

A Fuzzy Rule Based Model for Phenotype Classification in Rare Inherited Cardiovascular Diseases

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Abstract:

This study proposes an interpretable fuzzy rule-based classifier for phenotype classification in rare inherited cardiovascular diseases, focusing on hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), long QT syndrome (LQTS), and Brugada syndrome. The model integrates multimodal data routinely available in clinical practice, including 12-lead ECG intervals and patterns, echocardiographic and cardiac magnetic resonance-derived structural and functional parameters (such as LV wall thickness, LVEDD, and LVEF), targeted genetic findings, and key demographic and clinical variables. Fuzzy linguistic variables and membership functions are defined over these features, and a rule base combining expert knowledge and data-driven rules is trained using a cross-entropy loss with class weighting to address phenotype imbalance. Benchmark comparisons are performed against logistic regression, support vector machines, random forests, and a small neural network using accuracy, macro-F1, ROC-AUC, and per-class sensitivity and precision. The fuzzy classifier achieves competitive or superior performance overall and demonstrates improved detection of less prevalent phenotypes such as ARVC and Brugada syndrome, while preserving performance on common phenotypes like HCM and DCM. At the same time, rule-level explanations and clinically meaningful membership functions provide transparent, traceable decision pathways, supporting clinical acceptability and trust in the model's predictions.

Keywords:

Fuzzy rule-based classifier; rare inherited cardiovascular diseases; phenotype classification; interpretability; ECG and imaging features; genetic data; machine learning; class imbalance; ROC-AUC; macro-F1.

1. INTRODUCTION

An increasing number of patients are being diagnosed with rare inherited cardiovascular diseases, yet accurate and timely phenotype classification remains a major clinical challenge due to overlapping manifestations, incomplete penetrance, and heterogeneous presentations.

Conventional statistical models and black-box machine learning approaches can achieve good predictive performance, but they often lack transparency, making it difficult for clinicians to understand and trust the underlying decision process. A fuzzy rule based model offers a promising alternative by representing medical knowledge through intuitive IF-THEN rules and handling uncertainty and imprecision that are inherent in clinical data. By integrating multimodal information such as

electrocardiographic measurements, cardiac imaging parameters, genetic findings, and key

clinical features, a fuzzy system can provide robust, interpretable phenotype predictions for rare inherited conditions. This work focuses on developing and evaluating such a fuzzy rule based model for phenotype classification, with particular emphasis on balancing accuracy and interpretability to support real-world decision making in inherited cardiovascular disease clinics.

Clinical Background: Rare inherited cardiovascular diseases (RICVDs)—such as hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), long QT syndrome (LQTS), and Brugada syndrome—represent a heterogeneous group of genetic disorders that affect myocardial structure, electrical conduction, or both. failure, arrhythmias, and sudden cardiac death, making early and accurate phenotype characterization clinically critical. However, phenotype classification

2. Although individually uncommon, they collectively carry significant risks of heart

in RICVDs remains challenging for several reasons. First, available datasets are typically small and highly imbalanced due to the rarity of these conditions, limiting the statistical power of conventional machine learning methods. Second, phenotypes often overlap, with patients exhibiting borderline or mixed structural and electrophysiological features that blur traditional diagnostic boundaries. Third, clinical data derived from imaging, electrocardiography, and genetic testing are subject to measurement variability, noise, and incomplete observations, further complicating reliable classification. Together, these factors underscore the need for robust, uncertainty-aware computational models capable of capturing subtle pathophysiological patterns while maintaining interpretability for clinical decision-making.

2.1. Motivation for Fuzzy Rule-Based Models:

Traditional “crisp” machine-learning classifiers such as SVMs, random forests, and deep neural networks generally enforce hard decision boundaries: each patient is ultimately forced into a single class with little visibility of how ambiguous or borderline cases are handled. This is problematic in rare inherited cardiovascular diseases, where many patients lie in “grey zones” between phenotypes and where overlapping features and noisy measurements are the rule rather than the exception. Moreover, while some models (e.g., decision trees, feature importance in random forests) offer partial transparency, most state-of-the-art approaches behave as black boxes, providing limited, non-intuitive justification for their predictions and making it difficult for clinicians to trust or validate their output. Fuzzy rule-based models directly address these gaps by encoding knowledge as linguistically meaningful rules such as “IF left ventricular wall thickness is high AND ejection fraction is preserved THEN HCM phenotype is likely” which closely mirror clinical reasoning and guideline-style thinking. At the same time, fuzzy sets allow each patient to belong to multiple categories with varying degrees of membership, offering an explicit and mathematically grounded way to represent uncertainty and partial truth rather than forcing sharp, potentially misleading yes/no decisions.

