

# A novel framework to enhance scientific knowledge of cardiovascular MRI biomarkers and their application to pediatric cardiomyopathy classification

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**Abstract.** Cardiovascular Magnetic Resonance Imaging (CMRI) has become a powerful popular non-invasive tool for detecting biomarkers of various types of subtle pediatric cardiomyopathies yielding BIG temporal, high-resolution data. The complexities associated with the annotation of images and extraction of markers, necessitate the development of efficient workflows to acquire, manage and transform this data into actionable knowledge for patient care. We develop and test a novel framework called CMRI-BED for biomarker extraction and discovery from pediatric cardiac MRI data involving the use of a suite of tools for image processing, marker extraction and predictive modeling. We applied the workflow to obtain and analyze a small dataset containing CMRI-derived biomarkers for classifying positive versus negative findings of cardiomyopathy in children. Preliminary results show the feasibility of our framework for processing such data while also yielding actionable predictive classification rules that can augment knowledge conveyed in cardiac radiology outcome reports.

**Keywords:** Cardiovascular MRI, Cardiomyopathy classification, Bayesian Rule Learning

## 1 Introduction

Cardiovascular Magnetic Resonance Imaging (CMRI) is currently regarded as the gold standard for the non-invasive acquisition and processing of high-resolution temporal images for heart tissue characterization. CMRI is routinely used clinically to discover sources of abnormalities in cardiac structure, function and dynamics. Its applicability to the detection and diagnosis of genetic cardiomyopathies, particularly in pediatric populations, is of immense significance for effective treatment options and follow-up care by the primary physician in consultation with cardiac radiologists and specialists. The large amounts of CMRI data acquired per patient leads to several

complexities associated with the annotation of images and extraction of markers to differentiate the various subtle and rare forms of cardiomyopathies. These complexities necessitate the development of efficient workflows to acquire, manage and transform this data into actionable knowledge for patient care.

Past work in this area has typically been in the image processing domain, wherein the effort has gone into imaging bio-marker extraction, segmentation of global and local regions of interest [1], extraction of quantitative metrics such as volume estimation, morphological, functional or flow-based features [2, 3] and finally automated tools for multi-modal image registration. To our knowledge, the clinical workflows associated with the CMRI data acquisition and processing have not been studied from a machine learning perspective to identify areas of inefficiencies wherein intelligent computational tools could be developed to aid cardiac radiologists in the assessment of cardiomyopathies using a multitude of imaging biomarkers. In this paper, we develop and test a novel framework called CMRI-BED (Cardiovascular Magnetic Resonance Imaging Biomarker Extraction and Discovery) that includes predictive modeling of retrospective CMRI data to extract classification rules that augment knowledge obtained from standard practice. We present our preliminary findings from the application of this workflow to a dataset containing positive and negative findings for a subset of pediatric patients evaluated for cardiomyopathies.

## 2 Background

Cardiovascular disease is the #1 leading cause of death worldwide [4]. Cardiomyopathy (CM) generally refers to a diverse group of diseases of the heart muscle and are classified according to anatomy and physiology into the following types: Hypertrophic cardiomyopathy (HCM), Dilated cardiomyopathy (DCM), Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), Restrictive cardiomyopathy (RCM) and unclassified cardiomyopathies (NCM). In 1996, a highly cited scientific statement from the American Heart Association (AHA) proposed contemporary definitions and classification of primary and secondary cardiomyopathies that took into account molecular genetics in cardiology [5]. A recent article thoroughly illustrates the various types of common and rare cardiomyopathies, and their classification based on specific morphological and functional phenotypes [6].

CMRI has become a popular non-invasive technology for cardiomyopathy assessment. The basic protocols for cardiomyopathy assessment using CMRI are discussed and illustrated in [6]. A further discussion of assessment of rare cardiomyopathies using CMRI is presented in [7]. Standardized CMRI protocols are reviewed in [8]. CMRI has recently emerged as a powerful tool for detecting cardiovascular biomarkers [9]. It is helpful in making a differential diagnosis between different types of cardiomyopathies [10-12]. In pediatric populations, genetic cardiomyopathies are of particular significance due to the need for timely intervention to prevent morbid outcomes.

