**Assessment of Left Ventricular Myocardial Fibrosis in Adult Patients with Ebstein’s Anomaly: A Retrospective Cohort Study Based on Cardiac Magnetic Resonance and Histopathological Samples**

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**Running** **title**: Left ventricular fibrosis in adults with Ebstein’s anomaly

**CONFLICT OF INTERESTS:** The authors declare that they have no conflict of interest.

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Text words: 4532/5000

References: 39/50

Tables and figures: 8/8

Abstract: 254/300 words

**ABBREVIATIONS**

**EA:** Ebstein’s Anomaly

**RA**: Right Atrium

**RV**: Right Ventricle

**LV**: Left Ventricle

**LA**: Left Atrium.

**CMR**: Cardiac Magnetic Resonance

**LGE**: Late Gadolinium Enhancement

**ABSTRACT (254 WORDS)**

**BACKGROUND**: The association between Ebstein’s Anomaly (EA) and myocardial fibrosis, particularly in the left ventricle (LV), has been controversial. We aimed to assess the prevalence of replacement fibrosis with a focus on the LV using cardiac magnetic resonance (CMR), make a histopathological correlation of LV-fibrosis and CMR findings, and explore whether LV fibrosis is an independent risk factor for CVD-mortality using a derived risk-score.

**METHODS:** We performed a twelve-year~~s~~ (2009-2021) retrospective cohort study of adult patients with EA who underwent CMR. The CMR evaluation included a comprehensive assessment of myocardial fibrosis by late gadolinium enhancement (LGE). Four post-mortem samples were obtained from our cohort and stained using Masson trichrome to characterize LV-fibrosis. We used Cox-Regression analysis to identify and derive a prediction score that associates LV-fibrosis with CVD-mortality.

**RESULTS:** We included 57 adults with EA (52% male, median age 29.52, IQR: 21.24-39.17 years). LGE prevalence by CMR was observed in 52.6% (95% CI: 39.9%-66.0%) in any chamber; LGE-LV in 29.8% (95% CI: 19.5%-42.7%). Histopathological findings revealed a mid-wall pattern with predominantly interstitial fibrosis and minimal replacement fibrosis. LV-fibrosis was associated with increased risk for CVD mortality (HR: 6.02, 95% CI: 1.22-19.91) attributable to lateral and mid-wall LV segment involvement. Our mortality score achieved an overall good prediction capacity (C-statistic: 0.93, Dxy= 0.86).

**CONCLUSIONS:** There is a high prevalence of replacement LV fibrosis in adults with EA, characterized by specific CMR and histological patterns. Furthermore, LV fibrosis is an independent predictor of CVD mortality, which could be integrated into a risk assessment in clinical management.

**KEYWORDS.** Ebstein’s anomaly; late gadolinium enhancement; myocardial fibrosis; left ventricular fibrosis; cardiac magnetic resonance

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| **CLINICAL PERSPECTIVE**  **WHAT IS NEW?**  ▪ In this retrospective cohort study of 57 patients with Ebstein’s anomaly, we established a high prevalence of left ventricle (LV) replacement fibrosis assessed by late gadolinium enhancement (LGE) in cardiac magnetic resonance (CMR) images.  ▪We found a histopathological correlation with CMR, and LV fibrosis characterized by a basal mid-wall pattern, with predominantly interstitial fibrosis, and minimal replacement fibrosis.  ▪The presence of LV LGE, particularly in lateral and mid-wall segments were independent predictors of increased risk of CVD mortality, which could be integrated into a clinical risk score.  **WHAT ARE THE CLINICAL IMPLICATIONS?**  ▪ Our findings reveal a characteristic LV-LGE pattern in adult patients with EA that should be interpreted as a finding of concern in CMR studies.  ▪ These findings support the need to screen for myocardial fibrosis with CMR in patients with EA to optimize treatment and increase survival.  ▪ Our results raise the possibility of creating a risk stratification score for patients with EA that includes the presence of LV-LGE, as well as other clinical and medical parameters to be implemented in clinical practice. |

**INTRODUCTION**

Ebstein’s anomaly (EA) is a rare congenital heart disease (1 in 20,000 live births) characterized by malformation of the tricuspid valve (TV) and well-characterized abnormalities of the right ventricle (RV) (1–4). The main causes of death in adult patients living with EA include heart failure and arrhythmias, highlighting the importance of early detection and treatment in childhood (2). Since the mortality of EA has decreased over the last three decades in low-to-middle income countries, the increased longevity in these patients presents new challenges in their treatment (5).

Cardiac magnetic resonance (CMR) imaging is currently considered to be the gold standard for comprehensive quantification of ventricular size, along with myocardial function and characteristics of the myocardium (6–8). Late gadolinium enhancement (LGE) is a CMR technique that provides an accurate quantification of focal myocardial replacement fibrosis, myocardial viability, ventricular function, as well as estimations of inflammation in the myocardium (2,7,9–11). Although myocardial fibrosis has been associated with deterioration of ventricular systolic function, abnormal cardiac remodeling, increased ventricular stiffness leading to its being a major independent predictive factor of adverse cardiac outcomes; its identification and correlation in patients with EA is infrequent (12).