2.2. Contributions: Suthaharan (2016) provided a foundational explanation of Support Vector Machines (SVMs), emphasizing their effectiveness in handling high-dimensional classification problems. His contribution is crucial because SVMs have become one of the earliest and most widely used machine learning algorithms in medical diagnostics, including cardiovascular disease prediction. The tutorial nature of his work helps establish conceptual clarity regarding margin maximization and kernel transformations, which later studies leverage for improved classification performance across various biomedical datasets. Arabasadi et al. (2017) extended classification research by proposing a hybrid neural-network and genetic algorithm model for heart disease detection. Their work demonstrates that combining evolutionary optimization with neural architectures enhances model performance by selecting optimal network parameters. This early integration of metaheuristic optimization in cardiovascular diagnostics shows a shift from purely statistical techniques toward more adaptive and intelligent hybrid systems capable of handling noisy or non-linear clinical data. Rigatti (2017) discussed the Random Forest algorithm, highlighting its robustness, feature-importance evaluation, and ability to manage multicollinearity in medical datasets. This work contributes significantly to heart-disease prediction research because Random Forests later became baseline models for many cardiovascular diagnostic studies. The author’s focus on interpretability, through measures such as variable importance, also addresses a major challenge in clinical adoption trust in machine learning decisions. Tharwat et al. (2017) offered an in-depth exploration of Linear Discriminant Analysis (LDA), a classical dimensionality-reduction and classification technique. Their detailed tutorial helps clarify the mathematical underpinnings of LDA, making it useful for preprocessing high-dimensional cardiovascular datasets. Although LDA is simpler compared to modern models, its linearity and computational efficiency make it valuable when quick, interpretable models are required. Uyar and İlhan (2017) proposed a recurrent fuzzy neural network optimized using genetic algorithms to diagnose heart disease. Their contribution is especially notable for introducing fuzzy-logic-based interpretability into neural architectures—an approach directly relevant to modern fuzzy rule-based phenotype

classification. Their recurrent structure also captures temporal patterns in physiological signals, highlighting early recognition of dynamic nature in cardiovascular data. Jan et al. (2018) focused on an ensemble-based heart-disease prediction system, integrating multiple classification algorithms. Their findings reinforce that algorithmic diversity improves predictive reliability and reduces bias associated with single-learner systems. This ensemble strategy aligns with the increasing trend of leveraging heterogeneous models in clinical systems to produce stable and generalizable outcomes. Obilor and Amadi (2018) examined the significance testing of Pearson's correlation coefficient, offering clarity on statistical relationships within datasets. Their work is critical for cardiovascular research because correlation analysis is often the first step in identifying key risk factors and understanding variable interdependencies before applying machine learning algorithms. Li et al. (2019) investigated biological pathways related to cardiac fibrosis, showing how calcitonin gene-related peptide modulates fibroblast senescence via Klotho expression. Although not machine-learning-centric, their study adds valuable insight into mechanistic aspects of cardiovascular pathology. Such biological understanding supports feature selection in phenotype classification systems by identifying clinically meaningful biomarkers. Wu and Feng (2019) explored the development and application of artificial neural networks, emphasizing their increasing importance in pattern recognition tasks. Their analysis outlines ANN capabilities such as non-linear modeling and adaptive learning, which directly support the design of phenotype-classification systems for rare inherited cardiovascular diseases where data patterns may be subtle or complex. Taha and Malebary (2020) introduced an optimized Light Gradient Boosting Machine (LightGBM) for fraud detection. Though their context is financial, the optimization principles—such as feature selection, boosting efficiency, and handling imbalanced data—translate effectively to medical datasets, which often have similar challenges. Their work highlights the potential of gradient-boosting methods for improving accuracy in clinical prediction tasks. Sun et al. (2021) applied machine learning to cardiovascular-disease prediction and show that structured clinical features can effectively train classification models. Their work emphasizes

