Review Article

Beyond Arrhythmogenic Right Ventricular Cardiomyopathy: A Scoping Review of Arrhythmogenic Cardiomyopathy Variants

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Abstract

Background: Arrhythmogenic cardiomyopathy (ACM) is a rare heart muscle disorder consisting of three variants: arrhythmogenic right ventricular cardiomyopathy (ARVC), arrhythmogenic left ventricular cardiomyopathy (ALVC), and arrhythmogenic biventricular cardiomyopathy (ABVC). This condition is a significant cause of sudden cardiac death (SCD), especially among young athletes.

Objectives: Due to the lack of research on the clinical outcomes associated with each ACM variant, this study aims to explore the entire phenotypic spectrum of ACM through a comparative lens and to explore its recent reconceptualization as a biventricular condition rather than primarily right-sided cardiomyopathy.

Methods: Using a combination of keywords, a database search was performed on PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Science Direct and Google Scholar databases. Through thorough discussion, authors collectively extracted, elaborated, and assessed their findings to enhance reliability.

Results: Our findings suggested that ABVC may be the most prevalent and least favorable form of ACM, followed by ALVC and ARVC. While right ventricular involvement in ACM has been linked to a higher arrhythmic burden, left ventricular involvement was associated with higher risks of heart failure, cardiac transplantation, and Hot phases. The recently proposed European Task Force Criteria report can potentially rectify previous underdiagnosis and diagnostic delays associated with ALVC and ABVC. This study also highlights the paucity of clinical trials on ACM.

Conclusion: Distinct outcomes have been associated with each variant, suggesting that tailored management for each variant of ACM may be required. Further research into the clinical outcomes and management of each variant of ACM is essential to improve patient care.

Background

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a rare heart muscle disorder that is common among Caucasian men, typically aged between 30-50 years and has an incidence rate of 1: 2500 to 5000.[1,2] It is a significant cause of sudden cardiac deaths (SCD) among young athletes.[1,3] ARVC patients may clinically present with palpitations and syncope or directly succumb to SCD.[1]

The demonstration of left ventricular (LV) involvement in most ARVC cases has prompted the adoption of the umbrella term Arrhythmogenic Cardiomyopathy (ACM) to describe the diverse phenotypic expression of the disease.[4] ARVC is now recognized as a subtype of ACM, characterized by fibrofatty myocardial replacement in the right ventricle, leading to right ventricular (RV) dysfunction.[1] The 2020 International Consensus document defined ACM as a cardiac muscle condition affecting either the right ventricle, left ventricle, or both, whose hallmark is the fibrofatty replacement of myocardium, which compromises ventricular function and predisposes to life-threatening ventricular arrhythmias. ACM has been classified into three variants: Typical ARVC (Right Ventricular Involvement), ALVC - Arrhythmogenic Left Ventricular Cardiomyopathy (Left Ventricular Involvement) and ABVC - Arrhythmogenic Biventricular Cardiomyopathy (Biventricular Involvement).[5] It can thus be affirmed that "Every ARVC is an ACM, but not every ACM is an ARVC."[6] The three ACM variants are pathologically characterized by the non-ischaemic myocardial scarring and gradual replacement of cardiac myocytes with fibrofatty tissue which act as arrhythmogenic substrates and disrupt the electrical rhythm of the heart; thereby causing severe ventricular arrhythmias.[2,7] According to the recent European Task Force consensus report, the diverse etiology of ACM includes inherited, acquired, or idiopathic causes.[7] Treatment modalities for ACM include exercise restriction, pharmacological therapy (Beta Blockers as first-line drugs), catheter ablation, Implantable cardioverter-defibrillator (ICD), and Cardiac Transplantation.[1]

Implementing the 2010 revised International Task Force Criteria (TFC) for diagnosing ACM has led to the underdiagnosis of patients exhibiting the ALVC and ABVC variants due to its inability to identify left ventricular involvement.[7] Furthermore, the diverse etiology and genetic background covering all three variants of ACM were not adequately characterized.[5] The recently proposed European TFC refined the 2020 Padua criteria and aimed to fill this gap by facilitating the diagnosis of all ACM variants while also detailing their etiology.[7] However, significant limitations remain in

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the management and prognosis of each variant of ACM due to the lack of research and evidence addressing the clinical outcomes and the necessity of tailored management protocols with each variant. This general lack of literature on ACM is more pronounced with ALVC and ABVC than with ARVC.

