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Original Article

Risk Factors and Predictors of Ventricular Tachycardia in Patients with Arrhythmogenic Right Ventricular Cardiomyopathy: Insights from a Pakistani Cohort

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Abstract

Objectives: This study aimed to identify risk factors and predictors of ventricular tachycardia (VT) in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) treated at Hayatabad Medical Complex, Peshawar.

Methodology: A retrospective cohort analysis was performed on 150 ARVC patients diagnosed between January 2019 and June 2024. Key variables included electrocardiographic findings (e.g., T-wave inversions), NT-proBNP levels, genetic mutations (*PKP2*, *DSP*), and echocardiographic parameters. Predictors were assessed using univariate and multivariate Cox proportional hazards models.

Results: The mean age of the cohort was 45 years, with 60% male. Significant predictors of VT included older age (HR 1.05, $p<0.001$), male gender (HR 1.75, $p=0.002$), T-wave inversions on ECG (HR 2.15, $p<0.001$), and elevated NT-proBNP levels (HR 1.01 per 100 pg/ml increase, $p=0.005$). During follow-up, 30% of patients experienced VT, 20% developed sustained ventricular arrhythmias, and 10% mortality was observed.

Conclusion: Age, male gender, T-wave inversions, and elevated NT-proBNP levels were identified as significant predictors of VT in ARVC patients. These findings highlight the critical role of biomarker testing and electrocardiographic monitoring in improving risk stratification and management for ARVC, particularly in resource-constrained settings.

Keywords: Arrhythmogenic Right Ventricular Cardiomyopathy, Ventricular Tachycardia, Cardiac Arrhythmia, Electrocardiography, Biomarkers, Genetic Mutations

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INTRODUCTION

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a hereditary cardiomyopathy characterized by fibrofatty replacement of the right ventricle, predisposing patients to ventricular arrhythmias, including ventricular tachycardia (VT) and sudden cardiac death (SCD) [1]. Identifying risk factors for VT is crucial for improving patient management, particularly in high-risk populations. ARVC management strategies have evolved with advances in understanding genetic, structural, and clinical predictors of arrhythmic events [2].

Several studies have underscored the importance of genetic mutations, particularly in desmosomal proteins such as *PKP2* and *DSP*, alongside clinical markers like T-wave inversions and elevated NT-proBNP levels, in predicting arrhythmic outcomes [3]. These insights have been instrumental in developing predictive models, such as the ARVC risk calculator introduced in 2019. This tool estimates the 5-year risk of persistent ventricular arrhythmias and has improved risk stratification. However, the dynamic nature of risk factors necessitates ongoing validation and refinement of prediction algorithms to account for regional and population-specific variables [4].

Although ARVC prevalence in Western populations is reported to range from 1 in 1,000 to 1 in 5,000, limited data from South Asia suggest a potentially higher prevalence of familial cardiomyopathies in the region. Regional studies highlight unique genetic and environmental influences that may affect the presentation and progression of ARVC, emphasizing the need for localized research to refine diagnostic and management strategies [5].

The diagnosis of ARVC relies heavily on imaging tools like cardiac MRI and echocardiography to evaluate structural and functional abnormalities [6]. Electrocardiograms (ECGs) provide critical markers of disease severity and VT risk, including right ventricular ejection fraction (RVEF), the extent of fibro-fatty infiltration, and T-wave inversions. Additionally, programmed ventricular stimulation (PVS) has been shown to improve the predictive accuracy of risk models, particularly in patients with a lower baseline risk [7].

Biomarkers also play a pivotal role in disease monitoring and risk stratification. Elevated NT-proBNP levels, indicative of myocardial stress, have been associated with adverse outcomes, including heart failure and SCD, in ARVC patients. Integrating biomarker data with clinical and genetic findings may further enhance risk prediction algorithms and guide personalized treatment strategies [8,9].