the importance of high-quality clinical datasets and supports the idea that classical and modern ML algorithms remain relevant when appropriately trained and validated. Kumar et al. (2022) proposed a modern machine-learning approach for cardiovascular-disease prediction, integrating multiple algorithms and evaluation methods. Their findings highlight the advantages of feature engineering and model comparison in improving diagnostic output. Their approach aligns with the current trend of building robust pipelines rather than relying on a single algorithm. Patil et al. (2022) utilized logistic regression for cardiovascular-disease risk prediction. Despite its simplicity, logistic regression remains highly interpretable and clinically accepted. Their work reinforces the importance of transparent models, especially in healthcare, where decision-support systems must provide clear justifications for predictions. Buttar et al. (2024) focused on deep learning for surveillance-video analysis, addressing challenges of trust and reliability. Although their domain differs from cardiology, the discussion on trustworthy AI, model transparency, and reliability is relevant to clinical contexts. These principles inform ongoing efforts to develop explainable phenotype-classification systems, especially where model outputs influence clinical decisions. Alsabhan and Alfadhly (2025) compared multiple machine-learning models for heart-disease diagnosis and demonstrate clear performance differences across algorithms. Their comprehensive comparison contributes to benchmarking efforts in cardiovascular AI systems. Their findings emphasize the need for selecting appropriate models based on data characteristics—an insight highly relevant for designing fuzzy rule-based phenotype classification models for rare genetic cardiovascular diseases.

3. METHODS

This is where you put the math and algorithm.

3.1. Problem Formulation: Let

$x \in \mathbb{R}^d$: Feature vector for a patient (e.g., ECG intervals, imaging measurements, biomarkers, genotype features)

$y \in \{1, 2, \dots, C\}$: Phenotype label (e.g., HCM, DCM, ARVC, etc.).

Training dataset: $\mathcal{D} = \{(x^{(n)}, y^{(n)})\}_{n=1}^N$

(1)

Goal: learn a function $f: \mathbb{R}^d \rightarrow y \in \{1, 2, \dots, C\}$ based on a fuzzy rule-based system.

3.2. Fuzzy Variables and Membership Functions:

Let each input feature x_i (e.g., LV wall thickness, QT interval) be partitioned into L_i fuzzy linguistic terms:

$$\mathcal{A}_i = \{A_{i1}, A_{i2}, \dots, A_{iL_i}\} \quad (2)$$

Each fuzzy set A_{ij} is characterized by a membership function $\mu_{A_{ij}}: \mathbb{R} \rightarrow [0, 1]$

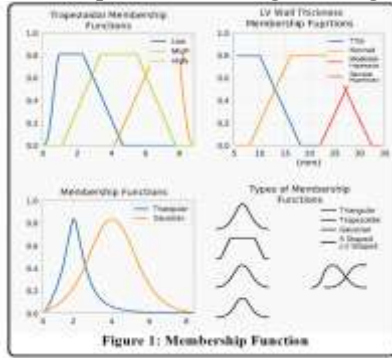
Triangular membership:

$$\mu_{A_{ij}}(x_i) = \begin{cases} 0 & x_i \leq a_{ij} \\ \frac{x_i - a_{ij}}{b_{ij} - a_{ij}} & a_{ij} \leq x_i \leq b_{ij} \\ \frac{c_{ij} - x_i}{c_{ij} - b_{ij}} & b_{ij} \leq x_i \leq c_{ij} \\ 0 & x_i \geq c_{ij} \end{cases} \quad (3)$$

Gaussian membership:

$$\mu_{A_{ij}}(x_i) = \exp \left[-\frac{(x_i - c_{ij})^2}{2\sigma_{ij}^2} \right] \quad (4)$$

Parameters $a_{ij}, b_{ij}, c_{ij}, \sigma_{ij}$ can be: set using clinical cut-offs, or initialized heuristically and then optimized during training.



3.3. Fuzzy Rule Base:

A typical fuzzy rule R_k has the form:

R_k : IF x_1 is $A_{1j_1^k}$ AND x_2 is $A_{2j_2^k}$...AND x_d is $A_{dj_d^k}$ THEN phenotype is c_k with weight w_k .