This study aims to elucidate ACM's entire phenotypic spectrum and expand on its reconceptualization as a biventricular condition, challenging its conventional perception as a primarily right-sided inherited cardiomyopathy. We shall also explore the interpretation of the recent European TFC for the classification and diagnosis of ACM. Through a comparative analysis of the three ACM variants, this study ultimately seeks to enhance scientific understanding for medical practitioners and researchers to aid clinical decision-making and improve patient care.

Methods

Database search was performed on PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Science direct and Google Scholar databases using the following keywords: "Arrhythmogenic Right Ventricular Cardiomyopathy" OR "Arrhythmogenic Right Ventricular Dysplasia" OR "ARVD" OR, "ARVC" OR "Arrhythmogenic Right Ventricular Cardiomyopathy-Dysplasia" OR "Ventricular Dysplasia, Right, Arrhythmogenic" OR "Right Ventricular Dysplasia, Arrhythmogenic" OR "Arrhythmogenic Right Ventricular Dysplasia-Cardiomyopathy". Our search was limited to only full-text English articles with no time restriction. Following independent screening by each author, 37 articles were included for data analysis. These articles comprised review articles, meta-analyses, clinical trials, and prospective and retrospective studies describing ACM and its variants. The authors provided their perspectives by elaborating on their findings for each section of the paper, ensuring the integrity and accuracy of the information gathered. Findings were assessed to ensure the fulfillment of the study's objectives and to achieve a comprehensive understanding of the topic.

Results

Data collection for this paper presented challenges owing to the evident scarcity of literature and high-quality evidence studies dedicated to ACM and its variants. With the term ACM and its classification being relatively new, most of the historical research in this domain has predominantly centered around the classical ARVC variant. Such deficiency in high-quality evidence studies is more pronounced for the ALVC and ABVC, particularly regarding their distinct risk stratification, treatment modalities, and prognosis.

Epidemiology

In the most extensive multicenter autopsy study on ACM conducted by Miles et al., which examined 202 diagnosed ACM cases, findings revealed that 70% presented histopathological changes in both ventricles. In contrast, 17% displayed alterations solely in the left ventricle and 13% exclusively in the right ventricle.[8] These findings suggest that ABVC may be the most prevalent form of ACM, followed by ALVC and ARVC. In another study by Bariani et al., left ventricular involvement (encompassing both ALVC and ABVC) was more common in females.[9] [Table 1]

Table 1: A comparative overview of the characteristics of the three variants of ACM, focusing on their respective Epidemiology, Etiology, Clinical manifestation, Diagnosis, Differential Diagnosis, Treatment, and Prognosis.

Arrhythmogenic Cardiomyopathy Variant		Right Ventricular	Left Ventricular	Biventricular
Epidemiology	Occurrence*[8]	13%	17%	70%
	Gender Distribution[9]	Male > Female	Male < Female	Male < Female
Etiology[10]	Desmosomal Gene Mutations	✓	✓	✓
	Non Desmosomal Gene Mutations	✓	✓	✓
	Exclusive Genetic Mutations	PKP2, TMEM43, TGFB3, CTNNA3 , CDH2	DMD, DMPK	-
	Inherited Neuromuscular disorders (DMD or DMPK)	-	✓	-
	Post-Viral Myocarditis	-	✓	-
	Auto-immune diseases (SLE, polymyositis, scleroderma)	-	✓	-
	Cardiac Sarcoidosis	✓	✓	✓
	Chagas Disease	✓	✓	✓
	Idiopathic	✓	✓	✓

Clinical Manifestations[1,5,10, 11, 12]	Palpitations & Syncope	Present	Present	Present
	Characterization of Ventricular tachycardia	LBBB Morphology	RBBB morphology	Both LBBB and RBBB Morphology
	Sudden Cardiac Death	High Risk	Higher risk due to diagnostic delay	Higher risk due to diagnosis delay
Diagnosis[10]	Diagnosis wish the 2010 revised TFC	✓	X	X
	Diagnosis with the 2020 "Padua Criteria"	✓	✓	✓
	Diagnosis using the European TFC	✓	✓	✓
Differential Diagnosis[7,10]		Congenital heart abnormalities - Atrial Septal defects and Partial Anomalous pulmonary venous drainage Pulmonary Artery Hypertension Athlete's Heart Syndrome Chest Deformities - Pectus Excavatum or carinatum and Pericardial absence	Dilated Cardiomyopathy	Dilated Cardiomyopathy
Treatment[2,5,13]	Conservative treatment	Exercise Restriction, Pharmacological therapy (Beta Blockers as First line Drugs)	Exercise Restriction, Pharmacological therapy (Beta Blockers as First line Drugs)	Exercise Restriction, Pharmacological therapy (Beta Blockers as First line Drugs)
	Surgical Intervention	ICD, Catheter Ablation and Cardiac Transplantation	ICD, Catheter Ablation and Cardiac Transplantation	ICD, Catheter Ablation and Cardiac Transplantation
Prognosis †[14,15]	Life-threatening arrhythmia	31%	14%	38%
	Heart Failure	1%	6%	19%
	Sudden Cardiac Death	3%	1%	5%
	Hot Phases	5%	14%	9%

