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ORIGINAL RESEARCH

China Multi-Center Cohort Study on Risk Evaluation of Arrhythmogenic Cardiomyopathy

The ChinaCORE ACM Registry

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ABSTRACT

BACKGROUND Arrhythmogenic cardiomyopathy (ACM) patients in China exhibit unique genetic and clinical characteristics. There is a lack of prognostic models specific to Chinese ACM patients.

OBJECTIVES This study aims to establish a large, national ACM patient cohort with uniformly collected, high-quality data for future risk prediction.

METHODS This study includes patients with definite or borderline ACM diagnoses, along with their genotype-positive relatives. At baseline, comprehensive data collection includes medical history, electrocardiograms, imaging data, genetic testing, and laboratory evaluations. Outcome data include heart failure events and malignant ventricular arrhythmias.

RESULTS As of September 2024, the registry has enrolled 622 participants, including 552 probands (88.7%) and 70 family members (11.3%) carrying ACM-related variants. Preliminary cohort includes 577 patients (92.8%), of whom 495 were diagnosed with definite arrhythmogenic right ventricular cardiomyopathy. The median age of symptom onset was 33.0 years (Q1-Q3: 22.0-45.0 years), with 41.6% experiencing arrhythmia-related symptoms. Abnormal electrocardiogram findings included T-wave inversion (72.7%) and epsilon waves (24.8%) in leads V_1 to V_3. Imaging evaluation revealed RV dilatation in 44.6% and left ventricular dilatation in 29.8%, with a mean left ventricular ejection fraction of 53.0% $\pm$ 14.5%. Regarding outcomes, malignant ventricular arrhythmias occurred in 255 (40.1%) individuals, while 21.9% developed end-stage heart failure, including 35 individuals who died of heart failure and 101 patients who underwent heart transplantation.

CONCLUSIONS The ChinaCORE ACM (China Multi-Center Cohort Study on Risk Evaluation of Arrhythmogenic Cardiomyopathy) registry is a national, longitudinal, observational cohort study. This study contributes to expanding the understanding of the disease spectrum of Chinese ACM patients and improving prognostic predictions.

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Arrhythmogenic cardiomyopathy (ACM) is a heritable cardiomyopathy characterized by fibrofatty replacement of the ventricular myocardium, a high risk of life-threatening ventricular arrhythmias, sudden cardiac death (SCD), and progressive heart failure.[1,2] Although its prevalence is estimated to be 1 in 1,000 to 1 in 5,000, ACM is an important cause of sudden death in young people and athletes.[3-5] Given the limited awareness and recognition of this disease, no large-scale epidemiological studies on ACM have been conducted in China to date.

Previous studies suggest that approximately 50% of ACM patients carry 1 or more variants in genes encoding structural proteins, particularly those related to cardiac desmosomes including plakophilin-2 (*PKP2*), plakoglobin (*JUP*), desmoglein-2 (*DSG2*), desmocollin-2 (*DSC2*), and desmoplakin (*DSP*).[6,7] The phenotypic expression and clinical outcomes of ACM patients vary significantly across different genotypes.[8-10] Unlike European and North American ACM patients, where *PKP2* and *DSP* were identified as the predominant pathogenic genes, our previous research showed that *DSG2* variants account for a relatively high proportion among Chinese patients.[11,12] Notably, compared with *PKP2* carriers, patients with *DSG2* variants experienced a higher risk of developing end-stage heart failure.[13,14] This suggests that ACM patients in China may have a distinct spectrum of disease characteristics and clinical outcomes caused by differences in genetic profile. However, large-scale studies comprehensively analyzing the genotype and phenotype characteristics of Chinese ACM patients remain lacking.

Patients typically present between ages 20 and 60 years with arrhythmic symptoms, and in over one-half of probands, SCD is the initial manifestation.[15] Although various clinical indicators, including syncope, nonsustained ventricular tachycardia (NSVT), and the number of T-wave inversions on electrocardiogram (ECG), are associated with the risk of malignant ventricular arrhythmia (MVA) in ACM, there is limited research quantitatively assessing the prognostic value.[16-18] The research team from Johns Hopkins University, in collaboration with 14 clinical centers worldwide, reported a new clinical risk prediction model for MVA in ACM patients.[19] However, this model primarily included ACM cohorts from Europe and North America, and its validation performance in Asian populations was suboptimal, which might be attributed to underlying genetic heterogeneity.[20] Currently, there are limited reports on risk prediction models for East Asian ACM patients.