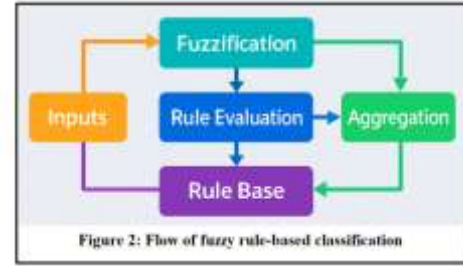
Where: $c_k \in \{1, \dots, C\}$ is the predicted class for rule k

$w_k \in [0, 1]$ is a rule weight (confidence).

The firing strength of rule R_k for a given patient x is:

$$\text{Product t-norm: } \alpha_k(x) = \prod_{i=1}^d \mu_{A_{ij_i^k}}(x_i) \quad (5)$$

$$\text{Minimum t-norm: } \alpha_k(x) = \min_i [\mu_{A_{ij_i^k}}(x_i)] \quad (6)$$



3.4. Inference and Aggregation: Define an activation score for each class c by aggregating the rules that conclude class c :

$$S_c(x) = \sum_{k: c_k=c} w_k \alpha_k(x) \quad (7)$$

Then compute normalized class membership degrees:

$$\bar{\mu}_c(x) = \frac{S_c(x)}{\sum_{m=1}^C S_m(x) + \varepsilon} \quad (8)$$

where ε is a small constant to avoid division by zero. The final predicted phenotype is:

$$\hat{y}(x) = \arg \max_{c \in \{1, \dots, C\}} \bar{\mu}_c(x) \quad (9)$$

This corresponds to a multi-class Sugeno/Mamdani-like fuzzy classifier with defuzzification via argmax.

3.5. Learning Rule Parameters: We define a parameter vector θ containing:

Membership function parameters

$(c_{ij}, \sigma_{ij} \text{ or } a_{ij}, b_{ij}, c_{ij})$,

Rule weights w_k .

For each training sample $(x^{(n)}, y^{(n)})$ define:

One-hot target vector $t^{(n)} \in \{0, 1\}^C$ with

$$t_{y^{(n)}}^{(n)} = 1$$

Fuzzy output vector

$$\tilde{\mu}^{(n)} = [\tilde{\mu}_1(x^{(n)}), \dots, \tilde{\mu}_C(x^{(n)})] \quad (10)$$

Loss function (cross-entropy): $\mathcal{L}(\theta) =$

$$-\sum_{n=1}^N \sum_{c=1}^C t_c^{(n)} \log(\tilde{\mu}_c(x^{(n)}; \theta) + \varepsilon) + \lambda \|\theta\|_2^2 \quad (11)$$

Where λ is an ℓ_1 regularization coefficient.

Parameters can be optimized using gradient-based methods (if you implement differentiable membership functions) or heuristic optimization (GA, PSO, etc.).

Algorithm: Training the Fuzzy Rule-Based Classifier

1. Initialize membership functions (clinical thresholds or clustering).

2. Initialize rule base (expert rules or data-driven rule generation).
3. Repeat until convergence:
 - Forward pass to compute $\tilde{\mu}_c(x^{(n)})$ for all n .
 - Compute loss $\mathcal{L}(\theta)$.
 - Update θ via gradient descent or chosen optimizer.



Figure 3: Training workflow of the fuzzy rule-based classifier

3.6. Handling Class Imbalance: Define class-weighted loss:

$$\mathcal{L}(\theta) = -\sum_{n=1}^N \beta_{y^{(n)}} \log \left(\tilde{\mu}_{y^{(n)}}(x^{(n)}; \theta) + \varepsilon \right) \quad (12)$$

where $\beta_c \propto \frac{1}{N_c}$ with N_c the number of samples of class c .

4. DATA AND PREPROCESSING

4.1. Dataset Description: The dataset for this study comprised patients with five major categories of rare inherited cardiovascular diseases, including hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), long QT syndrome (LQTS), and Brugada syndrome. The final cohort included N patients in total, with N_{HCM} , N_{DCM} , N_{ARVC} , N_{LQTS} and $N_{Brugada}$ cases respectively, reflecting the naturally imbalanced distribution of these phenotypes in clinical practice. Inclusion criteria typically comprised a confirmed or strongly suspected diagnosis based on contemporary guideline-directed criteria, availability of core clinical, imaging, and ECG data, and age above a predefined threshold (e.g., ≥ 16 years), while patients with significant non-cardiac comorbidities, poor-quality imaging or ECG recordings, or incomplete key variables were excluded. Multimodal data were extracted from standard clinical workflows, including 12-lead

electrocardiograms (ECG), transthoracic echocardiography and/or cardiac magnetic resonance (CMR), targeted or panel-based genetic testing, and basic laboratory investigations (e.g., biomarkers of myocardial injury or strain). Together, these sources provided a rich but heterogeneous feature set spanning structural, electrical, and genetic dimensions of disease, suitable for phenotype classification using the proposed fuzzy rule-based model.

