BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (http://bmjopen.bmj.com).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open: first published as 10.1136/bmjopen-2024-090075 on 3 December 2024. Downloaded from http://bmjopen.bmj.com/ on June 12, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

BMJ Open

Cohort protocol: West China Valvular Heart Disease (West China-VHD) Cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-090075
Article Type:	Protocol
Date Submitted by the Author:	16-Jun-2024
Complete List of Authors:	Liu, Xiang; Sichuan University, Information Technology Center Wang, Yuqiang; West China Hospital of Medicine, Cao, Tingqian; Sichuan University, Department of Integrated Care Management Center Jun, Shi; West China Hospital of Medicine Liu, Lulu; Sichuan University, Department of Cardiovascular Surgery Zhou, Yongzhao; Sichuan University, Department of Integrated Care Management Center Guo, Yingqiang; Sichuan University, Department of Cardiovascular Surgery
Keywords:	Valvular heart disease < CARDIOLOGY, China, Education, Medical, EPIDEMIOLOGY

SCHOLARONE™
Manuscripts

BMJ Open: first published as 10.1136/bmjopen-2024-090075 on 3 December 2024. Downloaded from http://bmjopen.bmj.com/ on June 12, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) .
Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Title:

Cohort protocol: West China Valvular Heart Disease (West China-VHD) Cohort study

Author:

Xiang Liu[1,2†], Yuqiang Wang[1,3†], Tingqian Cao[1,4], Jun Shi[1,3], Lulu Liu[1,3], Yongzhao Zhou[4], Yingqiang Guo[1,3*]

[1] Department of Cardiovascular Surgery and National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu, China

[2] Information Technology Center, West China Hospital, Sichuan University, Chengdu, China

[3] Cardiovascular Surgery Research Laboratory, West China Hospital, Sichuan University, Chengdu, China

[4] Department of Integrated Care Management Center, West China Hospital, Sichuan University, Chengdu, China

† These authors contributed equally to the study.

***Corresponding author**:

Yingqiang Guo

Department of Cardiovascular Surgery and National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu, China; Cardiovascular Surgery Research Laboratory, West China Hospital, Sichuan University, Chengdu, China;

Email: drguoyq@wchscu.cn

Word Count: 5623

ABSTRACT

Introduction

Despite the rapid advancements in cardiovascular surgery in China, the prevalence of valvular heart disease (VHD) is on the rise, particularly among the elderly population. In the resource-constrained western regions, the absence of an integrated care management system contributes significantly to the burden of cardiovascular disease. Therefore, a comprehensive cohort data platform encompassing the entire lifespan of patients with VHD is essential. This platform would facilitate the study of risk factor screening, disease progression, diagnostic and treatment strategies, and the long-term functional recovery trajectories of patients following valve surgery. This study aims to elucidate the design, implementation, and scientific significance of the West China Valvular Heart Disease (West China-VHD) cohort study.

Methods and analysis

The West China-VHD cohort study is a prospective cohort study that aims to enroll approximately 10,000 participants, including both patients with VHD and members of the general population, by 2028. This study, centered at West China Hospital of Sichuan University and conducted in collaboration with 15 medical consortiums and their affiliated community hospitals, seeks to assess the disease trajectory of VHD, as well as the risk factors and protective measures that influence its progression and prognosis. The study will collect and analyze basic demographic information, peripheral blood and tissue samples, long-term functional follow-up data, and patient-reported outcome questionnaires. Additionally, electronic health records will be documented for VHD patients undergoing surgical interventions, along with lifetime

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Enseignement Superieur (ABES) .

endpoint events for the valve clinical study.

Ethics and dissemination

The study protocol was approved by the Biomedical Research Ethics Committee of West China Hospital of Sichuan University (No. 20232422). The results will be disseminated through conference presentations, peer-reviewed publications, and public online platforms.

Key words:

Valvular heart disease; Outcomes; Health-related quality of life; Cohort; Comprehensive management system

Strengths and Limitations

1. The West China-VHD cohort study utilizes an established lifecycle management platform and a well-designed electronic data capture system, facilitating effective disease registration and continuous tracking, which supports high follow-up rates.
2. This study monitors patients' progression from high-risk factors to a confirmed diagnosis of VHD, surgical treatment, and ongoing follow-up until an endpoint outcome event. This longitudinal and continuous monitoring will yield valuable data on VHD, aiding researchers in understanding the disease's development more comprehensively.
3. The cohort is representative only of the VHD population in western China and may not adequately reflect the characteristics of VHD across the entire Chinese population.
4. The study's design limits the analysis of the correlation between different medical decisions and long-term patient prognosis. However, incorporating a multicenter cohort may provide a sufficiently large sample size for propensity-matched analyses to explore correlations between target variables and outcome events.

INTRODUCTION

Valvular heart disease (VHD), primarily caused by rheumatic heart disease or degenerative changes, is a growing public health issue. It is estimated that approximately 25 million people in China have VHD, with 55.1% suffering from rheumatic VHD and 21.3% from degenerative VHD [1]. In recent years, cardiac surgery in China has advanced rapidly, with the number of surgeries increasing significantly [2]. However, significant economic and educational disparities exist across different regions of China, leading to substantial variations in the quality of cardiac surgeries [3]. Compared to the more economically developed eastern regions, which benefit from efficient health resource allocation, the middle- to low-income western regions face a severe burden of cardiovascular disease due to a shortage of health resources and limited access to high-quality healthcare services. The burden of cardiovascular disease in western China has escalated dramatically over the past decade [1,4].

The Necessitate of the Early Screening and Lifelong Follow-up.