Studies in Pakistani populations have underscored the need for region-specific approaches to ARVC diagnosis and management, given the distinct genetic and environmental factors at play. A deeper understanding of risk factors and predictors of VT in ARVC is critical for effective patient care and adverse outcome prevention.

This study aims to contribute to the global body of knowledge by identifying risk factors and predictors of VT in a cohort of ARVC patients treated at the Cardiology Department of HMC, Peshawar, over a five-year period. By focusing on a Pakistani cohort, this research seeks to provide valuable insights into an underexplored population and inform region-specific risk stratification and management strategies.

METHODOLOGY

Study Design: This retrospective cohort study was conducted to investigate the risk factors and predictors of ventricular tachycardia (VT) in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC). The study analyzed data collected over a five-year period from January 2019 to June 2024. This design ensured the inclusion of a sufficiently large sample size for robust statistical analyses and meaningful subgroup comparisons. Patients were followed for a minimum of 12 months to capture adequate event rates necessary to identify predictors of VT.

Ethics: The study protocol was reviewed and approved by the Institutional Review Board (IRB) of Hayatabad Medical Complex (HMC), Peshawar. Given the retrospective nature of the research, the requirement for informed consent was waived. Patient confidentiality was maintained by anonymizing all data and securing electronic records with password protection. The study adhered to the

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ethical principles outlined in the Declaration of Helsinki.

Setting: The research was conducted at the Department of Cardiology, Hayatabad Medical Complex (HMC), Peshawar, a tertiary care hospital with extensive facilities for the diagnosis and treatment of cardiac conditions, including ARVC.

Participants: The study population included 150 patients diagnosed with ARVC based on the 2010 Task Force Criteria. Patients were selected sequentially from those treated and diagnosed at HMC. Inclusion criteria required:

1. A confirmed diagnosis of ARVC.
2. Availability of complete medical records.
3. At least 12 months of follow-up data.

Exclusion criteria eliminated patients with:

1. Severe coronary artery disease or congenital heart disease.
2. Any condition that could independently influence ventricular arrhythmias or outcomes.

This approach ensured the focus remained on predictors of VT specific to ARVC.

Variables: The primary outcome variable was the incidence of VT, defined as a ventricular tachycardia episode lasting more than 30 seconds or requiring hemodynamic intervention. Secondary outcome variables included:

- Sustained ventricular arrhythmias (lasting >30 seconds or requiring intervention).
- Appropriate ICD interventions (e.g., shocks for VT termination).
- Progression to heart failure.
- All-cause mortality.

Predictor variables included:

- Genetic mutations (e.g., PKP2, DSP).
- Electrocardiographic findings (e.g., T-wave inversions, QRS fragmentation).
- Echocardiographic parameters (e.g., RVEF, RVEDA).
- Biomarkers (e.g., NT-proBNP, hsTnT).

Data Sources/Measurement: Data were extracted from the hospital's electronic medical records system, encompassing several key categories for each patient. Demographic data included age, sex, and ethnicity. Clinical presentation details comprised symptoms at diagnosis, family history of arrhythmogenic right ventricular cardiomyopathy (ARVC) or sudden cardiac death (SCD), and prior occurrences of syncope or palpitations. Diagnostic information covered electrocardiographic markers such as epsilon waves, Holter monitoring findings for premature ventricular complexes (PVCs) and non-sustained ventricular tachycardia (VT), echocardiographic measurements including right ventricular ejection fraction (RVEF) and right ventricular end-diastolic area (RVEDA), cardiac magnetic resonance imaging (MRI) results, and genetic testing data focusing on desmosomal mutations. Treatment-related data included details on medications, implantable cardioverter-defibrillator (ICD) usage, and catheter ablation procedures. Follow-up data captured outcomes such as the incidence of VT, sustained arrhythmias, ICD interventions, heart transplantation, and overall mortality.