* According to an autopsy-based study
† Occurrence rates

Etiology

According to the European Task Force consensus report, ACM may arise from inherited, acquired non-genetic, or idiopathic causes. The inheritance patterns underlying ACM predominantly involve defects in both desmosomal and non-desmosomal genes (Genocopies). Notably, there is substantial genetic overlap among all three variants of ACM. Exclusive genetic defects in ARVC involve PKP2, TMEM43, TGFB3, CTNNA3, and CDH2 genes. ALVC was commonly associated with specific mutations in DMD and DMPK. Common mutations in both ARVC and ALVC include JUP and SCN5A. Additionally, genetic defects shared between ARVC and ABVC consist of only DSC2, while anomalies in both ALVC and ABVC involve DSG2, FLNC, DES, and LMNA genes. Notably, genetic defects across all ACM variants encompass DSP and PLN. Two inheritable cardio-cutaneous syndromes associated with desmosomal gene defects can also present as ACM, which are Naxos disease, characterized by a genetic mutation in the JUP gene, which can manifest as either ARVC or ALVC and Carvajal disease, marked by genetic mutations in the DSP gene, often presenting as ALVC. Additionally, three hereditary neuromuscular disorders linked to non-desmosomal gene defects may exclusively manifest as ALVC: Duchenne muscular dystrophy, Becker muscular dystrophy (Both associated with DMD gene mutation), and Myotonic dystrophy/Steinert disease (Associated with DMPK gene mutation). Acquired non-genetic causes of ACM, termed phenocopies, include inflammatory conditions and parasitic infections. Inflammatory conditions such as post-viral myocarditis and autoimmune disorders (e.g., Systemic Lupus Erythematosus, polymyositis, scleroderma) are exclusively associated with the ALVC variant. Cardiac sarcoidosis and parasitic infections like Chagas disease can manifest in any ACM variant. The etiology of any ACM variant may also be idiopathic.[10]

Clinical Manifestations

The ABVC and ALVC subtypes of ACM may present with symptoms similar to the classic ARVC, with most commonly palpitations and syncope that suggest ventricular tachycardia (VT).[5,11] On an electrocardiogram (ECG), the classic ARVC present with VT of left bundle branch block (LBBB) morphology, ALVC with VT of right bundle branch block (RBBB) morphology, and ABVC with VT of both RBBB and LBBB morphology.[1] All three variants of ACM bear a significant risk of SCD, which can be the initial symptom. This Risk of SCD is notably higher in ALVC and ABVC due to diagnostic delays associated with their under-recognition.[5,12] Of Note, ACM was shown to be a significant cause of SCD among young athletes, with the risk of SCD potentially being 2.5 times higher when associated with physical activity.[16] Unlike ARVC, ALVC and ABVC patients may often manifest with "Hot Phases" which are characterized by acute myocarditis-mimicking features such as chest pain, elevated troponin levels, and acute ECG changes despite the absence of ischemia.[10] LV involvement in ARVC can fasten the course toward congestive heart failure, which is considered the end stage of ACM.[1,11] Moreover, woolly hair and palmoplantar keratoderma, which are hair and skin abnormalities seen in cardio-cutaneous syndromes like Naxos disease and Carvajal disease, are also associated with ARVC and ALVC subtypes.[4,10]

Diagnosis Tools:

a. Guideline Recommendations:

The 2010 revised International Task Force criteria (TFC) has been criticized for exclusively targeting right ventricular involvement, which prevented the diagnosis of the ALVC and ABVC variants, and for lacking the incorporation of tissue characterization by late-gadolinium enhancement (LGE) CMR imaging in its criteria. Consequently, the 2020' Padua Criteria' endeavored to incorporate the entire phenotypic spectrum of ACM by introducing new diagnostic criteria for left ventricular involvement and the integration of LGE-CMR for tissue characterization.[2]