In addition to arrhythmic phenotypes, ACM patients also experienced progressive cardiac dysfunction, typically beginning in the right ventricle and subsequently involving both ventricles.[15,21,22] A minority of patients displayed biventricular or predominantly left ventricular involvement, particularly those with *DSP* gene variants.[10,23] As the disease progressed, around 20% of patients developed end-stage heart failure (ESHF), leading to death or requiring heart transplantation, and over 50% exhibited heart failure phenotypes during the course of the disease.[24] Therefore, progressive ventricular dysfunction emerges as another major contributor to mortality in ACM patients. Our previous study on an ESHF prediction model identified that traditional clinical parameters, such as left ventricular ejection fraction (LVEF), serum creatinine levels, tricuspid regurgitation, and atrial fibrillation, were important prognostic factors.[21] Novel parameters including impaired atrial and ventricular strain were also used for assessing heart failure outcomes.[25] However, few quantitative prediction models incorporating clinical and novel factors for ESHF risk stratification in ACM patients have been reported.

The ChinaCORE ACM (China Multi-Center Cohort Study on Risk Evaluation of Arrhythmogenic Cardiomyopathy) registry aims to establish a national, multicenter observational cohort of ACM patients to

ABBREVIATIONS AND ACRONYMS

ACM = arrhythmogenic cardiomyopathy

ARVC = arrhythmogenic right ventricular cardiomyopathy

ESHF = end-stage heart failure

LVEF = left ventricular ejection fraction

MVA = malignant ventricular arrhythmia

SCD = sudden cardiac death

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define the natural history and prognostic factors of ACM in Chinese patients. Second, this project seeks to collect high-quality, multidimensional data by integrating genetic, imaging, and clinical information, incorporating both established parameters from previous models and newly identified variables, thereby ensuring a robust data set for future research. Meanwhile, multiple statistical methods, including regression model, machine learning, and deep-learning models, will be utilized to develop risk prediction models for arrhythmia and heart failure outcomes. The performance of these models will be systematically compared and validated to further identify the most accurate and clinically applicable prediction equation for Chinese ACM patients.

METHODS

OVERVIEW OF RESEARCH DESIGN. The ChinaCORE ACM registry is a national, multicenter observational cohort study conducted in China (ChiCTR2500098971). At baseline, comprehensive data were collected, including medical history, ECGs, Holter recordings, imaging measurements, genetic testing, and laboratory evaluations. An individualized follow-up schedule was subsequently developed based on each participant's enrollment date. Patients will be followed at regular intervals, with follow-up visits scheduled at 1, 2, and 5 years after enrollment. During each follow-up, comprehensive clinical assessments are conducted, including symptom evaluation, 12-lead ECG, echocardiography, and the occurrence of outcome events (Supplemental Table 1).

STUDY POPULATION. Starting from January 2009, patients with a definite or borderline diagnosis of ACM, along with their genotype-positive relatives,