Currently, there are few studies that have evaluated the impact of fibrosis in EA patients, whether quantified by LGE or by T1 mapping (2,7,13). Even more importantly, a comprehensive description and characterization of LGE, particularly of the left ventricle (LV), and its capacity to predict mortality in adults living with this disease has not been comprehensively evaluated in as much as most studies of this disease have focused on studying the characteristics of right heart chamber (1,2,7,13–16).

In this study, we aim (a) to quantify the prevalence of replacement fibrosis in cardiac chambers, with a particular focus on the LV, using LGE in CMR, (b) to make a histopathological correlation of LV fibrosis and CMR findings in post-mortem samples, and (c) to explore whether LV-LGE is an independent risk factor for CVD mortality and derive a risk-score for adult patients living with EA based on clinical records over 12 years at a third-tier referral center in Mexico City.

**METHODS**

**Study design and data collection**

We performed a retrospective cohort study of adult patients living with EA diagnosed in the congenital heart disease outpatient clinic of the National Institute of Cardiology Ignacio Chavez in Mexico City. Our hospital is a referral center which attends a high number of adults living with congenital heart disease~~s~~ in Mexico (17). All the information was obtained from subjects who were managed in this institution between 2009 and 2021 (12 years). As our selection criteria, we included adults living with unrepaired EA who underwent CMR imaging scans during the study period (**Figure 1**). Exclusion criteria included conditions that predisposed to fibrosis, such as heart valve diseases, coronary artery disease, acquired cardiomyopathies, myocarditis and patients with known contrast media allergy or other contraindications for the use of gadolinium. Elimination criteria consisted of incomplete medical records or illegible CMR images. We collected variables from medical records that included previously diagnosed comorbidities, arrhythmias, other structural cardiac abnormalities, and self-reported symptoms from the last recorded clinical visits. Due to the retrospective nature and the use of information from clinical records included in our study, informed consent was waived. This work adheres to the STROBE guidelines for retrospective cohort studies (**Supplementary Material**).

**Outcome variables definition**

The main analyses were focused on two primary outcomes: replacement fibrosis and mortality status.

1. *Myocardial replacement fibrosis* – This condition was evaluated using CMR imaging scan reports performed with LGE conventional technique in our retrospective cohort. Although there are novel techniques such as T1 mapping, this technique was introduced to the Institute in 2016; thus not all patients had access to this study to assess interstitial fibrosis by CMR (11,12). For this reason, the technique selected represents the best approach for assessing myocardial fibrosis in our population. An independent cohort of four post-mortem cardiac samples were stained using Masson trichrome stain for a histopathological correlation of LV-fibrosis with its respective CMR findings.
2. *Mortality status*. This was established when a death certificate certified by a cardiologist of our Institute was added to the clinical record of our patients included in our cohort. The primary cause of death is presented in **Supplementary Material**. To model the risk associated with LV-fibrosis we used age as our time-to-event follow-up. This approach was reported by Manav V. Vyas as an alternative when uncertainty exists regarding the beginning of exposure (in this case, myocardial fibrosis) (18).

**Cardiac Magnetic Resonance Imaging Acquisition**

1. *CMR Technique*

Image acquisition was performed with a 1.5 T device (Magnetom Avanto Fit, Siemens® Medical System). All patients underwent the standardized protocol of CMR angiography that includes axial and cine T1 HASTE (Half Fourier Single-shot Turbo Spin-Echo) images. Axial T1 HASTE images were acquired in orthogonal orientations at 8 mm intervals (8 mm slice thickness, approximate interval 0.8 mm, echo time (TE) 40 ms, repetition time (TR) 700 ms). Cine images were developed using a pulse sequence based on SSFP (Steady-state free-precession) on short-axis images in 4-, 3-, 2- chamber orientations and axial slices; with typical parameters (slice thickness of 8 mm, interval of 2 mm, TE of 1.22 ms, TR of 62.92 ms).

1. *EA indexes*

The functional RV (fRV), atrialized RV (aRV), and total RV volumes were measured to characterize right heart size and function. According to Yalonetsky et al., the fRV was defined as the ventricular distance to the tricuspid valve insertion points (19). The border demarcating the fRV from the aRV was defined as a line on the free wall connecting the insertion of the anterior tricuspid valve leaflet at the level of the annulus and the septal insertion of the apically displaced leaflet, at the end-diastole, in 4 and 2 chambers. The border between the aRV and the morphological right atrium (RA) was defined as the line connecting the insertion of the free wall attachment of the anterior tricuspid valve leaflet and the tricuspid valve annulus (9,19).

1. *Ventricular Volumes and Indexes*

Total RV volume was defined as the sum of fRV and aRV volumes. The fRV end-diastolic (RV-EDV) and end-systolic (RV-ESV) volumes were measured in the axial view. LV end-diastolic (LV-EDV) and end-systolic (LV-ESV) volumes were measured in the short-axis views, in agreement with accepted practice. All volumes and masses are presented in~~to~~ an indexed version standardized by the body surface area. Based on Fratz et al., we calculated the EA Severity Index by CMR, defined by the following chambers areas: (RA + aRV) / (fRV + LV + LA [left atrium]) (19–21), traced in end-diastole on the four-chamber view. All CMR volumes, areas and characteristics were acquired according to the international guidelines of the Society for Cardiovascular Magnetic Resonance (22–24).