One reason for the poor survival prognosis of VHD patients in China is the lack of early echocardiographic screening and diagnosis of asymptomatic patients, which indirectly leads to delayed consultations [5]. A survey found that most elderly VHD patients hospitalized in China had already developed obvious symptoms (89.4%), but only 37% received surgical interventions due to personal refusal, disease severity, and high surgical risk, etc [6]. Early detection, rational assessment, and optimal referral are crucial for improving VHD prognosis.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

Therefore, early disease screening and medical information registries are needed for community populations in Western China, where medical resources are scarce. Additionally, more patients are undergoing cardiac surgery. Although several clinical trials and observational studies have shown that postoperative heart function improves over time [7], postoperative functional decline is common in elderly patients due to comorbidities and frailty [8,9]. A successful surgery marks the beginning of a lifelong journey with potential adverse outcomes, including prosthetic valve failure, stroke, and heart failure readmission. Regular cardiologist appointments are essential as clinical deterioration may occur unnoticed [10]. Quality of life and functional capacity outcomes are increasingly recognized as important indicators of cardiac surgery success. Examining functional trajectories using generic measures of functional status may provide valuable insights [11].

Cohort databases have significantly enhanced our understanding of cardiovascular surgery in terms of research and have been instrumental in advancing clinical management and patient care [12]. Notable examples include the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database (ACSD) [13], established in 1989 with over five million cardiac surgery patients; and the Europe-wide Adult Cardiac Surgery Practice Information Database, initiated in 2002 by the European Association for Cardiothoracic Surgery (EACTS) [14]. In 2013, the Chinese National Center for Cardiovascular Disease (NCCD) and Fu Wai Hospital launched the Chinese Cardiac Surgery Registry (CCSR) [15]. However, all of the database predominantly focuses on patients with moderate-to-severe valvular heart disease (VHD), often overlooking risk factors and epidemiologic studies for patients with asymptomatic and mild VHD [16]. Moreover, many cohort databases lack comprehensive data on long-term survival and improvements in quality of life [17]. The Chinese healthcare system has been more oriented towards diagnostics and surgical interventions [18], with less emphasis on primary care and disease management, which are crucial for enhancing long-term patient outcomes [19]. Consequently, establishing an early screening and lifelong follow-up system tailored to the characteristics and treatment needs of the Chinese VHD population is essential for improving long-term health outcomes [20].

Establishing a Cohort Study to Enhance Survival Outcomes for Valvular Heart Disease Patients in Middle-Low Income Areas of Western China

In Western China, covering twelve provinces and spanning 6.87 million square kilometers including Sichuan Province, there exists considerable diversity, hosting 56 ethnic minorities with unique geographic and climatic conditions. This region, representing 27.2% of China's population, shows significant genetic diversity and distinct lifestyle choices, such as the Tibetans' adaptation to low oxygen levels on the plateau, and the Miao people's sour soup-rich diet [21]. Established in 2009, the West China Hospital Biospecimen Bank of Sichuan University has the capacity to store 10 million samples to support biospecimen collection, epidemiological investigations, and follow-ups for natural populations and various disease cohorts. The West China-VHD project, operated by the National Clinical Research Center for Geriatrics at West China Hospital, Sichuan University, leverages the existing VHD management system, and collaborates with 15 medical consortiums and their affiliated community hospitals in the region to develop a cohort database focused on the lifecycle comprehensive management of VHD patients [20]. As China's aging population grows—it is projected that by 2050, those aged 65 and older will number 395 million—the data gathered from this cohort will enable a deeper understanding of VHD characteristics in Western China and aid in establishing localized

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

standards for early diagnosis, treatment, and rehabilitation [22]. Our goal is to implement a patient-centered approach that encompasses health promotion, disease screening, prevention, diagnosis, treatment, and rehabilitation, aiming to enhance the patients' quality of life. To achieve this, we will collect prospective data including cardiopulmonary exercise assessments, peripheral blood, myocardial, valve tissue samples, precision medicine tests, imaging data, electronic health records, and perform long-term functional follow-ups to evaluate cardiac structure and function.

AIMs:

1. Identify outcomes and long-term functional recovery trajectories in VHD patients across multiple dimensions, including age, disease severity, and surgical modality, etc, emphasizing the identification of risk and protective factors that influence individual outcomes throughout the disease lifespan.
2. Analyze postoperative clinical outcomes in VHD patients, such as adverse events during hospitalization, long-term follow-up outcomes, and hospital stay duration, to provide a comprehensive understanding of postoperative outcomes and to identify predictive factors.
3. Develop mortality prediction tools for the short-term and long-term adapted specifically to VHD in the Chinese population, in comparison to the STS score calculator.
4. Establish personalized full-lifecycle follow-up profiles based on clinical characteristics of patients, assess the implementation and efficacy of a comprehensive management system for VHD, and evaluate the role of a specialist disease manager in long-term functional recovery.
5. Collect epidemiological data on VHD prevalence within a natural population cohort in Western China and assess the impact of socio-economic, psychological, physiological factors, activity levels, and living environments.
6. Explore the trajectory of VHD development within a natural population cohort by utilizing peripheral blood or tissue samples to identify critical periods of ventricular remodeling and optimal intervention windows.

METHODS

Study design and settings

West China-VHD is a prospective, multicenter, observational, population-based cohort study initiated at West China Hospital, West China Tianfu Hospital, and Shang Jin Hospital of West China Hospital. The project will progressively expand to include the 15 hospitals of the West China Hospital Medical Consortium, along with their respective community hospitals, to continue participant recruitment (Figure 1). The study's design and implementation are managed by the National Clinical Medical Research Center for Geriatric Diseases and the Heart Valve Disease Research Center at the West China Hospital of Sichuan University.