FIGURE 1 Participating Centers, Pre-Specified Predictors and Participant Origins

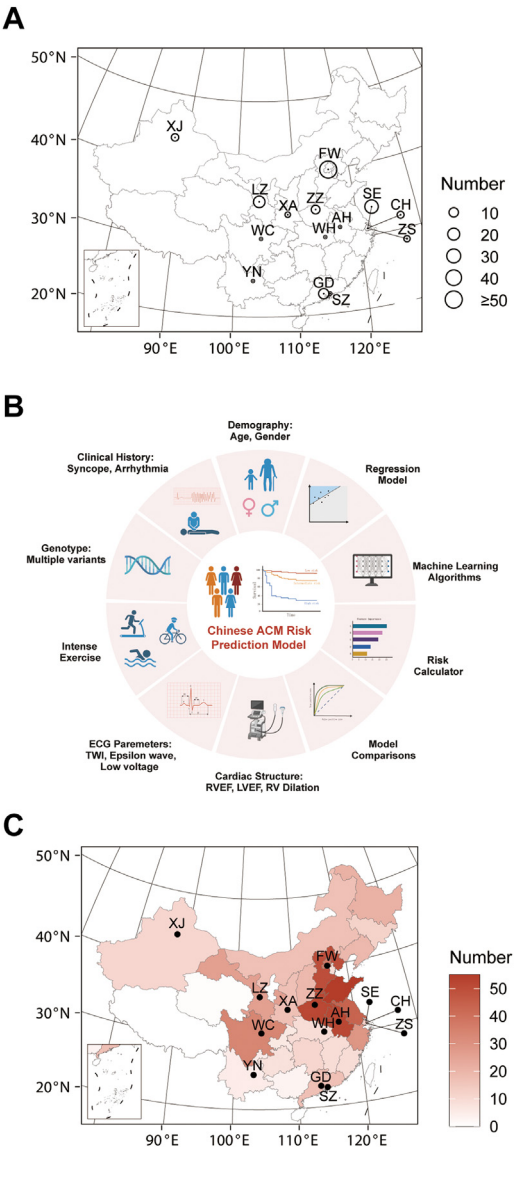

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FIGURE 1 Continued

(A) Geographic distribution of the 14 participating centers across 11 provinces in China, reflecting the national coverage of the ChinaCORE ACM (China Multi-Center Cohort Study on Risk Evaluation of Arrhythmogenic Cardiomyopathy) registry. The size of each circle indicates the number of patients enrolled at each center. (B) Overview of the prespecified clinical, electrocardiographic, imaging, and genetic predictors assessed in the cohort. The panel also outlines the statistical approaches, including Cox regression and machine learning algorithms, used for risk model development. (C) Distribution of participants origins by place of permanent residence. Darker color shades represent provinces with a higher number of participants according to their registered birthplace. AH = Anhui Provincial Hospital; CH = Children's Hospital of Fudan University; ECG = electrocardiogram; FW = Fuwai Hospital; GD = Guangdong Provincial People's Hospital; LVEF = left ventricular ejection fraction; LZ = The First Hospital of Lanzhou University; RVEF = right ventricular ejection fraction; RV = right ventricle; SE = Shanghai East Hospital; SZ = Fuwai Hospital Chinese Academy of Medical Sciences, Shenzhen Hospital; TWI = T-wave inversion; WC = West China Second University Hospital, Sichuan University; WH = The Central Hospital of Wuhan; XA = The First Affiliated Hospital of Xi'an Jiaotong University; XJ = The First Affiliated Hospital of Xinjiang Medical University; YN = Fuwai Yunnan Hospital, Chinese Academy of Medical Sciences; ZS = Fudan University Zhongshan Hospital; ZZ = The First Affiliated Hospital of Zhengzhou University.

were enrolled. To mitigate center-level heterogeneity and ensure cohort representativeness, study sites were selected based on 2 key criteria:1) demonstrated capability in providing high-quality cardiovascular care and accurate diagnosis; and 2) institutional and regional diversity, encompassing both national referral hospitals and regional tertiary centers. Current institutions are as follows (**Figure 1A**): Fuwai Hospital, The First Affiliated Hospital of Zhengzhou University, Shanghai East Hospital, The First Hospital of Lanzhou University, Guangdong Provincial People's Hospital, The First Affiliated Hospital of Xi'an Jiaotong University, The First Affiliated Hospital of Xinjiang Medical University, Anhui Provincial Hospital, Children's Hospital of Fudan University, Fudan University Zhongshan Hospital, Fuwai Hospital Chinese Academy of Medical Sciences, Shenzhen Hospital, Fuwai Yunnan Hospital, Chinese Academy of Medical Sciences, The Central Hospital of Wuhan, and West China Second University Hospital, Sichuan University. This study was approved by the Institutional Review Boards or ethical committees at each participating center, and written informed consent was obtained from all participants after comprehensive explanation. The inclusion and exclusion criteria are shown in detail as follows.

Inclusion criteria: definite or borderline diagnoses of ACM were made according to the 2010 Task Force Criteria and 2020 Padua criteria.[26,27] A "definite" diagnosis is established when a patient meets 2 major criteria, 1 major and 2 minor criteria, or 4 minor criteria from different diagnostic categories, including cardiac structure and function, histology, ECG, arrhythmia, and family history. A diagnosis of "borderline" is established when a patient meets 1 major and 1 minor criterion or 3 minor criteria from different categories. We excluded patients with diagnosed ischemic cardiomyopathy or other diagnosed cardiomyopathies (hypertrophic cardiomyopathy, noncompaction cardiomyopathy, cardiac sarcoidosis, amyloidosis, and myocarditis). The study aims to enroll 1,200 participants over the next 5 years, with the sample size estimated based on anticipated differences in key clinical outcomes, 80% power, a 2-sided alpha of 0.05, and an assumed 15% loss to follow-up.