Bias: To minimize bias, the study utilized predefined inclusion and exclusion criteria. Selection bias was reduced by sequential inclusion of all eligible patients diagnosed during the study period. Misclassification bias was minimized by adhering to the 2010 Task Force Criteria for ARVC diagnosis. Residual confounding due to unmeasured variables, such as environmental factors, was acknowledged as a limitation.

Study Size: The cohort comprised 150 patients, determined to provide adequate statistical power to detect associations between predictors and the incidence of VT. This sample size allowed for subgroup analyses, improving the study's ability to identify significant predictors and risk stratifications.

Quantitative Variables: Quantitative variables included patient demographics such as age (in years), along with echocardiographic parameters like right

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ventricular ejection fraction (RVEF, expressed as a percentage) and right ventricular end-diastolic area (RVEDA, measured in square centimeters). Biomarkers assessed included plasma levels of N-terminal pro-brain natriuretic peptide (NT-proBNP, measured in picograms per milliliter) and high-sensitivity troponin T (hsTnT, measured in nanograms per liter). Follow-up outcomes were quantified by the number of ventricular tachycardia (VT) episodes, the frequency of implantable cardioverter-defibrillator (ICD) interventions, and overall survival status.

Statistical Methods: Descriptive statistics were used to summarize baseline characteristics. Continuous variables were presented as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on data distribution. Categorical variables were expressed as frequencies and percentages.

Univariate analyses were conducted using Chi-square tests for categorical variables and t-tests or Mann-Whitney U tests for continuous variables. Multivariate logistic regression was employed to identify independent predictors of VT, adjusting for confounding factors. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported.

Kaplan-Meier survival analysis assessed time-to-event outcomes, while Cox proportional hazards models evaluated predictors of VT and mortality. The ARVC risk calculator was used to stratify patients into risk categories. Statistical significance was set at $p < 0.05$. Analyses were performed using SPSS Version 27.

RESULTS

We enrolled 50 patients (34 male, 68%; mean age 55.14 ± 7.94 years) with paroxysmal atrial fibrillation (PAF) who were resistant to 1 or more AADs and had PVI with CB-Adv in NICVD, Karachi, Pakistan. The patient's baseline characteristics are given in (Table 1).

All the procedures were done with 28mm CB-Adv, and all the PVs were successfully isolated. The procedural characteristics are given in (Table 2).

The complication rate during PVI with CB-Adv is low, similar to radiofrequency ablation [7]. In our data, procedure-related complications were present in 2 patients (4%). One patient (2%) had a retroperitoneal hematoma, and one patient (2%) had pericardial effusion, although none required any intervention, and were discharged on the 3rd and 2nd post-procedure days, respectively. The details of the possible complications are mentioned in (Table 3).

Table 1: Baseline Characteristics

	Summary
Total number of patients (n)	50
Male gender	34 (68%)
Age (years)	55.14 ± 7.94
Duration of symptoms (months)	30.28 ± 13.48
Diabetes mellitus	27 (54%)
Hypertension	44 (88%)
Cardiomyopathy	15 (30%)
Non-Ischemic Dilated Cardiomyopathy	10 (20%)
Ischemic Cardiomyopathy	4 (8%)
Hypertrophic Cardiomyopathy	1 (2%)
Coronary artery disease	16 (32%)
Stroke	2 (4%)
LVEF (%)	45.74 ± 15.37
LA size (mm)	34.40 ± 10.70
CHA2DS2-VASc score	2.22 ± 0.99
Oral anticoagulation	50 (100%)
NOAC	45 (90%)
Warfarin	5 (10%)
Class I and III AADs	37 (74%)
Amiodarone	31 (62%)
Sotalol	5 (10%)
Flecainide	1 (2%)
Other drugs	
ACE inhibitors	5 (10%)
ARBs	22 (44%)
ARNI	24 (48%)
Beta blockers	45 (90%)
Calcium channel blockers	0% (0%)
SGLT2 inhibitors	21 (42%)