Most recently, in 2023, a European TFC, which improved the 2020 'Padua criteria', was proposed. The latter consisted of new diagnostic measures for Left ventricular abnormalities and ventricular arrhythmias, the most important one being the identification of a "ring-like" pattern of myocardial LGE scar on CMR imaging as the diagnostic hallmark of ALVC, which facilitates its distinction from non-scarring differential diagnoses. Like the 2020 Padua criteria, the European TFC comprises two sets of criteria further divided into "major" and "minor" subsets.[10,17] (Table 2)

Table 2 : The European Task Force Criteria for the Diagnosis of ACM [10]
ACM: arrhythmogenic cardiomyopathy, BSA: body surface area, EDV: end diastolic volume, EF: ejection fraction, ITF: International Task Force, LBBB: left bundle-branch block, LGE: late gadolinium enhancement, LV: left ventricle, RBBB: right bundle-branch block, RV: right ventricle, RVOT: right ventricular outflow tract.

		Criteria for RV involvement	Criteria for LV involvement
I. Morpho-functional ventricular abnormalities by angiography, CMR or 2D echocardiogram	Major Criteria	• Regional RV dyskinesia , akinesia, or aneurysm plus one of the following: - Global RV systolic dysfunction, (defined as an increase in RV EDV based on imaging test-specific nomograms) or - global RV systolic dysfunction (defined as a decrease in RV EF on imaging test specific monograms)	
	Minor Criteria	• Regional RV dyskinesia, akinesia,, or aneurysm of RV free wall	• Global LV systolic dysfunction, whether or not accompanied by LV dilatation (defined as an increase in LV EDV based on imaging test-specific nomograms)

II. Structural myocardial abnormalities	Major Criteria	**By CE-CMR:** • Fibrous replacement of the myocardium in one or more sample, with or without fatty tissue, at histology	**By CE-CMR:** • "Ring-like" LV LGE exhibiting a subepicardial or mid-myocardial stria pattern) in three or more segments and validated across two orthogonal views.
	Minor Criteria	• Unequivocal RV LGE (confirmed in two orthogonal views) in one or more RV region(s) (excluding tricuspid valve)	• LV LGE exhibiting a subepicardial or mid-myocardial striated pattern in one or two Bull's Eye segments (observed in two orthogonal views) of the free wall, septum, or both, while excluding any patchy, focal, or septal junctional LGE.
III. Abnormalities in ECG repolarization	Major Criteria	• Negative T waves detected in the right precordial leads V1, V2, and V3 or further in individuals aged 14 years and older, occurring without a complete RBBB and not preceded by J-point or ST-segment elevation.	
	Minor Criteria	• Negative T waves observed in leads V1 and V2 in males aged 14 and older, in the absence of right bundle branch block and without prior J-point or ST-segment elevation. • Negative T waves observed in leads beyond V3 in patients with complete RBBB • Negative T waves observed beyond lead V3 in individuals aged less than <14 year-old	• Negative T waves detected in the left precordial leads V4 to V6 without the presence of LBBB
IV. Abnormalities in ECG depolarization	Major Criteria		• Low QRS voltages (less than 0.5 mV peak to peak) present in all limb leads, occurring without any other contributing factors such as cardiac amyloidosis, obesity, emphysema, or pericardial effusion.
	Minor Criteria	• Epsilon wave (characterized by reproducible low-amplitude signals occurring between the end of the QRS complex and the beginning of the T wave), observed in the right precordial leads (V1 to V3 • A terminal activation duration of the QRS ≥55 ms, measured from the lowest point of the S wave to the end of the QRS complex, including R', in leads V1, V2, or V3, observed without the presence of complete RBBB)	

V. Ventricular Arrhythmias	Major Criteria	• Frequent ventricular extrasystoles exceeding 500 per 24 hours, sustained or non-sustained ventricular tachycardia exhibiting LBBB morphology along with a non-inferior axis	
	Minor Criteria	• Frequent ventricular extrasystoles exceeding 500 per 24 hours, sustained or non-sustained ventricular tachycardia exhibiting LBBB morphology along with an inferior axis (characterized by an "RVPT" pattern) • A history of cardiac arrest caused by either ventricular fibrillation or sustained ventricular tachycardia of unknown morphology.	• Frequent ventricular extrasystoles occurring more than 500 times in 24 hours or those induced by exercise, displaying a RBBB morphology or multiple variations of RBBB morphology (excluding the "fascicular pattern") • Sustained or Non-sustained ventricular tachycardia exhibiting an RBBB morphology, excluding the "fascicular pattern." • A history of cardiac arrest caused by either ventricular fibrillation or sustained ventricular tachycardia of unknown morphology.
VI. Genotyping / Family history	Major Criteria	• Detection of a pathogenic variant in an ACM gene in the patient being assessed. • Confirmation of ACM in a first-degree relative who fulfils the diagnostic criteria • Pathological Confirmation of ACM at autopsy or surgery in a first-degree relative	
	Minor Criteria	• Detection of a potentially pathogenic variant in an ACM-related gene in the patient being assessed • A first-degree relative with a history of ACM, where it is impossible or impractical to establish whether or not the family member fulfills the diagnostic criteria • Premature sudden death before the age of 35 in a first-degree relative, suspected to be due to ACM • Confirmation of ACM pathologically or by fulfilment of diagnostic criteria in a second-degree relative	