QUESTIONNAIRE AND MEASUREMENTS. Basic information was collected through face-to-face interviews using a questionnaire (Supplemental Table 2), including demographic information (gender, ethnicity, location, date of birth, height, weight), present medical history (occurrence and age of symptoms before and at the date of enrollment), NYHA functional class, past medical history (myocarditis,[28] and so on), comorbidities (hypertension, dyslipidemia, diabetes mellitus, stroke, and so on), exercise history (exercise type, intensity, and duration), family history (family members diagnosed with ACM, other types of cardiomyopathies, NSVT or fibrillation, or SCD), and cardiovascular medication history (name, dosage, frequency, and efficacy). All data collection was performed by personnel who had received standardized training and met qualification requirements.

ELECTROCARDIOGRAM. ECG was performed on enrolled patients at baseline (paper speed 25 mm/s, 10 mm/mV gain). The analysis included heart rate, rhythm, QRS duration and pattern (left bundle branch block, right bundle branch block, or interventricular conduction disorders), repolarization abnormalities (T-wave inversion in precordial leads V_1 to V_6 and their count), depolarization abnormalities (including epsilon waves in right precordial leads V_1 to V_3, low QRS voltage and QRS fragmentation). 24-hour Holter ECG monitoring results will also be collected. After proper lead connection, patients were permitted normal activities while continuous ECG monitoring was conducted over a 24-hour period, avoiding intense physical exercise, heavy meals, alcohol consumption, and bathing. Whether beta-blockers were administered during Holter monitoring was documented for each patient. The analysis included total heartbeats, rhythm, and arrhythmias including premature ventricular complexes (PVCs) and their count, as well as NSVT.[29] The evaluation was independently conducted by at least 2 cardiologists. In cases of disagreement, a third cardiologist reassessed the ECG to reach a consensus.

ECHOCARDIOGRAPHY. Standardized 2-dimensional echocardiography was performed for enrolled patients using Philips Epic 7C or GE E9 ultrasound systems, equipped with S5-1 and M3S probes at frequencies of 1.7 to 3.4 MHz. Images were saved in DICOM format. Examinations were conducted at baseline and follow-up.

Standard views included the parasternal long-axis of the left ventricle, right ventricular inflow tract, parasternal short-axis, and apical 4-chamber, as well as additional nonstandard views as needed. ECG was connected to capture 5 cardiac cycles. Observations included any presence of left or right ventricular dilation, regional wall motion abnormalities, and ventricular aneurysm. Key echocardiographic parameters were recorded, including left atria diameter, interventricular septum thickness, LVEF, end-diastolic diameters of left and right ventricles, and

left ventricular end-systolic volume. Right ventricular outflow tract diameter was measured from parasternal long- and short-axis views. Other parameters including right ventricular fractional area change, free wall strain, and the degree and velocity of mitral and tricuspid regurgitation were evaluated from the apical 4-chamber view if available. Echocardiographic analyses were re-evaluated by 2 experienced senior echocardiographers at the core laboratory, and in case of disagreement, a third evaluator was consulted.

CARDIAC MAGNETIC RESONANCE. Cardiac magnetic resonance imaging was performed using the magnetic resonance scanner (3.0-T, Skyra or Vida, Siemens Healthineers). Scans were conducted using both ECG and respiratory gating. A balanced steady-state free precession sequence was used to acquire images in the right ventricular outflow tract, 3-chamber, 4-chamber, and short-axis views. Before contrast-enhanced imaging, gadolinium-based contrast (0.15 mmol/kg, Magnevist; Bayer Healthcare Pharmaceuticals) was administered intravenously, with scanning initiated 10 minutes postinjection. The delay trigger time was manually calculated based on the myocardial signal nulling time. CMR images were analyzed using CVI 42 software, which automatically delineates endocardial and epicardial borders at end-diastole, with manual adjustments made as needed. Additionally, manual measurements were cross-validated by 2 independent observers to further enhance reliability. All patient reports and original images were saved.