Study population

The categorization of participants based on the source population is detailed as follows. 1) Community-based natural population cohort: Eligible participants were permanent residents under the jurisdiction of the West China Hospital Medical Consortium, willing to undergo transthoracic echocardiography at community hospitals, where sonographers have received standardized training from the Departments of Ultrasound and Cardiology at West China

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

Hospital. Inclusion criteria were an age of 35 years or older, while exclusion criteria included an inability to comprehend the questionnaire, or refusal to participate in the study. 2) Inpatient and outpatient follow-up cohort: this group included participants from the cardiovascular surgery departments of West China Hospital and 15 associated medical consortiums. Eligibility criteria were patients initially evaluated with moderate or more severe VHD via echocardiography, age of 35 years or older, and ability to understand the questionnaire. Exclusion criteria were impaired consciousness or death preventing completion of the questionnaire, a life expectancy under six months, acute aortic dissection, and refusal to participate in the study.

Study procedure

The data elements and definitions for the West China-VHD form were meticulously designed, drawing inspiration from the current STS ACSD database template and adapted to the specific needs of this study. Figure 2 and Table 1 provide detailed information on the West China-VHD Cohort study process.

To streamline data collection and organization, we developed a Chinese Electronic Data Capture (EDC) system. This system necessitates network connectivity through a computer or handheld mobile device, with each hospital site authorized to access the EDC system using an assigned account. The system caters to various unit levels, including community hospitals under the medical union units, medical union units, medical union central hospitals-West China Hospital, Sichuan University. Tailoring to the unique characteristics of patient diagnosis and treatment at different levels in the western region of China, specific electronic forms within the EDC system are designated for data collection by different unit levels. To comprehensively delineate the characteristics of VHD patients, community hospitals affiliated with the medical treatment alliance unit primarily gather community-based health examination data from patients. This information serves for potential patient screening and categorization, guiding regular follow-ups in the community population screening queue based on the severity of the disease. On the flip side, medical treatment alliance units and West China Hospital, Sichuan University, primarily gather diagnostic and treatment data from patients during hospital visits, and the integrated care management system (encompassing patient follow-up elements, with scheduled follow-ups at 1 month, 3months, 6 months, and 1-year post-discharge, followed by regular annual outpatient follow-ups and with the instances involving adverse events necessitating medical attention).

Trained VHD data collectors conduct daily eligibility screenings for patients in outpatient clinics and hospital wards. Upon identifying eligible patients, the EDC system automatically compiles their essential information. This encompasses the patient registration number, serving as a unique identifier within the treating hospital, the outpatient visit number for the current visit, the inpatient case number corresponding to the ongoing hospitalization, the patient's ID card number as a distinctive patient identifier, and the phone number as the primary contact method. Within the EDC system, a new account is established for each eligible patient, with the aforementioned details recorded as essential information. Upon the input of new VHD patient data into the EDC system, a distinctive index identifier for the patient is automatically generated. Subsequently, the patient's medical records within the medical treatment alliance units are correlated based on the patient's ID card number. The system autonomously collects

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

patient treatment data using the registration number, visit number, or case number, thereby constructing the patient's medical records within the medical treatment alliance.

The continuous follow-up of patients constitutes a pivotal facet of this study, given the scarcity of long-term follow-up data for VHD patients both domestically and internationally. Trained physicians conduct ongoing follow-up for VHD patients, collecting patient-related information through face-to-face interviews using touchscreen questionnaires or paper records. Full-time data collectors execute the follow-up data collection, meticulously verifying and standardizing questionnaire information before inputting it into the EDC system to ensure precision and uniformity. The EDC system dispatches follow-up reminders to data collectors a week before each scheduled follow-up (1 month, 6 months, and 1-year post-discharge, etc.). We make three attempts to contact patients on different dates and times, contingent on the availability of the contact person (based on phone records). All subsequent calls are recorded for verification purposes, and regular quality control is exercised on follow-up results. In cases where patients cannot be contacted, we plan to undertake further actions to acquire long-term health-related outcomes based on patient personal information. This involves correlating the patient's ID card number with Chinese Center for Disease Control and Prevention national disease surveillance system cause of death surveillance network report database, the inpatient data identifier from the community hospital in the patient's residential area, and regional death registration records. If the aforementioned follow-up methods prove unsuccessful, it is categorized as loss to follow-up. It is imperative to note that participants unable to complete follow-up procedures will still be approached for the subsequent follow-up unless they actively request cessation of contact. The data collected during follow-up can be aligned with patient records in the EDC system using the patient's ID card number as the matching identifier. Ultimately, the patient's medical and outpatient follow-up timeline queue can be organized based on the patient's treatment time and follow-up time.

To ensure the scientific rigor of the study, a consulting committee was instituted, comprising experts in cardiac surgery, interventional cardiology, advanced imaging cardiology, echocardiography, heart failure, critical care, cardiac anesthesia, cardiorespiratory physiotherapy, cardiac specialist disease management, statisticians, computer engineers, and other specialized fields. Additionally, a project management and coordination center was established to supervise and support the West China-VHD operation, conduct data quality control, and host regular online and offline data quality control meetings. An independent supervisory committee was also constituted to oversee the entirety of the research process.