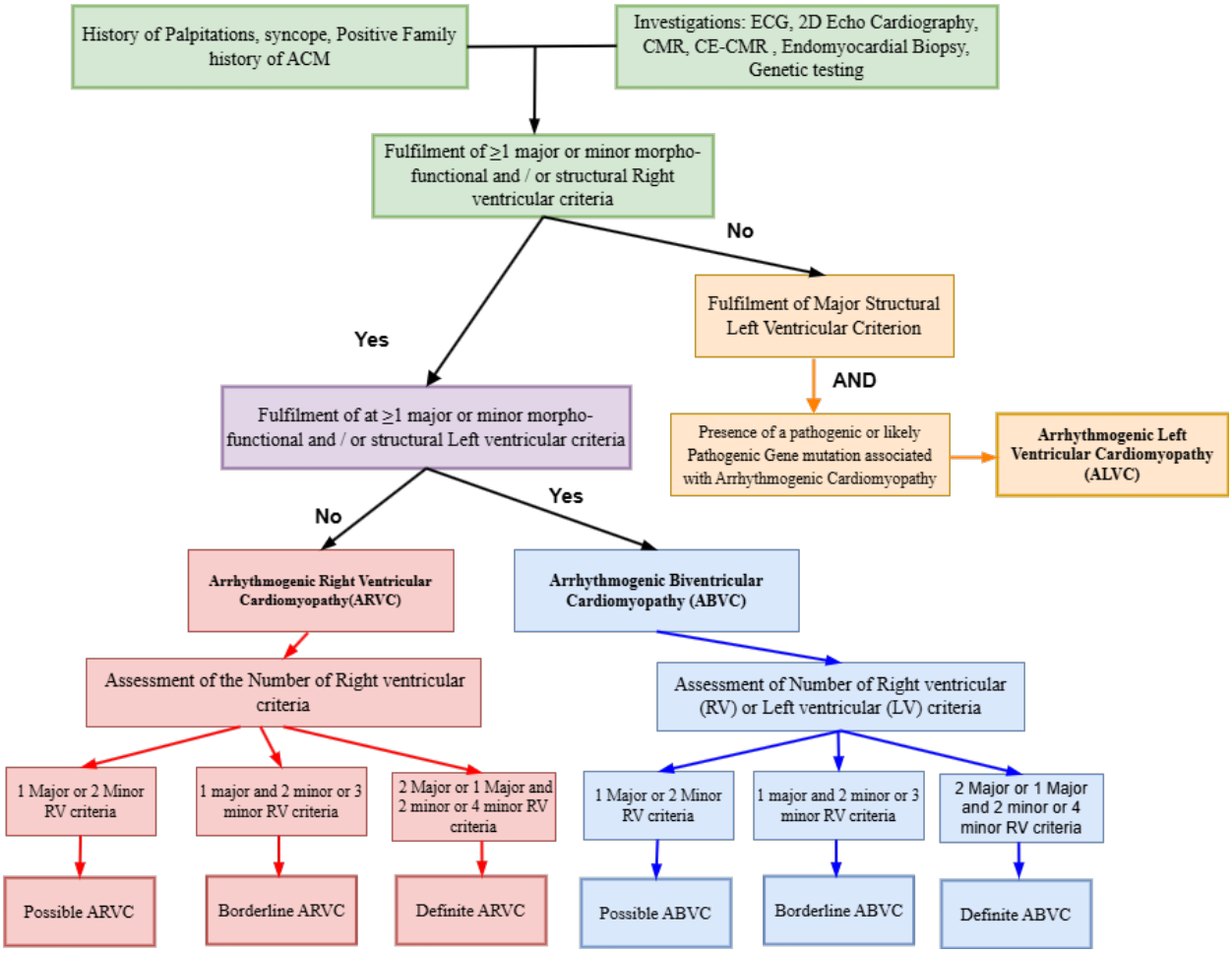

Figure 1: *Flowchart depicting the diagnostic approach for ACM variants based on the European Task Force Criteria*[17]