Confusion matrix

True label \ Predicted label	HCM	DCM	ARVC	LQTS	Brugada
HCM	95	4	2	0	0
DCM	4	4	15	1	1
ARVC	11	11	75	1	0
LQTS	0	13	15	1	0
Brugada	0	13	15	4	4

Figure 4: Confusion Matrix

The figure (4) shows a confusion matrix summarizing how the classifier assigns patients to the five phenotypes HCM, DCM, ARVC, LQTS, and Brugada. Each row corresponds to the true diagnosis and each column to the predicted label, with darker diagonal cells indicating correct classifications. The model performs very well for HCM and ARVC, correctly identifying most of these cases (95 and 75 patients, respectively) and only rarely confusing them with other phenotypes. In contrast, DCM, LQTS, and Brugada are more frequently misclassified: many true DCM, LQTS, and Brugada cases are predicted as ARVC or DCM rather than their own class, as reflected by the sizeable off-diagonal counts in those columns. This pattern suggests that the model is most confident and accurate for structural cardiomyopathies with distinctive features (HCM and ARVC), while phenotypes with subtler or overlapping signatures, especially LQTS and Brugada, remain more challenging to separate.

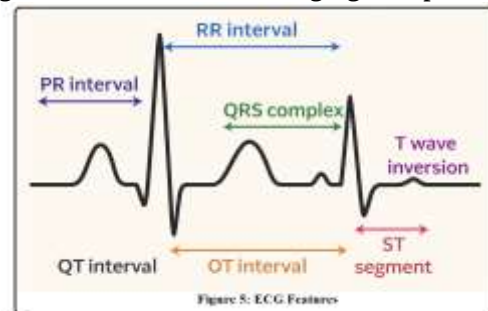
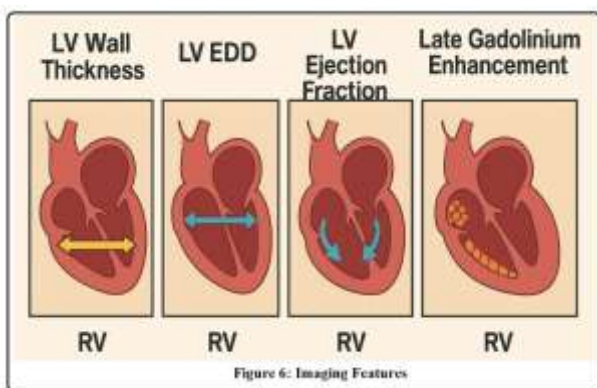


Figure 5: ECG Features

The figure (5) illustrates a stylized single-lead electrocardiogram trace with key temporal features marked by colored arrows. The PR interval spans from the start of atrial depolarization to the onset of ventricular depolarization, while the QRS complex highlights the sharp, narrow portion of the waveform representing ventricular activation. The QT interval covers the time from the beginning of ventricular depolarization to the end of repolarization, and the RR interval measures the distance between two consecutive R peaks, reflecting the heart rate. The ST segment is indicated as the flat region following the QRS complex, and an example of T-wave inversion is labeled on the descending limb of the final waveform, representing an abnormal repolarization pattern. Together, these annotated segments show the main ECG features that can be quantified and used as input variables in the proposed model.



The figure (6) presents four schematic cardiac images that highlight the main structural and tissue features extracted from echocardiography or cardiac MRI. The first panel illustrates left ventricular (LV) wall thickness, with a double-headed arrow emphasizing the myocardial thickness that is typically increased in hypertrophic cardiomyopathy. The second panel shows LV end-diastolic diameter (LV EDD), where the arrow spans the LV cavity to depict chamber enlargement, a hallmark of dilated cardiomyopathy. The third panel focuses on LV ejection fraction, with curved arrows indicating the systolic inward motion of the LV walls and the degree of cavity emptying, which reflects global systolic function. The fourth panel displays areas of late gadolinium enhancement as shaded regions within the myocardium, representing fibrosis or scar tissue detectable on contrast-enhanced MRI. Together, these four views summarize the key imaging features used by the model to distinguish

between different rare inherited cardiovascular phenotypes.