The parameters included the structure of the left and right ventricles: regional wall motion abnormalities, end-diastolic volumes, ventricular ejection fractions, adipose infiltration, and the location and extent of late gadolinium enhancement.[30]

BIOBANK OF BLOOD SAMPLES. Fasting blood samples were collected from the antecubital vein of enrolled patients in the morning at baseline. The following laboratory markers were measured: B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide, creatine kinase-MB, cardiac troponin, and blood lipids. Complete blood count was performed using whole blood samples.

Genetic testing was performed on all participants. We routinely analyzed variants in 10 genes (*PKP2, DSG2, DSC2, DSP, LMNA, DES, PLN, SCN5A, TMEM43, JUP*) recognized as highly associated with pathogenicity in ACM.[31] Meanwhile, new disease-causing genes were also recorded and explored.

The remaining plasma and whole blood samples from patients and relatives were stored long-term, providing a solid foundation for subsequent analysis and research in the ACM cohort.

TREATMENT. Treatment measures for enrolled patients were documented, including details of medication treatment (name, dosage, frequency, and efficacy), cardiac implantable electronic device implantation (date and remote monitoring), catheter ablation (date and reasons), and surgery treatment (heart transplantation and left ventricular assist device).[32]

DATA COLLECTION AND DEFINITION. A unique cohort identification number was assigned to each ACM patient as the sole identifier within this cohort. All research staff underwent standardized training before data collection, and all measurements will be obtained using standardized methods and equipment. Information from questionnaires and measurement results were manually extracted into EpiData software and stored as PDF documents. Any data modifications included an explanation and a record of the modification process. We prespecified potential predictors and risk criteria based on clinical expertise and previously identified risk factors for adverse events in ACM[33-37] (**Figure 1B**, Supplemental Methods).

OUTCOMES. Standardized case report forms were used for data collection, with follow-up conducted through face-to-face interviews or telephone calls after enrollment. Both primary and secondary endpoint events were recorded.

Primary outcomes referred to the occurrence of an ESHF event, including heart failure-related death, heart transplantation, listing for transplantation, or left ventricular assist device implantation.

Secondary outcomes referred to heart failure-related rehospitalization, or malignant ventricular arrhythmic events, including spontaneous sustained VT, ventricular fibrillation, SCD or aborted cardiac arrest, and appropriate implantable cardioverter-defibrillator therapy.[21,25]

PRELIMINARY DATA AND ANALYSIS. Continuous variables were presented as mean ± SD or median (IQR), depending on the results of normality testing performed prior to data presentation. The Shapiro-Wilk test was used to assess the normality of each continuous variable. Categorical variables were reported as counts and percentages.

RESULTS

As of September 2024, the registry has enrolled 622 individuals, including 552 probands (88.7%) and 70 genotype-positive family members (11.3%). The distribution of participants' origin was described in **Figure 1C**. Notably, participants were from 28 of 34

provincial-level administrative regions in mainland China, ensuring broad geographic coverage. The preliminary cohort included 577 patients (92.8%), of whom 495 (79.6%) were diagnosed with definite arrhythmogenic right ventricular cardiomyopathy (ARVC) (Table 1). The median age of symptom onset was 33.0 years (Q1-Q3: 22.0-45.0 years). Arrhythmia-related symptoms, including palpitations, dizziness, sweating, fainting, syncope or presyncope, were observed in 259 cases (41.6%), whereas SCD was the first presentation in 67 individuals (10.8%). Heart failure symptoms were observed in 111 individuals (17.8%), with NYHA functional classification of III and IV in 17.4% and 9.6% of patients, respectively, at the time of enrollment. Only 42 individuals (6.8%) exhibited abnormal ECG findings without symptoms. Additionally, 98 individuals (15.8%) experienced symptom onset before adulthood (age <18).

A total of 32 individuals (5.1%) were in atrial fibrillation rhythm at enrollment. TWI in leads V_1 to V_3 was observed in 373 participants (72.7%), and epsilon waves in leads V_1 to V_3 were present in 127 individuals (24.8%). Among the 470 participants with available Holter recordings, 234 (49.8%) had more than 500 PVCs, and 341 (72.5%) exhibited NSVT.

At enrollment, the mean LVEF was 53.0 ± 14.5%. Right ventricular dilatation was observed in 328 individuals (44.6%), and left ventricular dilatation was seen in 159 individuals (29.8%). A total of 130 participants (20.9%) underwent cardiac implantable electronic device implantation, the majority of whom (85.4%) received an implantable cardioverter-defibrillator. Among them, 50 individuals (42%) had the indication for primary prevention. Catheter ablation for ventricular arrhythmias was performed in 183 patients (29.3%).