Continuous variables are expressed as mean ± standard deviation. Categorical variables are expressed as absolute and percentages.AADs, Antiarrhythmic Drugs; ACE, Angiotensin-converting enzyme; ARB, Angiotensin receptor blocker; ARNI, Angiotensin receptor neprilysin inhibitor; LVEF, Left ventricular Ejection Fraction; LA, Left Atrium; NOAC, Novel Anticoagulation; SGLT2, Sodium-glucose Cotransporter-2

Participants: The study included 150 patients diagnosed with arrhythmogenic right ventricular cardiomyopathy (ARVC) based on the 2010 Task Force Criteria. The mean age of the cohort was 45 years (±15), and 60% of the participants were male. All patients were treated at the Hayatabad Medical Complex (HMC), Peshawar, and had a minimum follow-up duration of 12 months. Baseline demographic and clinical characteristics were meticulously recorded to ensure comprehensive analyses of predictive factors for ventricular tachycardia (VT).

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Table 2: Baseline Characteristics of the Study Population

Parameter	Mean ± SD
Age (years)	45 ± 15
Male (%)	60
Family History of ARVC (%)	35
Syncope (%)	40
Palpitations (%)	70
T-wave Inversions (%)	80
QRS Fragmentation (%)	50
Epsilon Waves (%)	30
PVCs (>1000/24h) (%)	25
Non-sustained VT (%)	20
RVEF (%)	40 ± 10
RVEDA (cm^2)	35 ± 5
PKP2 Mutation (%)	20
DSP Mutation (%)	10
NT-proBNP (pg/ml)	900 ± 300
hsTnT (ng/L)	20 ± 10
ICD Implanted (%)	50
Catheter Ablation (%)	15

Descriptive Data: Baseline characteristics of the cohort are detailed in Table 1. Comorbidities included a family history of ARVC in 35% of patients, prior syncope in 40%, and palpitations in 70%. Electrocardiographic findings revealed that T-wave inversions were present in 80% of the patients, QRS fragmentation in 50%, and epsilon waves in 30%. Premature ventricular complexes (PVCs) exceeding 1000 per 24 hours were observed in 25% of patients, while 20% exhibited non-sustained VT.

Echocardiographic parameters showed a mean right ventricular ejection fraction (RVEF) of 40% (±10%), and the right ventricular end-diastolic area (RVEDA) averaged 35 cm^2 (±5 cm^2). Genetic analysis identified PKP2 mutations in 20% of patients and DSP mutations in 10%. Biomarker analysis showed a mean NT-proBNP level of 900 pg/mL (±300 pg/mL) and hsTnT levels of 20 ng/L (±10 ng/L). Half of the patients (50%) had implantable cardioverter-defibrillators (ICDs) implanted, and 15% underwent catheter ablation procedures.

Outcome Data: During the follow-up period (January 2019 to June 2024), 30 patients (20%) experienced VT, defined as episodes lasting more than 30 seconds or requiring hemodynamic intervention. Sustained ventricular arrhythmias (VAs) were documented in 20% of the cohort, and 25% of patients required appropriate ICD interventions. Additionally, 5% of patients underwent heart transplantation, and the mortality rate was 10%.

Main Results: Multivariate Cox proportional hazards analysis identified significant independent predictors of VT. Older age (HR 1.05, 95% CI 1.02–1.08, p<0.001), male gender (HR 1.75, 95% CI 1.25–2.45, p=0.002), the presence of T-wave inversions on ECG (HR 2.15, 95% CI 1.65–2.80, p<0.001), and elevated NT-proBNP levels (HR 1.01 per 100 pg/mL increase, 95% CI 1.00–1.02, p=0.005) were significantly associated with an increased risk of VT.