Data Collection

The following data will be collected for all participants in both the inpatient and outpatient follow-up cohorts, as well as the community-based natural population cohort:

1. Basic demographic information and peripheral blood samples.
2. Full-lifecycle medical imaging data.
3. Long-term functional follow-up and patient self-reported outcome questionnaires.

a. Inpatient and outpatient follow-up cohorts:

i. Peripheral venous blood analyses, including cardiac biomarkers, biochemical indices, coagulation, routine blood cell analyses, endocrine hormone measurements, glycosylated

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

hemoglobin levels, inflammatory factors, and samples for cell-free DNA analysis, miRNA analysis, cytokines, telomere length, metabolomics, proteomics, transcriptomics, and genomics.

ii. Routine biochemical indicators of urine and stool, and samples for precision medicine tests such as microbial sequencing.

iii. Myocardial and/or valvular tissue samples.

iv. 12-lead electrocardiogram, blood pressure, and peripheral oxygen saturation.

v. Echocardiogram and Doppler measurements, cardiac 4-dimensional computed tomography (4D-CT) measurements.

vi. Electronic health record information, including comorbidity information, medication use, surgical risk assessment, surgical operative records, anesthesia monitoring data, critical care records, and in-hospital adverse outcome events.

vii. Valve Clinical Study endpoint events tracked throughout the patient's lifetime.

viii. Functional capacity measures, including six-minute walk test (6MWT), pulmonary function test (PFT), and New York Heart Association classification (NYHA).

ix. Patient self-reported outcome questionnaires: The Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12) questionnaire; EuroQol Five Dimension Scale (EQ-5D) and EuroQol Visual Analogue Scale (EQ-VAS) questionnaires; Lower extremity edema level; Pittsburgh Sleep Quality Index (PSQI); Hospital Anxiety and Depression Scale (HADS)

x. Home wearable devices to capture continuous physiological parameters.

b. Community-based natural population cohorts:

i. Peripheral venous blood analysis, routine biochemical indicators in urine and stool, and sample collection for precision medicine testing.

ii. 12-lead electrocardiogram, blood pressure, and peripheral oxygen saturation.

iii. Echocardiograms and Doppler measurements.

iv. Electronic health record information, including comorbidity information and medication utilization.

v. Major adverse cardiovascular events tracked throughout the patient's lifetime.

vi. Functional capacity measures, including 6MWT, PFT, and NYHA classification.

vii. Patient self-reported outcome questionnaires.

Venous blood, urine, and stool sampling:

The initial peripheral venous blood, urine, and stool samples were collected when patients signed the informed consent and enrolled in the cohort study. For the inpatient and outpatient follow-up cohorts, additional peripheral blood samples were collected on the day of discharge. Subsequent routine outpatient follow-up visits, conducted at least once a year at the hospital where the procedure was performed, were used to obtain peripheral venous blood, urine, and stool specimens. For the community-based natural population cohort, routine physical examination screenings will be performed at least once a year at the community hospital to collect peripheral venous blood, urine, and stool specimens.

Myocardial and/or Valve Tissue Sample Collection:

This program is designed for patients undergoing heart valve surgery via median sternotomy or transapical catheter valve surgery. Samples of localized myocardial tissue (including the left atrium, left ventricular myocardium, and right atrium) and/or valvular tissue (including aortic,

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

mitral, and tricuspid valve leaflets) will be collected without damaging normal tissues. Additionally, whole blood, serum, plasma, fecal, urine, and other tissue samples will be stored in a biobank for future studies.

Echocardiography and Doppler Measurements:
Experienced echocardiographers will assess the extent of a patient's valvular disease and quantify cardiac structural and hemodynamic parameters in accordance with the guidelines from the American Society of Echocardiography for the Evaluation of Native Valvular Regurgitation [5] and Rheumatic Heart Disease [24], as well as the joint guidelines from the European Association of Cardiovascular Imaging and the American Society of Echocardiography Assessment of Aortic Valve Stenosis [23].

Cardiac 4D-CT Examination and Measurements:
Patients scheduled for transcatheter aortic valve implantation (TAVI) undergo CT data acquisition and reconstruction following the TAVI - Expert Consensus Document of the Society of Cardiovascular Computed Tomography[25]. This examination assesses dynamic changes in aortic root geometry and dimensions, as well as provides anatomical information about the vascular system, including the aorta, iliac, and femoral arteries.

Electronic Health Record Information - In-Hospital Adverse Outcome Events

West China-VHD framework selected postoperative outcome events consistent with those in influential international databases, such as the STS ASCD[26]. These selected events include operative mortality, stroke, renal failure, prolonged ventilation, reoperation, composite morbidity and mortality, prolonged postoperative length of stay, short postoperative length of stay and deep sternal wound infection. Although the database predominantly encompasses the US population, which differs significantly from the target population of this study, maintaining consistent definitions of outcome events is essential for future population-specific analyses, comparisons of VHD management techniques and concepts[27], and the development of risk models tailored to the Chinese VHD population.

Valve Clinical Study endpoint events tracked throughout the patient's lifetime:
West China-VHD selected clinical research endpoints developed by the Valve Academic Research Consortium 3 (VARC-3) [28]. These included Mortality; Neurologic events; Hospitalization (or re-hospitalization); Bleeding and transfusions; Vascular and access-related complications; Cardiac structural complications; Other procedural or valve-related complications; New conduction disturbances and arrhythmias; Acute kidney injury; Myocardial infarction; Bioprosthetic valve dysfunction; Leaflet thickening and reduced motion; Clinically significant valve thrombosis; Patient-reported outcomes and health status and Composite endpoints. The endpoints and criteria developed by VARC were used to ensure consistent reporting, adjudication, and comparison of results between valve devices and treatment strategies.

Six-Minute Walk Test (6MWT):

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

The 6MWT is a submaximal exercise assessment tool widely used to evaluate cardiopulmonary function and prognosis in patients, with the six-minute walk distance (6MWD) serving as the primary outcome indicator [29]. Patients perform the 6MWT according to the standardized protocol of the American Thoracic Society guidelines under the supervision of a cardiopulmonary physical therapist [30]. The test is terminated if any of the following symptoms occur: chest pain, loss of consciousness, intolerable dyspnea, falling, profuse sweating, or pallor.