Regarding outcomes, 255 individuals (40.1%) experienced MVA. Additionally, 136 individuals (21.9%) developed ESHF, including 35 deaths caused by heart failure (5.6%) and 101 individuals (16.2%) who underwent heart transplantation.

TABLE 1 Baseline Clinical Characteristics of the Overall Cohort (N = 622)

Male	399 (64.1)
Body mass index, kg/m^2	23.4 ± 3.9
Proband	552 (88.7)
Patient	577 (92.8)
Definite diagnosed ARVC	495 (79.6)
Family history	
Family history of ARVC	62 (10)
Family history of DCM/HCM	15 (2.4)
Family history of VA	57 (9.2)
Clinical features	
Symptom onset age, y	33.0 (22.0-45.0)
Symptom onset <age 18 y	98 (15.8)
Symptom type	
Arrhythmia-related[a]	259 (41.6)
HF-related[b]	111 (17.8)
Abnormal ECG without symptom	42 (6.8)
SCD at first presentation	67 (10.8)
Syncope history before enrollment	163 (26.2)
History of Sustained VT/VF/SCD	208 (33.4)
NYHA functional class at enrollment (n = 500)	
I	234 (46.8)
II	131 (26.2)
III	87 (17.4)
IV	48 (9.6)
Arrhythmias	
Atrial fibrillation	32 (5.1)
Atrial flutter	8 (1.73)
Sinus node syndrome	7 (1.1)
Atrioventricular block	17 (2.7)
Available ECG (n = 513)	
TWI in V_1-V_3	373 (72.7)
TWI in V_4-V_6	217 (42.3)
Epsilon wave in V_1-V_3	127 (24.8)
Holter	
>500 PVCs	234 (49.8)
NSVT	341 (72.5)
Echocardiogram (n = 534)	
LVEF, %	53.0 ± 14.5
RV dilatation	328 (44.6)
RV dyskinesia	259 (48.5)
LV dilatation	159 (29.8)
LV dyskinesia	199 (37.3)

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DISCUSSION

We describe the methodology used to develop a multidisciplinary collaboration to study patients with ACM in China. ChinaCORE ACM registry is the largest national, multicenter observational cohort study of ACM patients, aiming to explore the natural history of ACM in the Chinese population and to evaluate clinical prognostic parameters. In summary, this study not only collected traditional prognostic indicators, including demographic characteristics and medical history, but also comprehensively gathered emerging potential risk factors, such as parameters from ECG, echocardiography, CMR, plasma biomarkers, and genetic characteristics. Eventually, critical prognostic factors will be determined, and the prediction models for MVA and ESHF outcomes will be built (Central Illustration).

Current ACM registries have generated valuable insights into the characteristics of the disease but are constrained by several limitations. The ACM registries from Johns Hopkins University (USA) and the Netherlands, derived from large specialty referral centers, may inherently introduce referral bias.[38,39] Additionally, compared with European and North

TABLE 1 Continued

Interventions	
Device Implantation, n = 130	
ICD	111 (85.4)
PM/CRT-P	11 (8.5)
CRT-D	8 (6.2)
Primary prevention	50 (42)
Secondary prevention	69 (58)
Catheter ablation	
Ventricular arrhythmia	183 (29.3)
Supraventricular tachycardia	19 (4.0)
Outcomes	
MVA	255 (40.1)
Death	35 (5.6)
Heart transplantation	101 (16.2)

Values are n (%), mean ± SD, or median (Q1-Q3). [a]Arrhythmia-related symptoms: palpitation, dizziness, sweating, fainting or (pre) syncope. [b]Heart failure (HF)–related symptoms: shortness of breath, fatigue and weakness, edema, reduced ability to exercise.

ARVC = arrhythmogenic right ventricular cardiomyopathy; CRT-D = cardiac resynchronization therapy defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; DCM = dilated cardiomyopathy; ECG = electrocardiogram; HF = heart failure; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter-defibrillator; LV = left ventricle; LVEF = left ventricular ejection fraction; MVA = malignant ventricular arrhythmia; NSVT = non-sustained ventricular tachycardia; PM = pacemaker; PVC = premature ventricular contraction; RV = right ventricle; SCD = sudden cardiac death; TWI = T-wave inversion; VA = ventricular arrhythmia; VF = ventricular fibrillation; VT = ventricular tachycardia.

