographic follow-up must be considered crucial to perform a precise prognostic evaluation in fetal life. However, legal limitations to carry out a TOP beyond 22–24 weeks of gestation existing in some countries may limit this possibility. Our data can be very valuable for the parents at the moment they have to face this complex CHD. In this way, the possibility of differentiating between cases of good (score 0/2) or bad prognosis (score 2/2) would not only allow to potentially reduce the rate of TOP but also to carry out a better individualized follow-up.

This study has several limitations. Since it was performed retrospectively, we could not evaluate some of the echocardiographic predictors described in the last studies, such as parameters of LV function. GA at diagnosis varied among cases, and although clinical management protocols were similar in both centers, some small differences might have an impact on the analysis of a poor prognosis. Another limitation was the high rate of TOP, which reduces the number of cases by nearly half and excludes the most severe cases.

Conclusion

Despite important advances in the prenatal diagnosis and management of CHD over the past decades, TOP and perinatal mortality in fetuses with EA remains remarkably high. Parental counseling is particularly difficult especially when the diagnosis is made in the second trimester of pregnancy, since data on the prognostic evaluation are scarce at this GA. Our study found that fetuses with a greater increase in the RA size (relative RA area ratio ≥0.29) and TV displacement (TVDI ≥0.65), presented the highest risk of dying in the perinatal stage. Our data, derived from a homogeneous cohort of fetuses with EA diagnosed in the second trimester of pregnancy, are limited by the small sample size; however, following confirmation in future studies performed in different populations, these novel easy-to-measure parameters could improve current prognostic evaluation in EA.

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Statement of Ethics

Published research complies with the guidelines for human studies and includes evidence that the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study was approved by the institutional ethics committees of both centers.

Disclosure Statement

The authors do not have any commercial interest or other association that might pose a conflict of interest, and they are independent from funders and sponsors.

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Author Contributions

All authors were involved in the drafting of the manuscript. All provided approval of the version to be published and agreed to be accountable for all aspects of the work. In addition to this, all authors further contributed in the undertaking of the study. N.M., O.G.R., JM.M., and A.G. were involved in the design and conception of the work. N.M., O.G.R., I.H., E.G-M., I.S., M.P-C., C.M-B., M.B., JM.M., and A.G. contributed to identified cases and acquisition of data. N.M., O.G.R., and I.S. contributed to acquisition, analysis, and interpretation of data. M.C.E.-D. and M.A.G. provided substantial contributions in the revision of the work and interpretation of the results.

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