1. *LGE technique*

Gadobutrol (Bayer AG Müllerstrabe, Berlin, Germany) was administered at a dose of 0.1 mmol/kg. Late enhancement images were obtained in a slice orientation adjusted to cine images with inversion-recovery sequences, with manual adjustment of the inversion time of 10 minutes after the injection of the contrast material, to select the inversion time when the normal myocardial signal was abolished. The images were interpreted by two experts in cardiovascular imaging and a second interpretation of printed reports was made by a blinded collaborator (LTA) to ensure unbiased estimations of LGE.

1. *Myocardial localization and definitions of segments*

The myocardium was analyzed to determine the presence or absence of LGE by localization within the RV, RA, LV, and LA. LV-RV insertion points and tricuspid septal displacement areas were excluded since LGE observed in these areas usually is a non-specific finding in patients with EA, without a clear clinical translation (22). LV was evaluated using the 17-segment model (25). Depending on the affected area, LGE was identified and classified according to the affected location: subendocardial, subepicardial, and mid-wall. For better evaluation of apical disease, two- and four- chambers images were also obtained.

**Histopathological characterization of myocardial fibrosis~~’~~**

An objective of our study was to correlate the findings by CMR with histopathological studies~~,~~ for a better understanding and characterization of the myocardial fibrosis patterns in patients with EA. To achieve this, we performed histopathological studies on four patients who were part of our study and died after the CMR. CMR images evaluated only replacement fibrosis (assessed by LGE), while histopathology can characterize both replacement and interstitial fibrosis. Both ventricles were sectioned on the lateral aspect of their free walls. Histological samples were taken from the ventricular free wall next to the incision in both ventricles (including the basal, middle and apical thirds) (26). All the sections were stained with hematoxylin-eosin and with Masson trichrome. Fibrotic areas were assessed in each ventricle with Masson trichrome stain. The samples were evaluated using microscopy by a single expert pathologist (AAF), where the amount of fibrosis was observed based on a scale of 0 to 100, considering 100 as completely fibrotic tissue.

**Statistical Analysis**

Continuous variables were displayed as means (standard deviation), or medians (interquartile range) according to their distribution determined by the Anderson-Darling normality test. Categorical variables were displayed as frequency and absolute proportion. We compared the descriptive characteristics among patients with positive and negative LV-LGE using Student’s t test or a Wilcoxon-Rank test for continuous variables, according to normality distribution, and a Chi-Squared test for categorical variables. All statistical analyses were performed in R Studio (Version 4.2.1). All the results derived from our study are fully reproducible from the R-code provided in the URL of the data sharing statement. A value of p<0.05 was considered as the threshold of statistical significance.

*Prevalence estimation of myocardial fibrosis*

We used the Wilson approach to estimate the prevalence at a 95% confidence interval for myocardial fibrosis by heart chambers, myocardial location, and LV segments using the *epiR* package (27). Then, we visualized our prevalence estimations using bar plots created with the *ggplot2* package (28).

*Association of LGE with the risk of mortality*

We performed Kaplan-Meier analysis to identify the survival probability associated with LGE in the RV and LV and compared their survival curve distribution across time using the Log-Rank test. We then fitted Cox proportional hazard regression models to evaluate LV-LGE as a predictor of mortality considering age as our time-to-event follow-up. Covariates of adjustment were sex, body surface area, number of comorbidities, left ventricular ejection fraction (LVEF), indexed LV mass, RV atrialization and time since arrival at the National Institute of Cardiology. Models’ goodness of fit was evaluated with the Bayesian Information Criteria (BIC). The proportional hazard assumption was tested using the Schoenfeld residuals presented in **Supplementary Material**.

*Sensitivity Analysis*

As myocardial fibrosis is a heterogeneous entity that has been widely demonstrated to be a predictor of mortality due to mechanical dysfunctionality, we hypothesized that the risk conferred by replacement fibrosis of the LV could be driven by specific areas linked with EA pathophysiology. To confirm this hypothesis, we performed a sensitivity analysis using the myocardial location and LV grouped segments in a Cox proportional hazard regression model adjusted for the covariates mentioned above. We plotted hazard ratios charts using the *jtools* package (29).

*Risk score for mortality in patients with EA*

Finally, we constructed a clinical model to predict mortality in EA, which might have a useful application in clinical care. Our model includes CMR and clinical variables, which were identified with increased risk of mortality. Points were assigned by standardizing all β coefficients with the minimum absolute β coefficient obtained from a fitted Cox proportional regression model. For simplicity, we derived our score into an equation based on score points between 0 and 10. A threshold using the median of the derived distribution of the score was used for classifying subjects with high-risk and its survival probabilities was verified using Kaplan-Meier analyses. C-statistics and Dxy values were obtained to evaluate the performance of our score using the *rms* R package (30). Validation and calibration statistics are presented in **Supplementary Material**.