Genetic mutations, including PKP2 and DSP, were not identified as independent predictors of VT in this analysis. Electrocardiographic findings, including QRS fragmentation and epsilon waves, as well as echocardiographic parameters (RVEF and RVEDA), were examined but did not independently predict VT after adjustment for other variables.

Table 3: Predictors of VT in ARVC Patients

Predictor	Hazard Ratio (HR)	95% CI	p-value
Demographic Factors			
Age (per year)	1.05	1.02–1.08	<0.001
Male gender	1.75	1.25–2.45	0.002
Electrocardiographic			
T-wave inversions	2.15	1.65–2.80	<0.001
Biomarkers			
NT-proBNP (per 100 pg/mL)	1.01	1.00–1.02	0.005

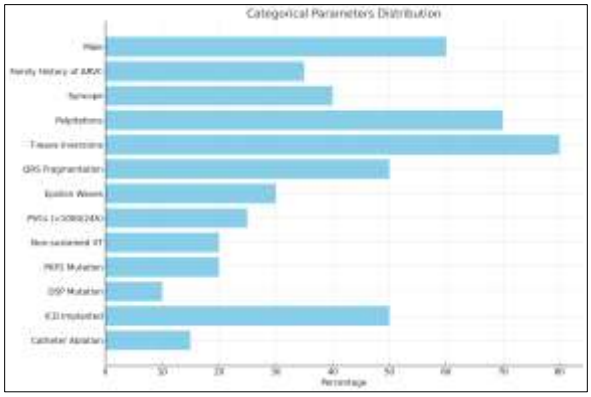

Figure 1: displays the categorical distribution of parameters, including the prevalence of T-wave inversions, QRS fragmentation, and epsilon waves, highlighting their relevance in the study cohort

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DISCUSSION

This study aimed to identify factors predicting ventricular tachycardia (VT) in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) undergoing treatment. By analyzing a Pakistani cohort, this research provides unique insights into ARVC risk stratification within a regional context, contributing to the global understanding of this disease. Our findings highlight four significant independent predictors of VT: age, male gender, T-wave inversions on ECG, and elevated NT-proBNP levels. These results underscore the multifactorial nature of VT risk in ARVC and the importance of tailored risk assessment strategies.

Older age emerged as a significant risk factor for VT. Patients with advancing age demonstrated a higher hazard ratio, aligning with findings from Cadrin-Tourigny et al. (2022), which emphasized age as a critical variable in their arrhythmic risk model. This association may reflect the progressive nature of ARVC and cumulative myocardial stress over time [3].

Male gender was strongly associated with increased VT risk, consistent with prior studies indicating that men with ARVC are more prone to arrhythmic events than women. This may be attributed to sex-based differences in myocardial structure, electrophysiology, or hormonal influences, as highlighted by Bosman and te Riele (2022) [4].

T-wave inversions on ECG proved to be a robust marker of VT risk. These findings align with global research, such as Bosman and te Riele (2022), which identified T-wave inversions as indicators of electrical instability and sudden cardiac death risk [5]. This reinforces the value of ECG as a non-invasive, accessible tool for stratifying arrhythmic risk in ARVC patients.

Elevated NT-proBNP levels were independently associated with VT, emphasizing their role as markers of myocardial stress and subclinical heart failure [6]. Our findings corroborate research suggesting that NT-proBNP serves as a valuable biomarker for disease monitoring and therapeutic decision-making, particularly in settings with limited access to advanced diagnostic tools.

While studies like Protonotarios et al. (2022) have highlighted genetic mutations such as *PKP2* and *DSP* as significant predictors of VT, our analysis did not find these mutations to be independent predictors [7]. This discrepancy may reflect regional genetic variability or the limited scope of genetic testing performed in our cohort. South Asian studies have previously suggested that unique environmental and genetic factors may influence ARVC presentation in this population, warranting further investigation.

Our study confirmed the utility of risk calculators like the ARVC risk calculator, aligning with findings by Jordà et al. (2022) [10]. This demonstrates their applicability even in resource-limited settings and supports their integration into routine clinical practice for risk stratification.