Table 1 depicts statistics on pediatric populations for genetic cardiomyopathies, which include HCM [13], DCM, ARVC/D, RCM (and iron mediated CM), NCM

[14], along with Tetralogy of Fallot(ToF) [15] that is a morphological congenital heart disease (CHD) associated with myopathy of the right ventricle. Some examples of CMRI-based quantitative and qualitative markers are also depicted. These biomarkers are representative of structure (morphology), function and dynamics (flow) of the heart muscle.

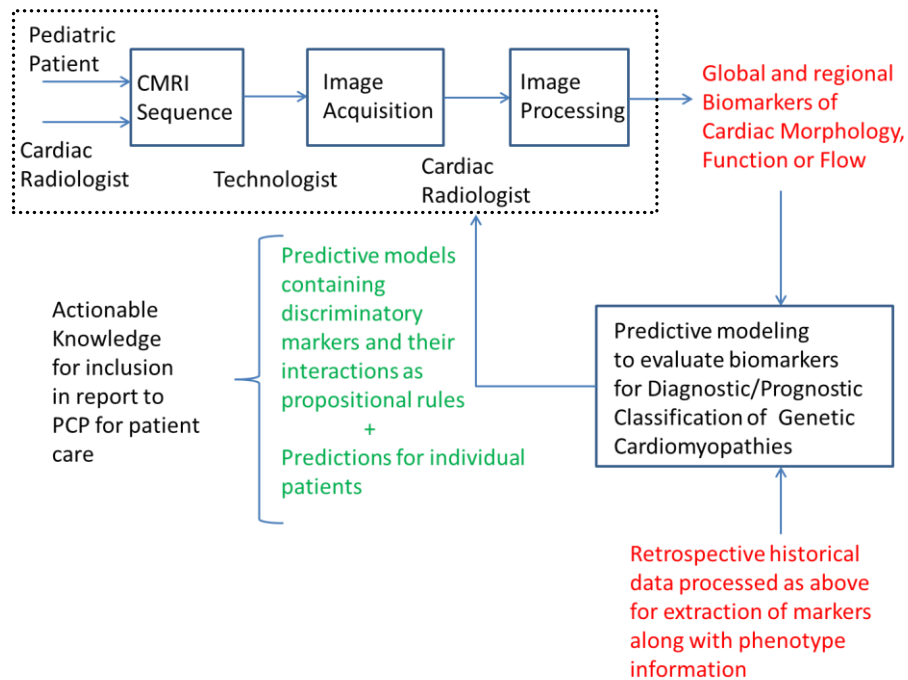
**Table 1.** Incidence, prevalence and other statistics for the five cardiomyopathies and a more prevalent pediatric CHD called ToF, with associated right ventricular abnormalities. Some examples of standard quantitative and qualitative markers from CMRI that are associated with observed normal (NL) or abnormal (ABNL) values in each disease based on patients seen at the Children’s Hospital of Pittsburgh (CHP) between 2000 and 2013. LV refers to Left Ventricular and RV to Right Ventricular regions.

CM Subtypes	HCM	DCM	ARVC/D	NCM	RCM & Iron mediated CM	ToF <sup>15</sup>
<b>Incidence (I) OR Prevalence (P)</b>	P = 1:500 in absence of aortic valve disease or systemic hypertension	I = 5-8 cases /100,000 P = 36 cases /100,000	I = 1/10,000	I = 0.05% to 0.24%	I = 11.4% to 15.1% in Thalassemia major patients Transfusion Dependent	I = 9/1000 live births
<b>#Patients evaluated for CM</b>	46	129	44	31	35	684
<b>Total number of positive diagnosis w/ CMRI CM</b>	11	18	4	15	12	119
<b>CMRI-based QUANTITATIVE markers</b>						
<b>LV myocardial wall thickness</b>	ABNL	ABNL	NL	ABNL	ABNL	NL
<b>LV mass index</b>	ABNL	ABNL	NL	ABNL	ABNL	NL
<b>LV Volume index</b>	ABNL	ABNL	NL	ABNL	ABNL	ABNL
<b>RV Volume index</b>	NL	ABNL	ABNL	NL	ABNL	ABNL
<b>CMRI-based QUALITATIVE markers</b>						
<b>Myocardial Delayed Enhancement</b>	+/-	+/-	+/-	+/-	+/-	+
<b>Wall motion abnormalities</b>	+/-	+/-	+/-	+/-	+/-	+/-