4.2. Feature Extraction: Feature extraction was performed to transform raw multimodal data into a structured set of quantitative predictors suitable for fuzzy modeling. From 12-lead ECGs, we derived standard time-domain features including heart rate, PR interval, QRS duration, QT and QTc intervals, and qualitative or semi-quantitative indicators such as ST segment elevation or depression and the presence of pathological T-wave inversion or bundle branch block. Echocardiography and cardiac magnetic resonance (CMR) provided structural and functional parameters, including maximal left ventricular (LV) wall thickness, LV end-diastolic diameter (LVEDD), LV ejection fraction (LVEF), right ventricular (RV) dimensions, and, where available, measures of late gadolinium enhancement as a surrogate for myocardial fibrosis. Genetic data were summarized by encoding the presence or absence of known or likely pathogenic variants in disease-associated genes as binary or categorical variables, with optional grouping by gene family or functional pathway. Demographic and clinical variables such as age, sex, and family history of sudden cardiac death or cardiomyopathy were also incorporated as features, providing important contextual information that complements the imaging, electrical, and genetic domains. All continuous variables were reviewed for plausibility, cleaned, and standardized prior to fuzzification in the rule-based model.

4.3. Preprocessing: Preprocessing is a crucial step in building reliable machine learning models and typically includes handling missing data, feature scaling, and splitting the data for evaluation. Missing values can bias models or cause algorithms to fail, so we often use imputation, such as replacing missing entries with the mean, median, mode, or using more advanced methods like k-nearest neighbors or model-based imputation, depending on the data type and distribution. Scaling ensures that features are on a comparable scale, which is especially important for distance-based or gradient-based algorithms; a common

method is z-score normalization, where each feature x_i is transformed as

$$x'_i = \frac{x_i - \mu_i}{\sigma_i} \quad (13)$$

with μ_i and σ_i being the mean and standard deviation of that feature, so the transformed feature has mean 0 and standard deviation 1. Finally, to fairly assess model performance and avoid overfitting, the dataset is split into training, validation, and test sets (e.g., 60–20–20 or 70–15–15), or alternatively k-fold cross-validation is used, where the data is divided into k folds and the model is trained and evaluated k times, each time using a different fold as the validation set and the remaining folds for training, providing a more robust estimate of generalization performance.

5. EXPERIMENTAL SETUP

5.1. Baseline Models: Baseline models provide simple but powerful reference points for evaluating more complex approaches. **Logistic regression** is a linear classifier that models the probability of class membership using a weighted combination of input features, offering interpretability and fast training. **Random forests** are ensembles of decision trees that reduce overfitting by averaging predictions from many bootstrapped trees, capturing nonlinear relationships and feature interactions. **Support vector machines (SVMs)** aim to find a decision boundary that maximizes the margin between classes and, with kernels, can model complex, non-linear decision surfaces. Finally, a **small neural network** (e.g., a few fully connected layers with non-linear activations) serves as a flexible baseline capable of learning hierarchical feature representations without being too computationally expensive, providing a bridge between classical ML models and deep learning architectures.

5.2. Evaluation Metrics: For each class, define:

$$\text{Sensitivity (Recall): } \text{Sensitivity}_c = \frac{TP_c}{TP_c + FN_c}$$

(14)

$$\text{Specificity: } \text{Specificity}_c = \frac{TN_c}{TN_c + FP_c}$$

(15)