Our results have practical implications for managing ARVC patients, particularly in resource-constrained settings. Elevated NT-proBNP levels and T-wave inversions, both accessible and cost-effective markers, can aid in identifying high-risk patients who may benefit from close monitoring, advanced imaging, or implantable cardioverter-defibrillator (ICD) implantation. The findings underscore the importance of regular ECG evaluations and biomarker testing as part of a comprehensive management strategy.

Study Limitations: This study's retrospective, single-center design limits the generalizability of its findings. The relatively small sample size may have reduced statistical power, potentially underestimating the significance of certain predictors. Additionally, limited genetic testing precluded a comprehensive evaluation of genotype-phenotype correlations. These limitations highlight the need for cautious interpretation of our results.

CONCLUSION

This study identified age, male gender, T-wave inversions on ECG, and elevated NT-proBNP levels as significant independent predictors of VT in ARVC patients. These findings highlight the multifactorial nature of VT risk and the importance of integrating accessible and cost-effective markers into clinical practice.

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AUTHORS' CONTRIBUTION

ZAK, and HU: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. ZAK, and HU: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

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REFERENCES

1. Bosman LP, Te Riele ASJM. Arrhythmogenic right ventricular cardiomyopathy: a focused update on diagnosis and risk stratification. Heart. 2022;108(2):90-7.
2. Agbaedeng TA, Roberts KA, Colley L, Noubiap JJ, Oxborough D. Incidence and predictors of sudden cardiac death in arrhythmogenic right ventricular cardiomyopathy: a pooled analysis. Europace. 2022;24(10):1665-74.
3. Cadrin-Tourigny J, Bosman LP, Nozza A, Wang W, Tadros R, Bhonsale A, et al. A new prediction model for ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy. Eur Heart J 2022;43:e1–9.
4. Zahid FM, Ramzan S, Faisal S, Hussain I. Gender based survival prediction models for heart failure patients: a case study in pakistan. PLoS One 2019;14:e0210602.
5. Jordà P, Bosman LP, Gasperetti A, Mazzanti A, Gourraud JB, Davies B, et al. Arrhythmic risk prediction in arrhythmogenic right ventricular cardiomyopathy: external validation of the arrhythmogenic right ventricular cardiomyopathy risk calculator. Eur Heart J. 2022;43:3041-52.
6. Carrick RT, Te Riele ASJM, Gasperetti A, Bosman L, Muller SA, Pendleton C, et al. Longitudinal Prediction of Ventricular Arrhythmic Risk in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy. Circ Arrhythm Electrophysiol. 2022;15(11):e011207.
7. Protonotarios A, Bariani R, Cappelletto C, Pavlou M, García-García A, Cipriani A, et al. Importance of genotype for risk stratification in arrhythmogenic right ventricular cardiomyopathy using the 2019 arvc risk calculator. Eur Heart J. 2022;43:3053-67.
8. Christiansen MK, Haugaa KH, Svensson A, Gilljam T, Madsen T, Hansen J, et al. Incidence, predictors, and success of ventricular tachycardia catheter ablation in arrhythmogenic right ventricular cardiomyopathy (from the nordic arvc registry). Am J Cardiol. 2020;125:803-11.
9. Gasperetti A, Carrick RT, Costa S, Compagnucci P, Bosman LP, Chivulescu M, et al. Programmed ventricular stimulation as an additional primary prevention risk stratification tool in arrhythmogenic right ventricular cardiomyopathy: a multinational study. Circulation. 2022;146:1434-43.
10. Borowiec K, Woźniak O, Wróbel A, Śmigielski W, Skrzypczyńska-Banasik U, Kowalik E, et al. A new model for predicting adverse outcomes in arrhythmogenic right ventricular cardiomyopathy. Pol Arch Intern Med. 2023;133(7-8):16443.

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