Machine learning methods are now routinely applied to predictive modeling of disease states from high-dimensional biomedical data. Both linear and non-linear modeling methods are available for classification tasks, wherein a classifier is learned using training data containing possible predictors (e.g. biomarkers) of a target class (e.g. the

presence of absence of a disease). A particular method that has been applied successfully to ‘omic’ biomarker discovery is the Bayesian rule learning (BRL) [16] system, which uses a Bayesian score to construct Bayesian networks (BNs) and to learn probabilistic rule models from them. The models produced are easily interpretable by the biomedical scientist and have been shown to have fewer markers and equivalent or greater classification performance in comparison to models derived from other rule learning methods [16, 17]. In this paper, we develop and apply a novel workflow that permits the application of BRL to CMRI-derived biomarkers for classification of positive versus negative findings of cardiomyopathy in pediatric patients.

**Fig. 1.** Overview of the Cardiovascular Magnetic Resonance Imaging Biomarker Extraction and Discovery (CMRI-BED) framework. Standard clinical practice is depicted as dotted box.



### 3 Methods

Figure 1 depicts the CMRI-BED workflow which represents a simplified process description by which CMRI-derived biomarkers can be extracted and interactions among the biomarkers can be assessed using state-of-the-art predictive rule models to assist in the accurate classification of genetic cardiomyopathies in children. The pediatric patient with a suspicion of cardiac disease based on presenting signs and symptoms is usually referred by the primary care physician (PCP) to consult with pediatric cardiology for basic initial clinical cardiac evaluation. Further evaluation for accurate diagnosis requires advanced cardiac MRI sequences as recommended by the experi-

enced cardiac radiologist based on initial clinical findings, family history of patient and published literature and guidelines laid down by the Society for Pediatric Radiology. These sequences dictate the preparation of the patient, and subsequent image acquisition by the technician who works together with the radiologist and technology to capture the appropriate sets of images, ensuring their quality. Phantom runs are made with a body of water placed in lieu of the patient with the same parameter settings to ensure that the values obtained by the technology are within acceptable ranges.

Once the images are acquired, which takes approximately two hours depending on the CMRI protocol, they are post-processed by the cardiac radiologist, an appropriately trained physician who can evaluate the large sets of images and mark regions and contours for biomarker quantification. The radiologist also provides qualitative assessments for several standard markers. Commercially available image processing software technology is used to assist the radiologist in performing these assessments, and is made available through the same vendor that makes the MRI scanning technology. The commercially available software technology permits the generation of standard reports that contain quantitative and qualitative assessments of the CMRI-based diagnosis, and these reports are sent to the referring pediatric cardiologist. Within the CMRI-BED, we propose to include our novel predictive modeling tools that can analyze retrospective data acquired for case/control discrimination from the hospital's database for performing hypothesis driven retrospective and prospective clinical research studies (see Table 1 for availability of subjects for different CM types). We will generate classification rules that can inform the cardiac radiologist, referring pediatric cardiologist and the PCP about the kinds of interactions between different markers that can better discriminate CM types based on a training dataset, and we will also be able to give a diagnosis/prediction for a given patient.

Using the proposed framework, we can extract both standard as well as novel CMRI biomarkers for diagnostic and prognostic purposes. An example of a novel regional imaging biomarker that was recently discovered based on our analysis of publicly available CMRIs within the Cardiac Atlas Project [18] databases is briefly discussed next. Cardiac MRIs of 25 symptomatic patients with coronary artery disease or left ventricle impairment and 25 asymptomatic patients were used to extract cardiovascular function metrics. This also led to the discovery of a new regional imaging biomarker of cardiac function that we call **RMS-P2PD** [19] which calculates the root mean square (RMS) error from average phase to phase regional left ventricular endocardial displacement, and is computed on a patient specific basis. The workflow depicted in Figure 1 is aimed to augment the efficiency and accuracy with which clinical radiologists detect and treat cardiovascular abnormalities in children.