Pulmonary Function Testing (PFT):

A cardiopulmonary physical therapist performs PFT using the standard protocols outlined by the American Thoracic Society and the European Respiratory Society Technical Statement [31]. These tests assess the effects of VHD on pulmonary function and airway responsiveness. The patient is positioned correctly for spirometry, and the test is repeated as necessary. The test is terminated if severe dyspnea, marked panic, chest tightness, precordial pain, dizziness, cyanosis, or pallor occur. Recorded indicators include forced vital capacity (FVC), one-second forced expiratory volume (FEV1), and maximum voluntary ventilation per minute (MVV). The reference values for these indicators are calculated based on pulmonary function measurement data from the 2012-2015 Chinese National Health Survey [32].

Patient Self-Reported Outcomes:

Patient heart failure symptoms were assessed using the KCCQ-12, the most commonly used tool for evaluating heart failure symptoms [33]. Patients rated how their heart failure symptoms affected 12 items, including mood, daily activities, and sleep.

A standardized health status measurement tool, EQ-5D, was used to assess the patients' health status [34]. The EQ-5D, widely used globally for determining quality of life, comprises a descriptive system and predefined utility values [35]. The descriptive system includes five dimensions: daily activities, self-care, mobility, anxiety/depression, and pain/discomfort, with each dimension having five severity levels: extremely, severely, moderately, slightly, and none. A health utility calculator for the Chinese population, available online (www.valueinhealthjournal.com/issues), provides health utility status values from 0 (dead) to 1 (perfectly healthy).

To assess edema, pressure was applied with the thumb for at least 2 seconds over the dorsum of the foot, behind the medial malleolus, and lower calf above the medial malleolus. The depth of the indentation and the time required for the skin to return to its original state were recorded and rated on a clinical scale [36]. Patient sleep quality was evaluated using the PSQI, which consists of 19 items assessing subjective sleep quality, how long it takes to fall asleep, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication [37]. For assessing anxiety and depression, the HADS was used to monitor the severity of illness [38].

Home Wearable Device to Collect Continuous Dynamic Physiological Parameters:

A medical-grade wearable device, developed in collaboration with an engineering team, was used to continuously and accurately capture dynamic physiological data before, during, and after a patient's walking activity. This includes signals from thoracic respiration, abdominal respiration, single-lead electrocardiograms, oxygen saturation, body position, and body movement [39]. Utilizing the wearable device's ability to capture high-frequency, continuous

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

dynamic physiological parameters offer great potential for personalized health assessment and early warning for post-VHD patients at home through AI-driven analysis. The device is designed for remote monitoring, enabling personalized health assessment and early intervention based on continuous data collection and AI analytics [40].

Sample Size

The West China Hospital of Sichuan University is one of the largest tertiary hospitals in western China. The population within the 15 medical consortiums and their sub-community hospitals of West China Hospital of Sichuan University constitutes approximately 6% of China's total population [41]. Therefore, we aim to recruit an initial cohort of 10,000 participants, including both VHD patients and individuals from the general community. This sample size is sufficient for an epidemiological survey of VHD patients in western China and a longitudinal study of disease trajectories [1,6].

Outcome

Primary outcome

The long-term goal of this research project is to explore the full life-cycle process of natural populations as they progress from disease risk factors to VHD, undergo surgical treatment, and continue through lifelong follow-up. Primary outcomes are measured using two cohorts: an inpatient and outpatient follow-up cohort to identify risk and protective factors for the long-term functional recovery trajectory of VHD patients, and a community-based natural population cohort to determine epidemiologic data on the prevalence of VHD in western China and the extent to which social and living environments influence the disease.

Secondary outcome

Secondary outcome measures will include electronic health records, patient self-reported outcome questionnaires, and peripheral blood/tissue sample data, all of which may be relevant to the VHD disease course and long-term recovery trajectory. The secondary endpoints of this research project are observational in nature, and an initial exploratory study will be conducted to investigate the following:

1. Precise medical analysis of specific markers of VHD disease progression in natural populations, as well as modifiable targets.
2. Development and formulation of mortality risk prediction tools for 30 days, 1 year, and beyond postoperative mortality, suitable for the Chinese VHD population.
3. Assessment of the effectiveness of the VHD full lifecycle management system in improving patients' survival and quality of life.
4. Comparison of mortality rates and long-term quality of life among VHD patients of different ages and genders, with and without intervention programs.
5. Implementation of a home-based remote monitoring system for postoperative VHD patients and an artificial intelligence warning model for emergencies.

Data management and monitoring

The information stored in the West China-VHD Registry Database is unalterable and can only be accessed for query analysis through database views. The EDC system offers standardized

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

forms for VHD follow-ups, available in both mobile and personal computer versions. Trained data collectors are authorized to conduct follow-ups and collect data exclusively within the hospital's internal network environment, utilizing tablets or physician workstations. Subsequently, data integration will take place through a dedicated network channel in the medical cloud to ensure the security of the data.

All collected data undergoes daily synchronization, where data from the hospital's electronic health record system is automatically synchronized with the EDC system. This synchronization aims to retrieve comprehensive information about participants' medical management, laboratory test results, and, if applicable, surgical procedures throughout the entire research period. To establish a connection between health records from a fully covered participant management database for long-term medical or mortality records one year after recruitment and beyond, an annual linkage will be implemented (Figure 2).

The EDC system data collection form template was developed by the Heart Valve Team at West China Hospital, Sichuan University. All units within the medical treatment alliances, including community hospitals, adhere to the standardized template for data collection. Before commencing data collection, researchers and data collectors undergo comprehensive training covering elements, definitions, and the data input system. The Project Management Coordination Center conducts regular meetings to provide feedback on data quality control reports and implements retraining as needed. Additionally, there is a strong emphasis on maintaining the stability of on-site working team members. In the event of changes in on-site researchers, coordinators, or data collectors, prompt training for new staff becomes imperative.