ACM: arrhythmogenic cardiomyopathy, ARVC: arrhythmogenic right ventricular cardiomyopathy, ALVC: arrhythmogenic left ventricular cardiomyopathy, ABVC: Arrhythmogenic Biventricular cardiomyopathy ECG: electrocardiography, CMR: cardiac magnetic resonance CE-CMR: contrast-enhanced cardiac magnetic resonance, RV: right ventricular, LV: Left ventricular

As illustrated in Figure 1, the diagnosis of any subtype of ACM is predicated on the fulfillment of major or minor morpho-functional and/or structural criteria. Diagnoses are classified as 'possible,' 'borderline,' or 'definite' according to the number of criteria fulfilled.[17] (Figure 1) Patients who are diagnosed as non-definite ACM ("Borderline" or "Possible") require continuous follow-up investigations to monitor the disease progression.[10]

b. Novel diagnostic tools

Besides the European TFC, some new diagnostic approaches have been introduced in recent years to enhance the diagnosis of ACM. Based on a retrospective review by Akdis et al. (2022), a combination of newly identified plasma biomarkers, namely sST2, GDF-15, and NT-proBNP, may be able to predict biventricular involvement in patients with the disease.[18] Zhang et al. (2022) also suggested a new diagnostic algorithm model to differentiate ACM from Dilated Cardiomyopathy (DCM).[19] Further research is required before these novel diagnostic tools can be implemented clinically.

Differential Diagnosis

Some myocardial diseases and chest abnormalities share clinical features with ACM but do not fit into the diagnostic criteria due to the absence of myocardial scarring. Some conditions that can mimic the ARVC variant include congenital heart disease, such as atrial septal defects or partial anomalous pulmonary venous drainage, which causes right ventricular volume overload. Pulmonary artery hypertension and athlete's heart syndrome may also mimic ARVC by inducing ventricular dilatation or dysfunction without myocardial scarring. Furthermore, the absence of the pericardium and chest deformities such as pectus excavatum or carinatum may also present with imaging and ECG abnormalities mimicking those of ARVC. Dilated Cardiomyopathy is an important differential diagnosis of both ALVC and ABVC Variants, and the LGE CMR imaging serves as an invaluable tool for differentiating these cardiomyopathies.[7,10]

Risk Stratification

Risk stratification in ACM aims to identify patients more prone to ventricular arrhythmias that can potentially lead to SCD and to support the justification of ICD implantation.[4] ACM risk factors of ventricular arrhythmias usually include prior ventricular tachycardias and left or right ventricular ejection fraction. However, multivariable models offer more precise and quantitative arrhythmic risk assessments.[20] Unlike ARVC, there is currently no validated risk stratification prediction model for ACM patients with left ventricular

involvement (ALVC & ABVC).[21] The 2019 ARVC risk calculator model developed by Cadrin-Tourigny et al.[22] and validated by Jordà et al.[23] has been criticized for the exclusion of genotype as a risk factor.[21] A recent study by Varrenti et al. (2024) showed that left ventricular involvement in ACM increases the risk for arrhythmias.[21] Risk stratification still requires adaptation to all three variants of ACM.

Treatment

Our study highlights the scarcity of Randomized Controlled Trials (RCT) on ACM and the absence of guidelines specifically describing treatment protocols for each ACM subtype. Furthermore, a proper management strategy tailored for the left ventricular involvement in ACM was lacking.[13] As there are no absolute curative therapies, current treatment is designed to alleviate symptoms, halt the disease progression, and prevent SCD.[2] Current treatment modalities for ACM are Exercise Restriction, drug therapy with antiarrhythmic drugs, ICD (implantable cardioverter defibrillator), catheter ablation, and cardiac transplantation.[5]

a. Exercise Restriction

Avoidance of Vigorous exercise has been recommended by the 2023 European Society of Cardiology (ESC) guidelines to ACM patients.[24] The occurrence of arrhythmias and biventricular progression of the disease has been proved to be both reduced with a restriction of physical exertion to around 30 minutes of brisk walking per day.[4,25] Nonetheless, exercise restriction is not enough to obviate the need for ICD implantation.[25]