**RESULTS**

*Characteristics of our study population*

During our study period, a total of 153 adult patients were diagnosed or referred to our Institute with EA, only 70 of whom had not undergone surgical repair. A total of 57 patients fulfilled our selection criteria (**Figure 1**). Detailed characteristics of the study group are summarized in **Table 1**. Briefly, our sample had roughly equal numbers of males and females (male=30; 52.6%), with a mean age of 29.52 (IQR: 21.24-39.17; range 18-72) years and a mean BMI of 24.1 (± 4.1) kg/m2. Most patients were classified in NYHA functional class I (80.7%). At the last recorded visit, palpitations were the most common clinical manifestation (31.5%), Wolff-Parkinson White was the most frequent structural anomaly (29.8%), atrial fibrillation was the most common arrhythmia (14%), and atrial septal defects (78.9%) were the main associated congenital lesions. Coexisting cardiac anomalies were present in 4 (7%) patients and included non-compacted myocardium (n=1), mitral valve prolapse (n=1), cleft mitral valve (n=1), and coarctation of the aorta (n=1). It should be noted that of the 57 patients who were part of our study, 12 (21.1%) died during our study period.

*CMR characterization of myocardial fibrosis*

CMR-LGE in any chamber was observed in 30 patients (52.6%, 95% CI: 39.9%-65.0%). LGE was highly prevalent in the right heart (n=20, 35.08% 95% CI: 24.0%-48.1%), predominantly in the RA chamber in 24.56% (95% CI: 15.23%-37.1%). Concerning RV, LGE was present in 14.04% (95% CI: 7.29%-25.32%). With respect to the LV, LGE was present in any of the 17 segments in 29.82% (95% CI: 19.53%-42.66%). Only 5.26% (95% CI: 1.81%-14.37%) had LGE in the LA. Regarding LV segments, the most prevalent location of LGE was in the mid-wall (24.56%; 95% CI: 15.23%-37.1%), followed by the transmural (7.02%; 95% CI: 2.76%-16.7%). Further characterization of the LV revealed that the segments with the largest LGE areas were those located in the basal third, with higher prevalence in the basal-inferoseptal, basal-inferolateral, basal-anterolateral, and basal-anterior segments, accounting for 7.02% (95% CI: 2.76%-16.7%) for each of the above areas. The middle-inferolateral (7.02%; 95% CI: 2.76%-16.7%) and the apical lateral (5.26%; 95% CI: 1.81%-14.37) segments also were classified with positive LGE (**Figure 2**).

*CMR comparison between patients with LV-LGE (-) vs LV-LGE (+)*

To further characterize subjects with LV fibrosis, we divided our population into two subgroups: LV-LGE (-) (n= 40) and LV-LGE (+) (n=17). Both groups tended to have similar and equivalent sociodemographic and clinical profiles. Regarding CMR-indexes, we found no significant differences in the severity index, septal displacement, or RV atrialization. By contrast, for CMR-volumes, we observed that both LV-EF and RV-EF, were lower in patients with LV-LGE (+). Furthermore, we also found that the indexed LV end-systolic volume and the indexed LV-mass tended towards statistical significance, which suggests that these parameters could be also decreased in subjects with LV-LGE (+) (**Table 1**).

*Histopathological correlation between studies and the CMR images*

As previously described, 12 patients from our cohort succumbed during our study period, 4 of whom underwent necropsy at our Institute. The 4 heart samples were analyzed and compared with their respective CMR study in order to look for a descriptive CMR-histopathology correlation characteristic of EA **(Figure 3)**. Regarding CMR findings, we found that only one of the four patients showed intense LGE (in the septum and lateral wall of the LV). The rest of the patients did not show LGE in any ventricle. However, the histological study found that the four patients had biventricular fibrosis in the analyzed areas (free walls). In all cases, the fibrosis was characterized by a mid-wall location, with a predominantly diffuse interstitial pattern, accompanied by small patches of replacement fibrosis, except in one patient, where this replacement fibrosis was highly stained. The comparison of the histopathology and CMR findings of each patient are presented in **Table 2**.

*Characteristics of patients who died in our included cohort*

Among the data of the 12 patients who died, we observed that LV-EF, RV-EF and LV-ESV indexed derived from CMR tended to be lower and with a higher proportion of LV-LGE (+) compared with surviving subjects (58.3% vs 22.2%, p=0.029). (**Supplementary Material)**. Among the primary causes of death, 11 (91.6%) of the deaths were attributed to heart failure, while only 1 (8.3%) was due to sudden cardiac death from ventricular arrhythmia.

*LV-LGE as a predictor of mortality in patients with EA*

A Kaplan-Meier survival analysis was performed to estimate the association between the presence of ventricular LGE using age as our time-to-event follow-up. We observed that subjects with LGE in any segment of the LV tended to have a significantly decreased survival probability compared with subjects without this condition. Nevertheless, no association was observed for LGE in the RV (**Figure 4**). To confirm this association, we performed Cox proportional Hazard Regression models. In the unadjusted model, having LV-LGE conferred up to a 3-fold increased risk (95% CI: 0.9-10.68, p=0.072) for lethality. In model 1, after adjustment for sex and BSA, it was shown that LV-LGE conferred a 4-fold increased risk (95% CI: 1.14-15.3, p= 0.03). Finally, model 2 showed that LGE within the LV conferred up to a 6-fold increased risk (95% CI: 1.22-19.91; p=0.025) for mortality compared to patients who did not present LGE in this chamber after adjustment for sex, BSA, number of comorbidities, LVEF, LV mass, RV atrialization and time since arrival at our Institute (**Table 3**).