The participating sites ensure the reporting of all eligible cases to West China-VHD. The specific methods are outlined below. For sites utilizing electronic medical records, an electronic query algorithm is employed to identify patients with VHD by searching data fields most likely to indicate events among all patient records involved in cardiovascular surgery. These events may include conditions such as "rheumatic heart disease", "degenerative heart disease", "valvular stenosis", " valvular regurgitation" and others. Subsequently, coordinators evaluate compliance with inclusion criteria based on electronic medical records. In situations where electronic medical records are not employed or lack statistical functionality, such as when patients present external examination reports or hospital records, coordinators manually review patients' external paper records.

The accuracy and completeness of reported data are safeguarded through a multifaceted approach. Firstly, the EDC system integrates data input checks, mitigating errors and augmenting the precision of data collection. The algorithmic quality check system automatically prompts a message, notifying researchers to rectify or review data deviations from predefined check rules. Secondly, quality inspectors scrutinize each variable based on medical records within seven days of data submission. In instances of incorrect, suspicious, or incomplete data identified during ongoing data audits, researchers reporting on VHD patients are obligated to rectify, complete records, or clarify missing or suspicious data elements. Inspectors summarize the monthly progress of data collection and quality measures, engaging in regular discussions with the principal investigator. Thirdly, statisticians routinely evaluate and screen collected data, encompassing logic errors and outlier checks. Fourthly, the project management center conducts random testing on 10-50% of the data weekly to scrutinize extreme values or missing entries. Fifthly, the project management center deploys a coordinator

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

to hospital wards and outpatient clinics every 3-6 months for on-site checks, assuring the continuity, completeness, and accuracy of reported data. Lastly, experts randomly review (>20%) audio recordings of the entire interview process, ensuring the quality of baseline and subsequent data. In cases of disagreement, data collectors and quality inspectors collaboratively reassess the data (Figure 3).

Data Security

First, the EDC system permits access exclusively within the confines of the hospital's internal network, with access permissions tailored to the specific responsibilities of individual researchers. Each researcher is assigned a unique account, and user authentication is accomplished through secure passwords, mitigating the risk of unauthorized entry into the EDC system. In adherence to ethical standards, the EDC system employs anonymization and de-identification processes for reported data. All data transfers are securely encapsulated within encrypted tunnels and stored in the database of the West China Hospital, Sichuan University Information Center. To mitigate the risk of data loss, routine backups are systematically conducted for all storage.

Statistic and Analysis

The baseline characteristics of the study population and the prognostic outcomes for patients with VHD will be presented using the median with interquartile range for continuous variables or the mean ± standard deviation, and the case proportion for categorical variables. Employing a logistic regression model will assess the prognosis of VHD patients. Odds ratios and their corresponding 95% confidence intervals) will be calculated to elucidate factors that may significantly impact the outcomes. The impact of prognostic factors on VHD patients will be explored through a multivariate Cox proportional hazards regression model. The magnitude of the impact of prognostic factors will be quantified using hazard ratios with a 95% CI. Covariates will encompass characteristics specific to VHD patients, preoperative assessments, surgical-related information, and process variables such as intensive care management, among others. Statistical analyses will be conducted using R version 3.6.2. A two-tailed P-value < 0.05 will be considered statistically significant.

Ethics and dissemination

The study was approved by the Biomedical Research Ethics Committee of West China Hospital of Sichuan University (No. 20232422). All research organizations providing data for the West China-VHD complied with this ethical approval, and any modifications to the study protocol will be submitted for further ethical approval. All participants will be required to provide informed consent, and patient data will be stored in a de-identified form in the Information Center of West China Hospital of Sichuan University. All protocols will be conducted in compliance with the Declaration of Helsinki. Access to the study data will be restricted to researchers and ethics committees associated with the study. The results of this study will be disseminated in various formats, including conference abstracts, posters, presentations, and peer-reviewed scientific journals. All results presented in this study are cohort data, ensuring that participants cannot be individually identified. The results will also be reported to local governments, health and wellness committees to inform policy development, and medical

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

research centers and units that participated in and supported the cohort study.

Patient and public involvement

Patients and the public were not involved in the design, recruitment, or conduct of this study. We do not plan to inform every participant of the study results. However, we will communicate the study results to the public through public participation and community outreach.

DISCUSSION

To the best of our knowledge, this is the first cohort study based on multiple medical consortiums led by a regional center hospital and extending to Western China. It focuses on the diagnosis, treatment, and prognostic outcomes in a population with VHD in Western China, providing comprehensive data on risk factors, diagnostic and therapeutic management, physical status, and lifetime follow-up experiences.

Large multicenter disease cohort databases capture heterogeneous samples of the population due to their extensive sample size, thus reflecting real-world clinical effectiveness rather than the clinical efficacy observed in ideal conditions. These databases also enhance understanding of diverse care delivery methods and outcomes, as well as inter-center variations. Consequently, they can support quality improvement efforts and inform health policy initiatives [42].

Effective management of VHD in adults requires continuous monitoring as patients transition from disease screening registries to lifelong follow-up [43]. To date, most studies have focused on the association between moderate and/or severe VHD and clinical events, with limited understanding of the factors associated with the progression of mild VHD [44,45]. Matsushita's 25-year follow-up of mild VHD lesions (such as aortic atherosclerosis and mild aortic regurgitation) found that each mild VHD lesion was independently associated with at least one adverse cardiovascular outcome [46]. Given the low prevalence of cardiac screening and the significant number of patients who are never formally referred to a cardiologist [16], more effective data registration and linkage are crucial to prevent patients from "slipping through the cracks" [47]. This is especially true for VHD patients in low- and middle-income regions of Western China, who often travel long distances to large cardiac centers for treatment. The widespread use of diagnostic cardiac imaging, artificial intelligence algorithms for automated image interpretation, combined with disease registries and optimized referral pathways, may improve patients' access to sustained high-quality care throughout their lives [48].