Below we give an illustrative example for proof-of-concept of this framework. This example uses available data which is fairly noisy and comprises a small dataset. It should be noted that such data are still not easily available in individual radiology clinics, which further motivates the potential of our framework to enhance scientific understanding of the process by which standard and novel CMRI biomarkers can be assessed for validity with respect to classification of pediatric genetic cardiomyopathies. The framework can be used to assess whether or not certain types of CMRI biomarkers assessed using different technologies are suitable for classification of

pediatric cardiomyopathy, and if so, to what extent. An example would be to assess the value of strain quantification measures from myocardial tagging sequence using CMRI to detect the presence or absence of regional morphological changes as an early marker of cardiomyopathy [14, 15] in patients referred for cardiac imaging tests. Strain quantification is an upcoming method for clinical evaluation of these patients.

**Dataset:** Retrospective analysis was conducted on a set of 43 de-identified patients (22 males and 21 females) who were enrolled in a previous study [15] as described in the following subsection. Of these, one female 4-month old patient identified with cardiomyopathy had outlier values, and was removed from our predictive modeling analysis of these data. This provided us with a total of 15 patients identified as Positive for cardiomyopathy and 27 patients with findings as Negative. The dataset contained standard CMRI biomarkers along with gender, age and diagnosis. The original biomarkers are depicted in Table 2. It is to be noted that a few of the markers such as Fractional Shortening (FS), left and right ventricular ejection fractions, cardiac output and the indices are derived parameters.

We constructed new variables based on the “normal” ranges for the left and right ventricular end-systolic and end-diastolic volumes and *Stroke Volume* parameters [20]. The body surface area (BSA) of each de-identified patient had to be re-derived from the indices in the dataset, and then, we used the clinical charts provided in [20] to determine whether a patient’s volumes are within a normal range given his/her BSA. Patients with volumes within the 95% confidence bands on each chart were labeled with the corresponding parameter values as “Normal”, while those outside this threshold were labeled as “Abnormal”. Using this method, we created 5 new discrete variables *LVEDV Range*, *LVESV Range*, *RVEDV Range*, *RVESV Range* and *Stroke Volume Range*.

**Table 2.** Standard CMRI biomarkers.

<b>Left Ventricle (LV) Parameters</b>	<b>Right Ventricle (RV) Parameters</b>	<b>Overall Cardiac Parameters</b>
A.S. Wall (cm)	RV Major Axis (cm)	Stroke Volume (ml)
P.S. Wall (cm)	RV Minor Axis (cm)	Stroke Volume Index (ml/m <sup>2</sup> )
End Diastolic Dimension (cm)	RV End Diastolic Vol (ml)	Heart Rate (bpm)
End Systolic Dimension (cm)	RV End Systolic Vol (ml)	Cardiac Output (l/min)
LV End Diastolic Vol (ml)	RV Major Axis Index (cm/m <sup>2</sup> )	Cardiac Index (l/min/m <sup>2</sup> )
LV End Systolic Vol (ml)	RV Minor Axis Index (cm/m <sup>2</sup> )	
LV Ejection Fraction (%)	RV Ejection Fraction (%)	
LV End Diastolic Index (ml/m <sup>2</sup> )	RV End Diastolic Index (ml/m <sup>2</sup> )	
LV End Systolic Index (ml/m <sup>2</sup> )	RV End Systolic Index (ml/m <sup>2</sup> )	
Fractional Shortening (%)		

**Image Acquisition and Processing:** A previously approved research study [15] had enrolled and selected patients by convenience sampling in the order that they sought clinically indicated CMRI's at the Children's Hospital of Pittsburgh (CHP). Inclusion criteria for the patient group included 0-18 years old, repaired ToF, and exclusion criteria included having undergone pulmonary valve replacement. Inclusion criteria for the control group included 0-18 years old and absence of cardiac disease. The control patients sampled underwent clinically indicated CMRI's at the recommendation of their attending physicians due to concern for undiagnosed cardiac disease. Radiologists unaffiliated with that study analyzed the results from these CMRI's and documented that these patients had normal cardiac function and morphology, with no evidence of cardiac disease. Additional patient records and test results were accessed for confirmation of these results.