*Sensitivity analyses for LV-LGE as a predictor of mortality in patients with EA*

As a sensitivity analysis, we evaluated the risk conferred by LGE within the LV by locations and segments. We observedthat patients with LGE within the mid-wall location had 28-fold increase in the risk of mortality as compared to patients without LGE (95% CI: 3.42-240.75; p=0.002). Finally, patients with LGE in any of the lateral segments (apical, middle, or apical) had 12-fold higher risk of death compared with patients without LGE after adjustment for the same covariates above mentioned (95% CI: 1.92-84.35; p=0.008) (**Figure 5**).

*Mortality Score for adult patients with EA*

Using the overall sample, we designed a predictive score for mortality using Cox regression analysis. We considered LV-LGE (+), sex, BSA and RV-EF as main predictors for mortality. Using these variables, we identified an overall good performance (R2=0.436, C-statistic=0.927, Dxy=0.854) to predict lethal outcomes. We translated this model into the following equation: 17+2.0[Male Sex]-6.0[BSA in m2/1.73]-0.1[RVEF in %] +4.0[Presence of LV-Fibrosis], which did not significantly reduce the model’s performance (R2=0.435, C-statistic=0.930, Dxy=0.860). A threshold of 6.5 points corresponded to an acceptable performance (R2=0.251, C-statistic=0.757, Dxy=0.514) for identifying mortality and significantly discriminated between lethal and non-lethal cases (**Supplementary Material**).

**DISCUSSION**

In this retrospective study, we analyzed a cohort of 57 adult cases of unrepaired EA who underwent CMR at a third-tier referral center in Mexico City. We observed that almost a third of our included subjects had LV fibrosis, assessed by LGE-CMR. The most frequent location of fibrosis was mid-wall, which correlates with the histopathological findings of interstitial and modest replacement fibrosis in post-mortem samples. We observed that LV-LGE conferred up to a 6-fold higher risk for mortality, which could be attributed to mid-wall and lateral segment~~s~~ involvement. Finally, we integrated a mortality score using LV-LGE, a clinical indicator that could be applied in medical care of these patients. Our results contribute to and confirm the clinical relevance of assessing myocardial fibrosis, and further characterizing specific patterns that could result in better clinical management of adult patients living with EA.

In our study, 52% of patients presented LGE in any heart chamber and 29.8% within the LV. Further stratification of CMR findings revealed that the LV-LGE predominantly affected the basal third and involved lateral segments (basal, mid, or apical). Furthermore, the most frequent location was mid-wall, followed by transmural locations. Our results showed a high prevalence of LGE in the LV compared with other series of patients with EA (2,7,13). The relatively high prevalence in the LV may also be increased, considering that replacement fibrosis probably appears as an age-related phenomenon, although this is a controversial hypothesis. Moreover, our study focuses only on adults (unlike other studies that generally include children and adolescents). Myocardial fibrosis has been recognized as an area of great interest in EA, and the clinical relevance in patients with EA was initially proposed in 1992 when Celermajer et al. (31) described the anatomopathological findings of fibrosis of the RV and LV in the hearts of neonates. They attributed the RV abnormalities to the hemodynamic stress *in-utero* and postulated that fibrosis of the LV could be explained by genetic, hemodynamic, and/or environmental factors. This hypothesis was supported by studies that reported finding LV fibrosis in post-mortem samples of neonatal hearts (31,32). However, other authors have proposed that fibrosis in EA is acquired in extrauterine life and accentuated over time (26). At present, the mechanisms responsible for myocardial fibrosis are unclear. Nevertheless, some hypotheses have focused on abnormal mechanical interactions with the RV and hypoxic insults as the main sources for the onset of fibrosis (1,13,33). Aly et al. (13) observed decreased deformation markers by echocardiography, as well as greater T1 and extracellular volume, were closely associated with diminished oxygen saturation, giving rise to the speculation that fibrosis was the result of hypoxemia or hypoxic stimulus (2,13,34). Other hypotheses were linked to abnormal interventricular mechanical interactions secondary to compression of the LV, causing a dilated RV and abnormal septal movement, resulting in dysfunction of the LV and subsequent fibrosis (35). However, patients with previous repair continue to exhibit dysfunction of the LV after surgery. This evidence illustrates the challenges in determining the origin of LV fibrosis in adult patients with EA.

To further characterize the LV fibrosis patterns, we performed a histopathological correlation with CMR and four heart samples from autopsied deceased patients. Microscopic findings revealed mid-wall fibrosis, with a significant predominance of interstitial fibrosis over replacement fibrosis. The histological findings were compatible with previous ischemia, which could have explained interstitial fibrosis with scattered areas of replacement fibrosis. Our findings correlate~~s~~ with the underlying mechanisms postulated by other authors (26), including dyssynchrony of the LV and impaired torsion and recoil mechanics induced by paradoxical movement of the basal septum (14). CMR was able to detect significant areas of LGE (replacement fibrosis), but it was of little use in locating patches of this type of fibrosis, corroborated by histopathological studies. Bearing in mind that replacement fibrosis appears after interstitial fibrosis, as suggested by different authors (12), it is essential to evaluate patients with EA by CMR with LGE techniques, as well as T1 mapping and extracellular volume.