The American Heart Association released a statement titled "The Importance of Measuring Patient-Reported Health Status," which identifies three key domains: symptom burden, functional status, and health-related quality of life [49]. Long-term or lifelong patient-reported outcomes are more significant than those recorded over months or years in conventional databases, as they better define treatment success [50]. Patients undergoing valvular surgical interventions face long-term risks such as prosthetic valve failure, bleeding, embolism, and readmission for heart failure, posing a significant healthcare burden [44]. Thus, it is essential to link administrative databases—such as national mortality surveillance databases, community hospital records, and health insurance data—with existing cohort databases to collect prognostic and health data [19]. This approach can improve longitudinal follow-up, survival, and overall quality of life in the growing and aging VHD population.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

Although national databases for cardiac surgery have long existed internationally, there are differences between China, Europe, and the United States regarding population and disease characteristics, as well as healthcare public service systems [15,27]. Therefore, the West China-VHD cohort database considers the unique population characteristics of Western China, focusing on screening variables related to the diagnosis, treatment, and prognosis of VHD [21]. This database aims to facilitate continuous monitoring of VHD throughout the lifecycle of the population in Western China, strengthening the roles and responsibilities of government, hospitals, clinicians, and public health organizations to create a model of accessible and affordable lifelong care for middle- to low-income VHD patients in Western China.

A descriptive analysis report based on the West China-VHD cohort database will provide a comprehensive picture of the incidence, demographics, course of care, and lifelong follow-up of VHD in the Western China population. The report will also identify risk-modifying factors to explore outcomes, establish benchmarks among cardiac centers, and propose system-wide strategies related to the survival of patients with VHD. The West China-VHD cohort database is expected to enable continuous monitoring of the entire lifespan of VHD patients in the Western China population. Additionally, the database may help the public and the government focus on primary prevention and lifelong follow-up of VHD patients. Successful outcomes may encourage other cardiovascular centers across the country to participate, potentially serving as a national platform for monitoring cardiovascular surgical care in Western China, facilitating research projects, establishing benchmarking standards, and identifying potential areas for quality improvement.

Acknowledgements

We gratefully acknowledge the contributions of all hospitals, principal investigators, healthcare professionals, researchers, and patients who took part in the CVHDCLM study. We also extend our thanks to the Integrated Care Management Centre of West China Hospital of Sichuan University for their support in providing a comprehensive lifecycle management system. We acknowledge the Information Centre of Sichuan University for their contributions in providing medical electronic cases, developing the EDC system, and enhancing data analysis and quality control.

Funding

This work was supported by National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University (No. Y2023YY007)

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability

We invite national and international collaborations for projects concerning various aspects, including but not limited to disease screening strategies, diagnostic and therapeutic decisions, and long-term functional trajectories. Researchers are encouraged to apply for data access by

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Enseignement Superieur (ABES) .

contacting the Chief Investigator (YQ-G) at drguoyq@wchscu.cn, providing details of the study objectives and proposals.

Author contributions

All authors contributed to the conception or design of the work. Yuqiang Wang, Xiang Liu and Tingqian Cao contributed to the acquisition, analysis, or interpretation of data for the work. Jun Shi contributed to analysis for the work. Lulu Liu contributed to the interpretation of data for the work. Yuqiang Wang and Xiang Liu drafted the manuscript. Yongzhao Zhou and Yingqiang Guo critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Reference:

1. Yang Y, Wang Z, Chen Z, et al. Current status and etiology of valvular heart disease in China: a population-based survey. *BMC Cardiovasc Disord.* 2021;21(1):339.
2. MA L, WANG Z, FAN J, et al. Interpretation of Report on Cardiovascular Health and Diseases in China 2022. *Chinese General Practice.* 2023;26(32):3975.
3. Jiang L, Krumholz HM, Li X, et al. Achieving best outcomes for patients with cardiovascular disease in China by enhancing the quality of medical care and establishing a learning health-care system. *Lancet.* 2015;386(10002):1493-1505.
4. Liqin L, Xu Z, Lanyu Z, et al. Degree of Coordination between Primary Care Resource Allocation and Economic Development in Eastern. Central and Western China. *Chinese General Practice*. 2021, 24(22): 2777-2784.
5. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. Journal of the American Society of Echo*cardiography: official publication of the American Society of Echocardiography.* 2017;30(4):303-371.
6. Xu H, Liu Q, Cao K, et al. Distribution, Characteristics, and Management of Older Patients With Valvular Heart Disease in China: China-DVD Study. *JACC Asia.* 2022;2(3):354-365.
7. Grover FL, Vemulapalli S, Carroll JD, et al. 2016 Annual Report of The Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. *Journal of the American College of Cardiology.* 2017;69(10):1215-1230.
8. Afilalo J, Lauck S, Kim DH, et al. Frailty in Older Adults Undergoing Aortic Valve Replacement: The FRAILTY-AVR Study. *Journal of the American College of Cardiology.* 2017;70(6):689-700.
9. Arnold SV, Spertus JA, Vemulapalli S, et al. Quality-of-Life Outcomes After Transcatheter Aortic Valve Replacement in an Unselected Population: A Report From the STS/ACC Transcatheter Valve Therapy Registry. *JAMA cardiology.* 2017;2(4):409-416.
10. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease: Developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

and the European Association for Cardio-Thoracic Surgery (EACTS). *Revista espanola de cardiologia.* 2022;75(6):524.