American cohorts, including those from Nordic,[40] the Netherlands,[41] and Canada,[42,43] the Chinese ACM cohort exhibited distinct characteristics. The Chinese cohort exhibits an earlier age of onset, a higher prevalence of T-wave inversion in leads V_1 to V_3, and a relatively lower LVEF, which may be associated with left ventricular involvement (Supplemental Table 3). These differences underscore the importance of further investigating the unique characteristics of ACM in Chinese patients. However, clinical research on Chinese ACM patients is often limited by small sample sizes, single-center nature, and incomplete genetic data, leading to a limited understanding of ACM in this population.[12,20]

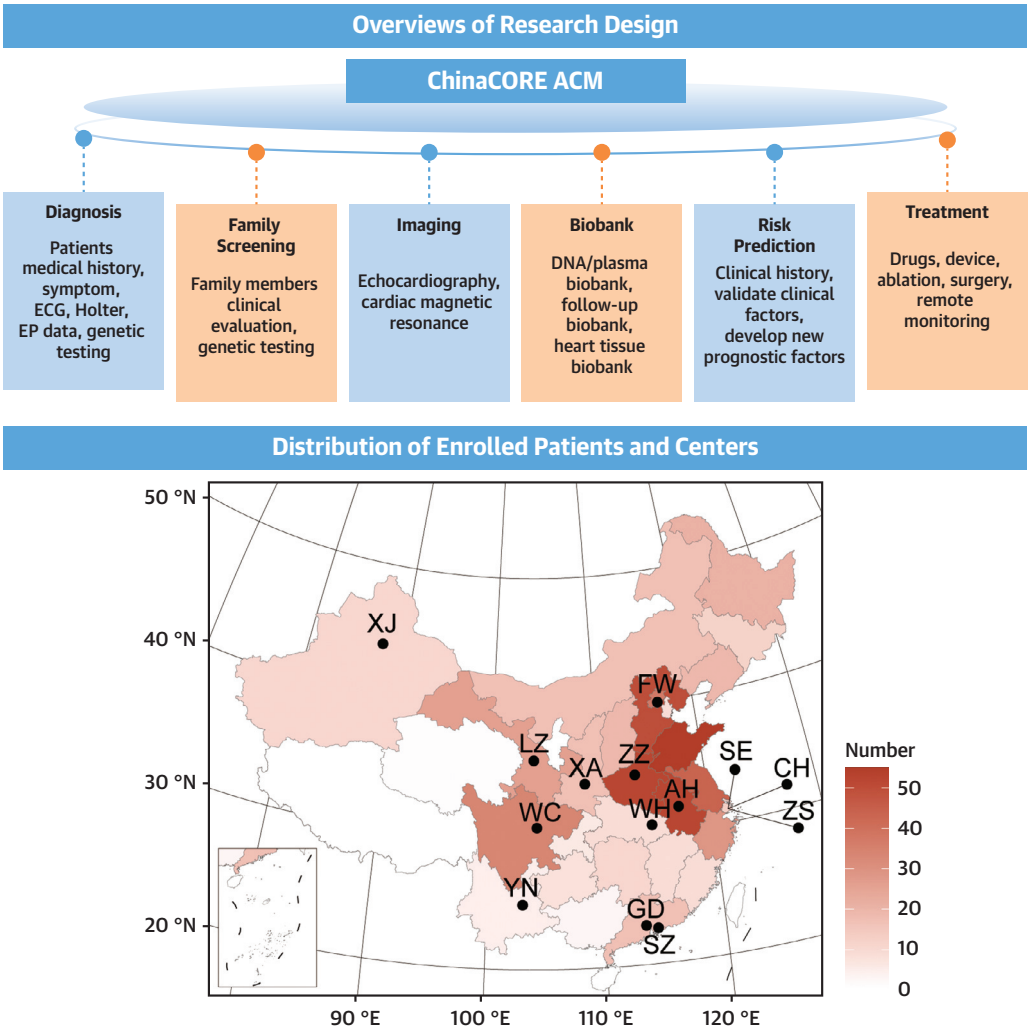
It is widely recognized that genotypic contributions to risk prediction in ACM are gaining increasing emphasis.[44] Previous studies have shown that ACM risk calculators perform best in *PKP2* variant carriers,[45] which may be partly attributed to the predominance of *PKP2* variants in Western populations. However, their predictive accuracy is significantly lower for patients with *DSP*[33] and *PLN*[36] variants. Moreover, data on less common ACM-associated genotypes in Western cohorts, such as *DSG2*, *DSC2*, and *JUP*, remain limited, hindering their integration into existing risk models. Therefore, conducting comprehensive genetic testing for ACM patients and their family members will allow for a more detailed characterization of ACM genotypes in the Chinese population, providing a foundation for integrating genetic data into future ARVC risk models. Moreover, this approach will facilitate the development of a gene-specific risk prediction model tailored to this cohort, ultimately enhancing risk stratification and clinical decision-making.