b . Pharmacotherapy

Beta-blockers are currently first-line medications in preventing arrhythmias in ACM.[4] Nonetheless, their effectiveness in reducing the risk of arrhythmias is still uncertain.[25] For example, in a study by Cappelletto et al., bisoprolol reduced the recurrence of Right ventricular arrhythmias only at doses above 5 mg. In contrast, in another North American Registry study by Marcus et al., no effect of beta-blockers on ventricular arrhythmias was seen.[26,27] Sotalol, which has been proven effective in reducing arrhythmic risk in the past, does not appear in the new guidelines due to conflicting outcomes from the various studies.[20,25] Administration of Amiodarone is generally reserved for complicated situations owing to contradictory evidence of its effectiveness and long-term side effects.[25,28] Additionally, evidence from the first RCT on ARVC indicated that a combination of flecainide and bisoprolol may reduce the burden of Premature Ventricular Complexes in ARVC.[29] In ACM-related heart failure, ACE inhibitors, ARBs, and diuretics are recommended despite the lack of RCTs establishing their efficacy. It is important to highlight that none of the mentioned medications definitively lower the risk of SCD in ACM.[20]

c. ICD

ICDs, either subcutaneous or transvenous, are the sole effective method to avoid SCD in ACM.[13] While subcutaneous ICDs have fewer device-related complications, they lack the anti-tachycardia pacing feature of transvenous ICDs. Hence, one must consider the risk of inappropriate shocks and device-related complications before ICD implantation.[25] Some patients may deny ICDs due to Financial or personal issues.[2]

d. Catheter Ablation

Radiofrequency Catheter Ablation should be used for those patients with recurrent VT despite pharmacological treatment. However, absolute freedom from ventricular arrhythmias may be impossible with CA alone due to the progressive course of ACM. Different studies reflect the better outcomes of epicardial catheter ablation, which has a relatively lower VT recurrence rate than the endocardial approach. However, applying both endocardial and epicardial approaches may yield better outcomes, mainly if there are intramural myocardial scars.[25] Romero et al. (2020) illustrated that the combined procedure of endo-epicardial ablation showed that there was a remarkable reduction in VT recurrence rate (26.4%) when compared with only endocardial ablation (49.6%).[30] It is also important to mention that catheter ablation does not eliminate the need for ICD implantation and that catheter ablation in the left ventricle can be tricky due to mid-myocardial fat deposition, impairs the sensitivity of the mapping system.[2]

e. Cardiac Transplantation

Cardiac transplantation has been shown to have good outcomes in patients with end-stage right ventricular dysfunction. By comparison, cardiac transplantation in ARVC has better results than in restrictive or ischemic cardiomyopathies.[2]

f. Future Therapies

Stereotactic radiotherapy, a recent therapy for ventricular arrhythmias, may be promising in the event of antiarrhythmic agents or catheter ablation being contraindicated or uneventful. However, further research is required to validate its effectiveness and safety. Future therapies, such as myocardial gene therapy with adenoviruses, GSk3b inhibition, and administration of honokiol, are still in the pilot stage and require further research.[25]

Prognosis

Among the three subtypes of ACM, ABVC may be associated with the poorest prognosis. In a recent study by Bariani et al. (2024), life-threatening arrhythmias occurred most commonly in ABVC (38%), followed by ARVC (31%) and ALVC (14%). Similarly, heart failure was more common in ABVC (19%) than in ALVC (6%) and ARVC (1%). Sudden cardiac death was noted in 5% of ABVC, 3% of ARVC, and 1% of ALVC. On top of that, hot phases were noted in 14% of ALVC, 9% of ABVC, and 5% of ARVC cases.[15] (See Table 1) Hence, it can also be inferred that ACM patients with RV involvement are associated with a higher arrhythmic burden. In contrast, those with LV involvement are associated with a higher risk of heart failure, cardiac transplantation, and Hot phases.[14,15]

Discussion

This paper provides a comparative analysis of the current literature on the different variants of ACM. The findings of this analysis are outlined in Table 1, which offers a contextual description of the characteristics and outcomes of each ACM subtype.

Most ARVC cases in a study by Miles et al. presented with abnormalities in both ventricles and very few cases were limited to the right or left ventricle alone.[4,8] Similarly, in another study by Zghaib et al., the "ARVC" cases included most frequently both ventricles.[31] These findings strongly indicate that ABVC might be the most common form of ACM. This also supports the preference for the umbrella term "ACM" over the original "ARVC" term, aligning with the modern concept of a biventricular heart muscle disease where left ventricular involvement may equal or surpass right ventricular severity.[2] The new Consensus report of the European Task Force has illuminated the heterogeneous Etiology of ACM to a great extent.[10] Prior to the consensus report, phenocopies such as neuromuscular cardiomyopathies, post-viral myocarditis, cardiac sarcoidosis, Chagas Disease, and autoimmune multisystem disorders were considered only as differential diagnoses of ACM.[7] Notably, the agreement of the Task Force has recognized such phenocopies as established causes of ACM since they fulfill the diagnostic criteria of LV phenotype.[10] Furthermore, due to extensive overlap between the nature of genetic defects underlying ACM variants, it is inaccurate to categorize them solely based on their association with desmosomal

or non-desmosomal genetic defects.