CMRI images were acquired with a GE SignaHDxt 1.5 Tesla MRI (GE Healthcare, WI, USA). Scans were performed by radiology technicians unaffiliated with this research project. Due to their young ages, 4 patients required general anesthesia during their MRI scans. A balanced steady state free precession sequence (FIESTA, GE) was used in the short axis to acquire images for biventricular volumetric analysis during 20 phases of the cardiac cycle. Relevant parameters included breath holds = 1-2 (none for patients under general anesthesia), number of excitations = 1 for patients with breath holds and 2 for patients under general anesthesia, repetition time = 3.6-4.0 ms, echo time = 1.5-1.7 ms, flip angle = 55°, slice thickness = 5-7 mm, and acquisition matrix = 256x256. Commercially available post-processing software ReportCARD™ (GE Healthcare, WI, USA) was used to determine volumetric data, flow and velocities.

## 4 Results

The CMRI-derived biomarkers (Table 2) dataset containing 15 positive cases and 27 negative controls was analyzed using our novel Bayesian Rule Learning (BRL) methods [16, 21]. BRL [16] works by searching for interactions between predictors that are favorable for discriminating the target class values, which for this dataset are represented by positive or negative MR diagnosis. BRL performs a heuristic, iterative search of the entire space of possible models (constrained BNs) representing interactions among potential predictors, and uses a Bayesian score to represent the uncertainty in the validity of each model. The top one thousand models are stored in the order of their Bayesian score during each search iteration and used to grow the interaction terms up to a user-specified maximum (default is 8 predictors).

We present below a BRL (Decision Tree) [21] model to illustrate the kinds of interactions between CMRI-derived markers that can be used for automatic classification. We used equal frequency binning (2 bins) available within BRL to discretize the input variables. We obtained a model from BRL that was developed by learning on the entire training data (15 positives, 27 negatives). This model (see rules below) was applied to the training data to make predictions, and fit the data with the following statistics – Accuracy = 83%, Sensitivity = 87% and Specificity = 82% for the Positive

class, and an Area under the ROC curve value = 91%. The model used 6 variables LVEF, CardiacIndex, LVESVRange, FS, RVSVRange, RVMajorAxisIndex (which are age and gender specific) as shown below:

1. IF (RVMajorAxisIndex  $\leq$  5.2) & (RVSVRange = Abnormal) & (LVEF  $\leq$  60.6) THEN (MRDx = Normal)  
Posterior Probability=0.909, P=0.011, TP=9, FP=0
2. IF (RVMajorAxisIndex  $>$  5.2) & (CardiacIndex  $\leq$  2.7) & (LVEF  $>$  60.6) THEN (MRDx = Normal)  
Posterior Probability=0.889, P=0.033, TP=7, FP=0
3. IF (RVMajorAxisIndex  $>$  5.2) & (CardiacIndex  $\leq$  2.7) & (LVEF  $\leq$  60.6) & (FS  $\leq$  32) THEN (MRDx = Normal)  
Posterior Probability=0.75, P=0.408, TP=2, FP=0
4. IF (RVMajorAxisIndex  $\leq$  5.2) & (RVSVRange = Abnormal) & (LVEF  $>$  60.6) & (LVESVRange = Abnormal) THEN (MRDx = Normal)  
Posterior Probability=0.625, P=0.639, TP=4, FP=2
5. IF (RVMajorAxisIndex  $\leq$  5.2) & (RVSVRange = Normal) THEN (MRDx = Positive)  
Posterior Probability=0.75, P=0.122, TP=2, FP=0
6. IF (RVMajorAxisIndex  $\leq$  5.2) & (RVSVRange = Abnormal) & (LVEF  $>$  60.6) & (LVESVRange = Normal) THEN (MRDx = Positive)  
Posterior Probability=0.667, P=0.357, TP=1, FP=0
7. IF (RVMajorAxisIndex  $>$  5.2) & (CardiacIndex  $\leq$  2.7) & (LVEF  $\leq$  60.6) & (FS  $>$  32) THEN (MRDx = Positive)  
Posterior Probability=0.667, P=0.357, TP=1, FP=0
8. IF (RVMajorAxisIndex  $>$  5.2) & (CardiacIndex  $>$  2.7) THEN (MRDx = Positive)  
Posterior Probability=0.625, P=0.009, TP=9, FP=5