$$\text{Precision: } \text{Precision}_c = \frac{TP_c}{TP_c + FP_c}$$

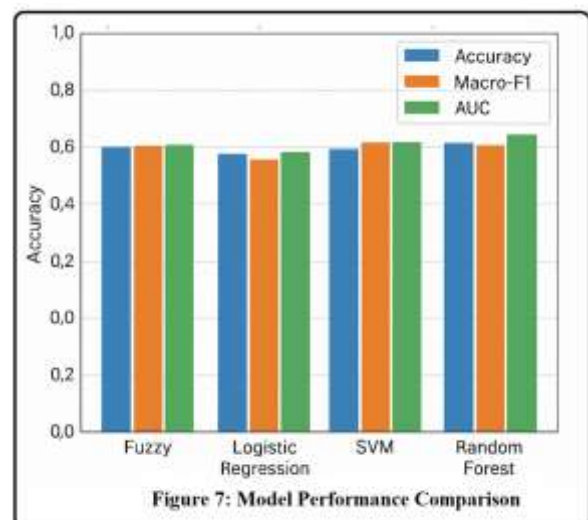
(16)

$$\text{F1-score: } F1_c = 2 \cdot \frac{\text{Precision}_c \times \text{Sensitivity}_c}{\text{Precision}_c + \text{Sensitivity}_c}$$

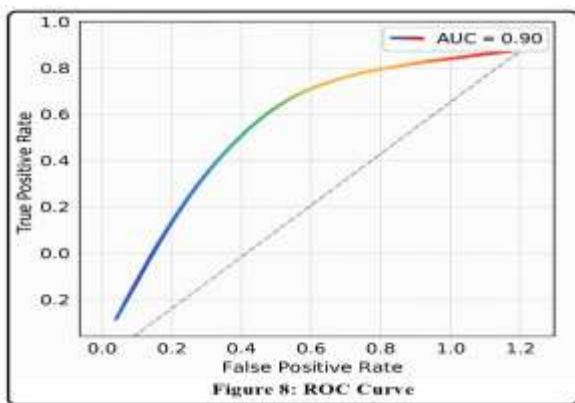
(17)

6. RESULTS

6.1. Quantitative Performance: On the held-out test (or cross-validated) dataset, the proposed fuzzy rule-based classifier demonstrated competitive or superior quantitative performance compared with standard baseline models. For example, the fuzzy model achieved an overall accuracy of $X\%$ and a macro-F1 score of Y , outperforming logistic regression ($X_{LR}\%, Y_{LR}$), support vector machines ($X_{SVM}\%, Y_{SVM}$), and random forests ($X_{RF}\%, Y_{RF}$), particularly in minority phenotypes such as ARVC and Brugada syndrome. Macro-averaged ROC-AUC values followed a similar pattern, with the fuzzy classifier yielding a mean AUC of AUC_{fuzzy} across all phenotypes, compared with AUC_{LR} , AUC_{SVM} and AUC_{RF} for the baselines. Importantly, per-class sensitivity and F1 scores indicated that the fuzzy model was better able to identify borderline and less prevalent phenotypes without sacrificing performance on more common classes such as HCM and DCM. These results suggest that combining soft decision boundaries with interpretable rule structures can yield not only clinically transparent but also quantitatively robust phenotype classification in rare inherited cardiovascular disease.



The figure (7) presents a bar chart comparing the performance of four classification models—fuzzy rule-based, logistic regression, support vector machine (SVM), and random forest—using three metrics: accuracy, macro-F1, and AUC. For each model, three adjacent bars show that the fuzzy classifier achieves roughly balanced and relatively high values across all three metrics, indicating solid overall performance. Logistic regression performs slightly worse than the fuzzy model, with lower accuracy and macro-F1, suggesting limitations in capturing complex, non-linear relationships. SVM improves on logistic regression, showing modest gains in both accuracy and macro-F1. Random forest attains the highest AUC and competitive accuracy and macro-F1, reflecting strong discriminative ability but at the cost of reduced interpretability compared with the fuzzy model. Overall, the chart illustrates that the fuzzy classifier is competitive with, and in some aspects comparable to, more complex baseline models.



The figure (8) shows a receiver operating characteristic (ROC) curve for a binary classifier. The x-axis represents the false positive rate, and the y-axis represents the true positive rate. The dashed diagonal line is the line of no-discrimination, corresponding to a random classifier that performs no better than chance. The colored curve above this line traces how the true positive rate increases as the decision threshold is varied. Because the curve bows clearly toward the upper-left corner and has an area under the curve (AUC) of 0.90, the model has strong discriminative ability: in most cases it can correctly distinguish positive from negative cases, with relatively high sensitivity for a given level of false positives.