To address these challenges, we have established and maintained a large, multicenter, longitudinal observational cohort including 14 centers across 11 provinces. In the ChinaCORE ACM registry, we implement standardized protocols, particularly for genetic, ECG, and imaging data analysis, to ensure the collection of uniform, high-quality data. Comprehensive demographic and clinical data are gathered, including disease phenotype, genotype, treatment, and outcomes, at multiple time points, enabling a deeper understanding of this condition.

Given the limited reports on risk prediction models for East Asian ACM patients, we plan to utilize multimodal data to identify prognostic risk factors for ESHF and MVA in the Chinese population and establish specific models to better guide risk stratification and treatment for these patients.[46] More importantly, the cohort aims to encourage the genetic counseling for family members of the index patient, and the information can also be used to provide education and decision-making for physicians and patients concerning ACM. Additionally, biobanks of Chinese ACM patients will facilitate further research on disease penetrance and the pathophysiological mechanisms of ACM.

STUDY LIMITATIONS. First, because of the observational nature of our registry, we do not interfere with diagnostic diagram and treatment strategies for each center, which may introduce variability in data collection and patient outcomes. Second, the study population predominantly consists of Asians, which may limit the generalizability of the findings to other ethnic groups. Third, although the patients included in our study were recruited from medical centers of varying levels, referral bias may still exist, because individuals with more severe disease may be overrepresented. Additionally, potential selection bias cannot be ruled out, because participation was voluntary, and not all eligible patients were enrolled. Last, although we have implemented rigorous data collection protocols, missing data remains an inherent challenge in multicenter registries. However, we will apply appropriate statistical methods,

CENTRAL ILLUSTRATION **Overview of Study Design and Participant Centers**



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ChinaCORE ACM (China Multi-Center Cohort Study on Risk Evaluation of Arrhythmogenic Cardiomyopathy) is a national, multicenter observational registry designed to collect high-quality, multidimensional data from arrhythmogenic cardiomyopathy patients and their family members. This includes integrated genetic, imaging, clinical, and biobank information, encompassing both established parameters from previous models and newly identified variables. The registry involves 14 centers and includes participants from 28 of 34 provincial-level administrative regions across mainland China, ensuring broad geographic representation. AH = Anhui Provincial Hospital; CH = Children's Hospital of Fudan University; ECG = electrocardiogram; EP = electrophysiological; FW = Fuwai Hospital; GD = Guangdong Provincial People's Hospital; LZ = The First Hospital of Lanzhou University; SE = Shanghai East Hospital; SZ = Fuwai Hospital Chinese Academy of Medical Sciences, Shenzhen Hospital; WC = West China Second University Hospital, Sichuan University; WH = The Central Hospital of Wuhan; XA = The First Affiliated Hospital of Xi'an Jiaotong University; XJ = The First Affiliated Hospital of Xinjiang Medical University; YN = Fuwai Yunnan Hospital, Chinese Academy of Medical Sciences; ZS = Fudan University Zhongshan Hospital; ZZ = The First Affiliated Hospital of Zhengzhou University.

including multiple imputation, to mitigate the impact of missing values on our analysis.

CONCLUSIONS

The ChinaCORE ACM Registry is a national multicenter observational cohort of ACM patients. Comprehensive data, including medical history, cardiac evaluations, and genetic information, were collected, with detailed follow-ups conducted at multiple time points. The study contributes to the development of prognostic models specific to Chinese ACM patients and facilitates future research.

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APPENDIX For an expanded Methods section and supplemental tables, please see the online version of this paper.