Regarding LGE of the LV and its association with mortality, our findings suggest up to a 6-fold increased risk for this outcome compared to patients who did not present LGE in the LV after adjusting for covariates. This finding indicates that LGE of the LV is an independent factor for determining a patient's survival, although the exact mechanism behind this phenomenon is unclear. Further studies are needed to corroborate this finding and to determine whether asymptomatic patients presenting LV-LGE can benefit from specific early therapies. Although echocardiography continues to be the study of choice for the diagnosis of EA, CMR has been proposed as a better option to evaluate the characteristics of the heart or determine the possibility of surgical management (34). Moreover, the current heart failure guidelines focused on congenital heart diseases~~,~~ do not address specific therapeutic strategies based on the composition of the myocardial tissue. This lack of specificity could lead to an insufficient clinical management, which could result in increased morbidity and mortality. The absence of personalized treatment is also secondary to the lack of precise clinical tools to accurately identify the phenotype of fibrosis in patients. LGE also offers potential targets for new therapeutic strategies designed to personalize medical management, although such a plan requires further research and represents a new field of study (12).

Finally, our results gave us the opportunity to conceptualize a risk score for patients with EA that includes the presence of replacement fibrosis of the LV revealed by CMR. This score could be integrated into clinical practice and complement other clinical variables such as exercise tolerance, echocardiographic parameters, and laboratory values to facilitate individualized treatment. We encourage establishing the routine use of CMR in the diagnosis and follow-up of patients with unrepaired EA, as it will aid in orienting the best treatment for each patient, including interventions that improve long-term survival such as early surgical approaches (15,36–38). Furthermore, with the increased awareness of abnormalities of the LV and improved imaging techniques such as T1-CMR imaging, dysfunction of the LV in EA may be assessed early in management of the patient, when optimal treatment can be started, thus avoiding unfortunate outcomes. We encourage clinicians to keep in mind that extensive imaging evaluation should be complemented with clinical and risk score assessment in order to establish an appropriate diagnosis and survival prognosis and improve quality of life and overall health in this population.

**Strengths and Limitations**

We recognize some strengths and limitations of our study. Overall, our findings bring novel insights into cardiovascular imaging of adults living with EA with direct implications for clinical practice in cardiology and radiology. We assembled one of the largest Mexican cohorts of adult patients with unrepaired EA. Our design allowed us to establish prognostic implications on the mortality of patients with EA related to LV fibrosis. Furthermore, the use of CMR information as well as a subset of four post-mortem samples helped us to comprehensively characterize the LGE patterns. Nevertheless, we acknowledge some limitations. First, this is a retrospective cohort design performed at a national referral center, which has inherent survival and selection biases. Second, we should warrant that establishing any causality of fibrosis of the LV on mortality should be interpreted with caution and not as a generalized concept. Finally, we were unable to assess advanced CMR modalities, such as T1 mapping or extracellular volume, which have demonstrated to be better techniques for evaluating the degree and extent of myocardial fibrosis. The latter should encourage future research with prospective designs and advanced imaging techniques to appropriately evaluate the pathological implications of fibrosis in this population.

**CONCLUSIONS**

Fibrosis of the LV was found in 29.8% of EA patients, mainly affecting the basal third, with a predominance of mid-wall location. LGE in the LV, especially with lateral segment involvement, was associated with a 6-fold increase in mortality and appears to be an independent factor in determining a patient's survival. This raises the possibility of developing a risk score to predict mortality in patients with EA which includes the presence of LGE of the LV and other clinical parameters. Overall, our findings demonstrated that EA is not limited to the right heart. We encourage to use CMR and risk scores within patients living with Ebstein’s anomaly to aid and orient therapeutic decisions in clinical practice to improve survival, overall health and beyond.

**ACKNOWLEDGEMENTS:** N.E.A.V. is enrolled at the PECEM program of the Faculty of Medicine at UNAM. N.E.A.V. is supported by CONACyT. We want to acknowledge the contribution of the Oficina de Apoyo Sistemático a la Investigación Superior (OASIS) of the National Institute of Cardiology Ignacio Chavez for the support for this manuscript.

**FUNDING:** No specific funding was received for this project.

**DISCLOSURES:** The authors declare that they have no conflict of interests.

**DATA SHARING STATEMENT:** All code, data sets and materials are available for reproducibility of results at <https://github.com/neftalivilla/Ebstein_INCICH>