In the 2010 revised TFC, the absence of specific diagnostic criteria for the left-sided variants of the disease has resulted in the underdiagnosis and undertreatment of patients exhibiting the ALVC and ABVC variants of the disease.[2] To improve diagnostic accuracy throughout the entire range of ACM phenotype, the European TFC refined the expected 2020 Padua criteria.[10] The clinical impact of the 2020 Padua Criteria for the diagnosis of left ventricular involvement was appraised by a 'post-hoc' application to 112 patients already diagnosed under the 2010 TFC criteria at the University of Padua from 2015 to 2019. The latter revealed an improvement in the diagnostic accuracy of ACM variants using the 2020 Padua Criteria.[32] Additionally, a retrospective study by Cicenia et al. (2022) involving a pediatric ACM cohort with LV involvement in fifty percent of the study participants also demonstrated enhanced diagnostic yield using the 2020 Padua criteria.[33] This Padua Criteria was also positively appraised in a study by Bariani et al. (2022), which showed a rise of 35% in the number of ACM cases diagnosed using the latter compared to the 2010 revised TFC.[9] This evidence strongly suggests that the recently proposed European TFC, a refinement of the 2020 Padua Criteria, also possesses the potential to improve the diagnostic accuracy of all ACM variants. Hence, additional research is required to implement this new TFC in clinical settings.[10] Given that the current risk stratification scoring systems exclusively target the ARVC variant, predicting arrhythmic risk for ALVC and ABVC may still be challenging.

The progressive nature and diverse phenotypic expression of ACM renders its treatment challenging. In addition, being a rare disease, the restriction of study populations to only small cohorts makes it unfeasible to carry out accurate clinical trials.[25] The 2023 ESC guidelines, the 2019 Heart Rhythm Society (HRS) instructions, and the 2015 International Task Force consensus report provide treatment recommendations for ACM that do not mention the necessity of implementing tailored treatment protocols for each of the three variants.[24,34,35] Malignant arrhythmic events (e.g., SCD, ventricular fibrillation-induced cardiac arrest, and appropriate ICD intervention), heart failure, heart transplantation, and unexplained syncope are the main clinical predictors of a poor prognosis in ACM.[6,36] It was revealed in a recent study by Bariani et al. (2024) that the ABVC variant had the highest occurrence of life-threatening ventricular arrhythmias, sudden cardiac death, and heart failure.[15] Likewise, a retrospective study by Bermúdez-Jiménez et al. also reported that left ventricular involvement in the disease was associated with a poorer prognosis.[37] These findings suggest that the ABVC variant of ACM may be the most unfavorable, followed by ALVC and ARVC. However, there remains a lack of research on each ACM subtype's short-term and long-term clinical outcomes.

This study stands out as one of the first to comparatively explore ACM's diverse phenotypic variants. A comprehensive understanding of this rare heart muscle disorder is provided by integrating the latest research findings on ACM and its variants. This study also highlights previously underrecognized and misdiagnosed ACM subtypes such as ALVC and ABVC. This paper's key strength lies in identifying significant research gaps in existing literature concerning ACM and its variants. It suggests further research questions on ACM to appraise and improve current management protocols for the disease. This paper, being a literature review, also has certain limitations. The relevant research papers were retrieved by the author's individual judgment and not through a systematic standard procedure during data collection. So, this paper's inclusion process can be prone to selection bias. Consequently, the authors critically reviewed the selected articles extensively through discussion in order to enhance reliability. Ultimately, this literature review has provided invaluable insights for future research on this rare heart condition.

Conclusion

A comparative analysis of ARVC, ALVC, and ABVC has revealed distinct clinical outcomes associated with the individual and concomitant involvement of each ventricle in ACM. ABVC emerges as the most prevalent and concerning subtype of ACM, being linked to the poorest prognosis, followed by ALVC and ARVC. Our findings suggest the possible need for tailored approaches and treatment protocols for ACM patients based on the phenotypic variant exhibited. Implementing the recently proposed European TFC can potentially rectify previous underdiagnosis and diagnostic delays associated with the left ventricular involvement in ACM. Alternatively, the general lack of clinical trials on ACM hinders the appraisal of current treatment protocols and the identification of the most treatment-responsive variant. Hence, further research into the clinical outcomes and management of all three phenotypic variants of ACM is essential to improving patient care.

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