The posterior probability for each classification rule is calculated by BRL. In addition, the rules also contain a p-value (P) that is calculated for each rule using Fisher's exact test. The number of true positives (TP) and false positives (FP) covered by each rule is also reported. We choose this model for purposes of illustration because we obtained at least a few general rules that are reasonable in terms of both accuracy and coverage as shown above. The above classification rule model is shown for illustrative purposes to depict how a parsimonious description of a complicated cardiac biomarker dataset can be obtained using our BRL methods. Access to a larger training dataset is clearly required along with independent test sets for validating



predictive models obtained from such CMRI data. While BRL was able to find rules that are established and well-known in the literature [20], it must be noted that different discretization methods lead to different cutoffs for the input variables. This issue must be addressed in order to enable stable models to be learned from such CMRI datasets.

## 5 Discussion

CMRI cardiomyopathy data is an example of a type of BIG data that presents several informatics challenges. As seen in the results section, the collaborative efforts between cardiac radiologists, data miners, biomedical engineers, technicians and biomedical informaticians will be crucial to establish and maintain databases or electronic repositories that can be used to create knowledge for transforming patient care. Based on our experience in applying the CMRI-BED framework, we identify the following three immediate informatics challenges that require elegant state-of-the-art solutions:

1. The need for a gold-standard, secure repository for storing the cardiac MR image sequence specific manually traced contours and image annotations performed on the entire sets of 2D, 3D and 4D images apart from the raw images acquired and stored in DICOM formats for each (de-identified) patient in clinical setting. Currently, these post-processed images are pushed to PACS for clinical reporting following the post-processing at the dedicated cardiac workstation at CHP. Image retrieval of post-processed images for clinical research is a cumbersome and deliberate time exhausting task which affects the clinical research flow.
2. The need for adequately trained personnel to perform such annotations on existing CMR images. On an average, it takes at least 1 year to adequately train a technologist who has met prerequisites for performing clinical cardiac MRI procedure.
3. The need for a series of systematic studies that can provide adequate age, gender and clinical history matched controls that are crucial for predictive modeling of CMRI data.

Challenge #1 can be met by secure, cloud-based architectures that permit large data storage and acquisition. Filling the second need can enhance the productivity of cardiac radiologists. A single pediatric radiologist reads and annotates about 350 cases in a year, because each case can take anywhere from four to eight hours to capture CMRI data and process it to generate and verify reports. Meeting challenge #3 will provide power to predictive modeling studies due to availability of matched case-controls in sufficient quantities to be able to better understand and differentiate cardiac diseases.

## 6 Conclusion

Pediatric cardiomyopathies are significant diseases that are routinely examined using CMRI. Pediatric cardiomyopathies are a heterogeneous group of serious disorders of the myocardium and are responsible for significant morbidity and mortality among children if not timely diagnosed. In this paper, we develop and test a novel workflow called CMRI-BED for biomarker extraction and discovery from CMRI data. The novelty arises from the iterative involvement and use of unique, predictive tools such as BRL to model retrospectively available CMRI data and provide physicians with knowledge that relates biomarker interactions to outcome classification. Moreover, the workflow is flexible, scalable and largely independent of technology. Advances in CMRI technology can lead to the development of new biomarkers, which can be easily incorporated into our modeling framework. Retrospective data can be obtained from multiple institutions and summarization of these using BRL will help in drawing more general conclusions. Extensions to this workflow can be also made to allow for integration of image biomarkers from multiple platforms using variants of extant algorithms for transfer learning of classification rules [22]. We believe that this CMRI-BED workflow will help in the assessment of CMRI biomarkers in a timely fashion for improved diagnosis and prognosis of pediatric cardiomyopathies.

### Acknowledgements

We thank Aditya Nemlekar for help in pre-processing of the dataset and preliminary analysis. We thank Jeya Balasubramanian for the latest version of the BRL system.

Grant support: The research reported in this publication was supported in part by the following grants from the National Institutes of Health: National Library of Medicine Award Number R01LM010950, and National Institute of General Medical Sciences Award Number R01GM100387. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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