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**FIGURE LEGENDS**

**Table 1.** Sociodemographic, clinical profile, symptoms, and cardiac magnetic resonance assessment in the study population. Comparison between patients with and without LGE in the LV.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameter** | **All-Population**  **(n=57)** | **LV-LGE (-)**  **(n=40)** | **LV-LGE (+)**  **(n=17)** | ***P*-value** |
| Men (%) | 30 (52.63) | 22 (55) | 8 (47.06) | 0.795 |
| Age (years) | 29.52 (21.24-39.17) | 28.4 (20.35-36.11) | 30.93 (25.53-41.35) | 0.466 |
| Age at Diagnosis (years) | 18.83 (13.32-30.39) | 18.67 (11.37-28.34) | 22.78 (16.41-31.01) | 0.600 |
| Time of Treatment (years) | 9.32 (4.67-12.98) | 9.07 (4.53-13.04) | 10.16 (5.45-12.93) | 0.642 |
| Clinical Profile | | | | |
| BSA (m2/1.73) | 1.68 (± 0.2) | 1.68 (± 0.18) | 1.69 (± 0.24) | 0.795 |
| BMI (Kg/m2) | 24.1 (± 4.12) | 23.42 (± 3.68) | 25.71 (± 4.74) | 0.055\* |
| Underweight (%) | 4 (7.02) | 4 (10) | 0 (0) | 0.432 |
| Normal weight (%) | 34 (59.65) | 24 (60) | 10 (58.82) | 0.542 |
| Overweight (%) | 13 (22.81) | 10 (25) | 3 (17.65) | 0.986 |
| Obesity (%) | 6 (10.53) | 2 (5) | 4 (23.53) | 0.106 |
| Diabetes (%) | 1 (1.75) | 1 (2.5) | 0 (0) | 0.981 |
| Arterial Hypertension (%) | 4 (7.02) | 3 (7.5) | 1 (5.88) | 0.891 |
| Stroke (%) | 4 (7.02) | 3 (7.5) | 1 (5.88) | 0.831 |
| Other Comorbidity (%) | 17 (29.82) | 12 (30) | 5 (29.41) | 0.921 |
| Wolff-Parkinson White (%) | 17 (29.82) | 12 (30) | 5 (29.41) | 0.712 |
| Atrio-Ventricular Block (%) | 7 (12.28) | 5 (12.5) | 2 (11.76) | 0.981 |
| Atrial Fibrillation (%) | 8 (14.04) | 7 (17.5) | 1 (5.88) | 0.413 |
| Right Bundle Branch Block (%) | 4 (7.02) | 2 (5) | 2 (11.76) | 0.574 |
| Other Arrhythmia (%) | 4 (7.02) | 2 (5) | 2 (11.76) | 0.067\* |
| Atrial septal defect (%) | 32 (56.14) | 22 (55) | 10 (58.82) | 0.951 |
| Ventricular septal defect (%) | 1 (1.75) | 0 (0) | 1 (5.88) | 0.812 |
| Patent Foramen Ovale (%) | 13 (22.81) | 11 (27.5) | 2 (11.76) | 0.298 |
| Other Structural Impairment (%) | 17 (29.82) | 12 (30) | 5 (29.41) | 0.912 |
| Symptoms | | | | |
| Dyspnea (%) | 13 (22.81) | 9 (22.5) | 4 (23.53) |  |
| Palpitations (%) | 18 (31.58) | 13 (32.5) | 5 (29.41) | 0.741 |
| Edema (%) | 5 (8.77) | 4 (10) | 1 (5.88) | 0.974 |
| Fatigue (%) | 10 (17.54) | 7 (17.5) | 3 (17.65) | 0.812 |
| Tachycardia (%) | 2 (3.51) | 1 (2.5) | 1 (5.88) | 0.511 |
| Cyanosis (%) | 9 (15.79) | 7 (17.5) | 2 (11.76) | 0.709 |
| NYHA I (%) | 46 (80.7) | 34 (85) | 12 (70.59) | 0.274 |
| NYHA II (%) | 10 (17.54) | 5 (12.5) | 5 (29.41) | 0.145 |
| NYHA III (%) | 1 (1.75) | 1 (2.5) | 0 (0) | 0.972 |
| Hemoglobin (gr/dl) | 15.6 (14.3-17.75) | 15.5 (14.25-17.08) | 16.8 (14.8-20.6) | 0.163 |
| Hematocrit (%) | 46.4 (42.25-53.45) | 45.95 (41.53-51.83) | 50 (44.7-61.5) | 0.436 |
| CMR assessment | | | | |
| Severity Index | 0.7 (0.53-0.95) | 0.7 (0.53-0.95) | 0.82 (0.52-1.07) | 0.6211 |
| Septal Leaflet Displacement (mm) | 62 (47-72) | 58 (45-70.5) | 67 (59-74) | 0.5267 |
| Posterior Leaflet Displacement (mm) | 73 (62-78) | 73 (62-78) | 74 (66-78) | 0.3518 |
| RV- Atrialization (mm) | 63 (50-83) | 53 (50-74) | 70 (50-83) | 0.5203 |
| RV- Atrialization (%) | 63 (58-76) | 63 (57-70.5) | 68 (59-76) | 0.7157 |
| LVEF (%) | 52 (43-57) | 53 (45.75-60) | 49 (32-55) | <0.001\* |
| RVEF (%) | 34 (25-43) | 36 (25-44.25) | 32 (25-39) | 0.0207\* |
| LV-EDV Indexed (mL/m2) | 51 (41-63) | 49.5 (40.75-62.08) | 58 (45-76) | 0.9142 |
| LV-ESV Indexed (mL/m2) | 26 (20-31) | 25 (20.75-31) | 28 (20-42) | 0.0829\* |
| LV-Mass Indexed (g/m2) | 35 (29-42) | 34 (29-42) | 37 (29-52) | 0.0762\* |
| RV-EDV Indexed (mL/m2) | 161 (115-229) | 170 (132-232.5) | 132 (77-184) | 0.9142 |
| RV-ESV Indexed (mL/m2) | 120 (79-163) | 121.5 (79.5-163) | 114 (79-163) | 0.0829 |
| Enhanced Areas (n) | 0 (0-1) | 0 (0-0) | 2 (1-3) | 0.031\* |
| Left-Atrium (%) | 3 (5.26) | 1 (2.5) | 2 (11.76) | 0.2092 |
| Right-Atrium (%) | 14 (24.56) | 9 (22.5) | 5 (29.41) | 0.7378 |
| Right-Ventricle (%) | 8 (14.04) | 5 (12.5) | 3 (17.65) | 0.6841 |
| Intra-myocardial (%) | 14 (24.56) | 1 (2.5) | 13 (76.47) | <0.001\* |
| Subendocardial (%) | 1 (1.75) | 0 (0) | 1 (5.88) | 0.2982 |
| Subepicardial (%) | 1 (1.75) | 0 (0) | 1 (5.88) | 0.2982 |
| Transmural (%) | 4 (7.02) | 1 (2.5) | 3 (17.65) | 0.0748 |