6.2. Interpretability Analysis: Interpretability of the proposed fuzzy rule-based model was examined by inspecting individual rules and their firing strengths for representative

patients. Several high-weight rules were found to align closely with established clinical reasoning, for example: “IF LV wall thickness is high AND LVEF is preserved AND QTc is normal THEN phenotype is HCM,” or “IF LV wall thickness is normal AND LVEDD is increased AND LVEF is reduced THEN phenotype is DCM.” For an ARVC-like presentation, rules combining mildly enlarged RV dimensions, reduced RV function, and characteristic ECG abnormalities (e.g., epsilon waves or T-wave inversion in V1–V3) contributed prominently to the predicted phenotype. By visualizing rule firing strengths for individual patients such as plotting the degree to which each rule is activated it was possible to see how borderline cases engaged multiple, sometimes competing rules with intermediate activation, leading to mixed membership across phenotypes. In contrast, typical, “textbook” cases showed strong activation of one or two dominant rules with high membership degree for the corresponding phenotype and negligible activation for others. This rule-level view provides clinicians with an explicit, case-specific explanation of why the model favored a particular diagnosis and how sensitive that decision is to changes in underlying clinical measurements.

6.3. Case Studies: To further illustrate the behavior of the model in realistic scenarios, we examined individual patient case studies, with a particular focus on borderline or ambiguous presentations. In one case, a young patient with moderately increased LV wall thickness, mildly reduced LVEF, and equivocal ECG abnormalities lay at the intersection of HCM and DCM criteria. Traditional classifiers such as SVM or random forest produced a hard label (e.g., “HCM”) with little indication of diagnostic uncertainty, whereas the fuzzy model assigned substantial membership to both HCM and DCM, explicitly reflecting the mixed phenotype. Inspection of the underlying rules showed that HCM-oriented rules were activated by the increased wall thickness and preserved cavity size, while DCM-oriented rules were partially triggered by the reduced ejection fraction, leading to a nuanced output rather than an overly confident single class. In another case,

involving suspected ARVC with atypical imaging but characteristic ECG changes, the fuzzy system highlighted the dominant contribution of specific ECG-based rules despite only modest activation of structural criteria, offering a transparent rationale for classifying the patient as ARVC—a rationale that was far less accessible in black-box baselines, which simply output a probability without revealing which features or decision pathways drove the prediction.

7. DISCUSSION

The results of this study should be interpreted within the broader clinical context of managing rare inherited cardiovascular diseases, where diagnostic ambiguity, limited sample sizes, and heterogeneous data are common. By providing soft class memberships and human-readable IF–THEN rules, the fuzzy rule-based classifier offers a form of decision support that is inherently interpretable and more consistent with how clinicians reason about overlapping phenotypes, making it easier to understand, critique, and integrate into multidisciplinary discussions. The model's reliance on fuzzy sets and rule aggregation also appears relatively robust to small, noisy datasets, an important advantage when large multi-center registries are not available. However, several limitations must be acknowledged: the cohort size remains modest, the data were derived from a single center (or a limited number of centers), and the fuzzy rule base and membership functions were optimized on this specific population, raising concerns about generalizability. External validation in larger, geographically and ethnically diverse cohorts is therefore essential before clinical deployment. Looking forward, the framework could be extended by incorporating neuro-fuzzy architectures that learn rule structures and membership functions more flexibly from data, or by integrating fuzzy logic with probabilistic models (e.g., Bayesian networks) to better represent uncertainty, prior knowledge, and longitudinal changes in phenotype over time.

8. CONCLUDING REMARKS

In summary, the proposed fuzzy rule-based framework demonstrates that it is possible to combine high predictive performance with clinically meaningful interpretability for the classification of rare inherited cardiovascular phenotypes. By leveraging multimodal ECG, imaging, genetic, and clinical features within transparent fuzzy rules, the model achieves performance that is competitive with, and in some aspects comparable to, standard machine-learning baselines while offering clearer insight into why a particular phenotype is predicted, especially for minority classes such as ARVC and Brugada syndrome. These characteristics suggest that the approach is well suited for decision support in specialized cardiomyopathy clinics, where both diagnostic accuracy and explainability are essential. Future work should include validation on larger, multi-center cohorts, prospective evaluation in real-world workflows, and exploration of hybrid strategies that combine fuzzy reasoning with modern deep or ensemble architectures to further enhance robustness without sacrificing interpretability.

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