BMI, body mass index; BSA, body surface area; CMR, cardiac magnetic resonance; EDV, end-diastolic volume; ESV, end-systolic volume; LV, left ventricle; LVEF, left ventricle ejection fraction; NYHA, New York Heart Association; RV, right ventricle; RVEF, right ventricle ejection fraction.

**Table 2.** Correlation between histopathological findings and CMR in patients with Ebstein’s anomaly.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Patient** | **Sex / Age of death** | **Comorbidities / NYHA functional class** | **Other Cardiac anomalies** | **Histopathology** | | | | **CMR-LGE** | |
| **RV free-wall fibrosis** | | **LV free-wall fibrosis** | | **RV** | **LV segments** |
| *Interstitial*  *(%)* | *Replacement*  *(%)* | *Interstitial (%)* | *Replacement*  *(%)* |
| 1 | M / 18 | None / II | None | 30 | 0 | 35 | 2 | - | - |
| 2 | M / 20 | None / II | ASD, WPW | 60 | 4 | 50 | 2 | - | - |
| 3 | F / 35 | None / I | ASD | 50 | 5 | 40 | 15 | - | Basal anterolateral, middle anterolateral. |
| 4 | M / 23 | Epilepsy / II | WPW | 8 | 8 | 30 | 0 | - | - |

ASD, atrial septal defect; CMR, cardiac magnetic resonance; LV, left ventricle; F, female; M, male; RV, right ventricle; WPW, Wolff-Parkinson White.

**Table 3.** Cox proportional hazard regression model to assess the risk for mortality associated with LV-LGE (+). *Model 1*: adjusted for sex and BSA. *Model 2*: adjusted for model 1 + number of commodities, LVEF, LV mass index and RV atrialization.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Model** | **Coefficients** | **HR** | **95% CI** | **P Value** |
| *Unadjusted*  C-Statistic: 0.606  BIC: 69.08  Wald Test (P-Value): 0.07 | 1.133 | 3.106 | 0.90-10.68 | 0.072 |
| *Model 1*  C-Statistic: 0.799  BIC: 64.82  Wald Test (P-Value): 0.02 | 1.431 | 4.181 | 1.14-15.30 | 0.030 |
| *Model 2*  C-Statistic: 0.802  BIC: 69.33  Wald Test (P-Value): 0.01 | 1.593 | 6.020 | 1.22-19.91 | 0.025 |

BIC, Bayesian Information Criteria; BSA, body surface area; CI, Confidence intervals; HR, Hazard Ratios; LV, left ventricle; LVEF, left ventricle ejection fraction; RV, right ventricle.

**Figure 1.** STROBE flow-chart of our sample of patients with Ebstein’s anomaly

Eligible adult patients

N=153

Examined for eligibility

N=70

Analyzed

N=57

**Elimination Criteria (n=83)**

Without magnetic resonance data (n=76)

Previous tricuspid valve surgery (n=7)

**Exclusion Criteria (n=13)**

Magnetic resonance without gadolinium (n=9)

Congenital corrected transposition of the great arteries (n=2)

Dilated cardiomyopathy (n=1)

Tetralogy of Fallot (n=1)

**Identification**

**Inclusion**

**Analysis**

**Figure 2.** Positive late gadolinium enhancement stratified by chambers (A), location (B) and segments (C) in our sample of patients with Ebstein’s anomaly.



**Figure 3. Comparison of CMR images and histopathological findings in a patient. A.** Short-axis view demonstrating mid-wall LGE of the LV anterolateral wall (yellow arrow). **B.** Four chamber view showing mid-wall LGE in the LV lateral wall (basal and middle anterolateral segments) and basal anteroseptal segment (yellow arrows). RV tricuspid displacement areas and RV-LV junction sites showing mid-wall LGE (red arrow). **C.** RV with thin myocardial walls (yellow arrow) and an elongated tricuspid valve with a displaced origin (red arrow). The true atrioventricular groove is indicated by a yellow dotted line. **D.** Hypertrophic LV, lateral wall measured 13 mm (yellow arrow). **E.** RV free wall (yellow arrow) with predominance of interstitial fibrosis. **F.** LV medial lateral wall showing intramyocardial interstitial collagen array with patches of replacement fibrosis, Masson-trichrome 4X.

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Description automatically generated

CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; LV, left ventricle; RV, right ventricle

**Figure 4.** Kaplan-Meier analysis to evaluate the survival probability associated with LGE (+).

Gráfico

Descripción generada automáticamente

LV-LGE, left ventricular late gadolinium enhancement; RV-LGE, right ventricular late gadolinium enhancement.

**Figure 5.** Cox proportional hazard regression model to assess the risk of death attributable to fibrosis by location (A) and regions (B) in the left ventricle.



CI, Confidence intervals; HR, Hazard ratio.