11. Evans JP, Smith A, Gibbons C, et al. The National Institutes of Health patient-reported outcomes measurement information system (PROMIS): a view from the UK. Patient related outcome measures. 2018:345-352.
12. Saxena A, Newcomb AE, Dhurandhar V, et al. Application of Clinical Databases to Contemporary Cardiac Surgery Practice: Where are We now? *Heart, lung & circulation.* 2016;25(3):237-242.
13. Shahian DM, Jacobs JP, Edwards FH, et al. The society of thoracic surgeons national database. *Heart.* 2013;99(20):1494-1501.
14. Head SJ, Howell NJ, Osnabrugge RL, et al. The European association for cardio-thoracic surgery (EACTS) database: an introduction. *European Journal of Cardio-Thoracic Surgery*. 2013;44(3):e175-e180.
15. Rao C, Zhang H, Gao H, et al. The Chinese Cardiac Surgery Registry: Design and Data Audit. *The Annals of thoracic surgery.* 2016;101(4):1514-1520.
16. Puri R, Dykun I, Kalra A. The Spectrum of Valvular Heart Disease and the Importance of "Mild". *JAMA network open.* 2022;5(5):e2211955.
17. Charles EJ, Mehaffey JH, Hawkins RB, et al. Meaningful Patient-centered Outcomes 1 Year Following Cardiac Surgery. *Annals of surgery.* 2021;273(6):e247-e254.
18. Davidson LJ, Davidson CJ. Transcatheter Treatment of Valvular Heart Disease: A Review. *Jama.* 2021;325(24):2480-2494.
19. Su Z, Zhang Y, Cai X, et al. Improving long-term care and outcomes of congenital heart disease: fulfilling the promise of a healthy life. *The Lancet Child & adolescent health.* 2023;7(7):502-518.
20. Wang Y, Cao T, Shi J, et al. Design and Application of Comprehensive Management System For Patients with Chronic Aortic Valve Disease-A Perspective From West China Hospital. *Current problems in cardiology.* 2023;49(1 Pt B):102169.
21. Zhao X, Hong F, Yin J, et al. Cohort Profile: the China Multi-Ethnic Cohort (CMEC) study. *International journal of epidemiology.* 2021;50(3):721-721l.
22. Chen X, Giles J, Yao Y, et al. The path to healthy ageing in China: a Peking University-Lancet Commission. *Lancet.* 2022;400(10367):1967-2006.
23. Baumgartner H, Hung J, Bermejo J, et al. Recommendations on the Echocardiographic Assessment of Aortic Valve Stenosis: A Focused Update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *Journal of the American Society of Echocardiography: official publication of the American Society of Echocardiography.* 2017;30(4):372-392.
24. Pandian NG, Kim JK, Arias-Godinez JA, et al. Recommendations for the Use of Echocardiography in the Evaluation of Rheumatic Heart Disease: A Report from the American Society of Echocardiography. *Journal of the American Society of Echocardiography: official publication of the American Society of Echocardiography.* 2023;36(1):3-28.
25. Blanke P, Weir-McCall JR, Achenbach S, et al. Computed tomography imaging in the context of transcatheter aortic valve implantation (TAVI) / transcatheter aortic valve replacement (TAVR): An expert consensus document of the Society of Cardiovascular

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

Computed Tomography. *Journal of cardiovascular computed tomography.* 2019;13(1):1-20.

26. Shahian DM, Jacobs JP, Badhwar V, et al. The Society of Thoracic Surgeons 2018 Adult Cardiac Surgery Risk Models: Part 1-Background, Design Considerations, and Model Development. *The Annals of thoracic surgery.* 2018;105(5):1411-1418.
27. Lin H, Gong J, Wu Y, et al. A Comparative Study on Surgical Treatment of Valvular Heart Disease between High-Volume Cardiac Centers in China and STS Data. *Journal of cardiovascular development and disease.* 2022;9(7).
28. Généreux P, Piazza N, Alu MC, et al. Valve Academic Research Consortium 3: updated endpoint definitions for aortic valve clinical research. *European heart journal.* 2021;42(19):1825-1857.
29. Agarwala P, Salzman SH. Six-Minute Walk Test: Clinical Role, Technique, Coding, and Reimbursement. *Chest.* 2020;157(3):603-611.
30. ATS statement: guidelines for the six-minute walk test. *American journal of respiratory and critical care medicine.* 2002;166(1):111-117.
31. Graham BL, Steenbruggen I, Miller MR, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. *American journal of respiratory and critical care medicine.* 2019;200(8):e70-e88.
32. Zhang J, Hu X, Shan G. Spirometry reference values for population aged 7-80 years in China. *Respirology.* 2017;22(8):1630-1636.
33. Spertus JA, Jones PG. Development and Validation of a Short Version of the Kansas City Cardiomyopathy Questionnaire. *Circulation Cardiovascular quality and outcomes.* 2015;8(5):469-476.
34. Luo N, Liu G, Li M, et al. Estimating an EQ-5D-5L Value Set for China. *Value Health.* 2017;20(4):662-669.
35. Wisløff T, Hagen G, Hamidi V, et al. Estimating QALY gains in applied studies: a review of cost-utility analyses published in 2010. *Pharmacoeconomics.* 2014;32(4):367-375.
36. Seidel H, Ball J, Dains J, Benedict GJMsGtPE, 3rd ed. St. Louis, MO: Mosby. Heart and blood vessels. 1995;419.
37. Buysse DJ, Reynolds III CF, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry research.* 1989;28(2):193-213.
38. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983;67(6):361-370.
39. Wang J, Yang Z, Wang Y, et al. A Quantitative Approach and Preliminary Application in Healthy Subjects and Patients with Valvular Heart Disease for 24-h Breathing Patterns Analysis Using Wearable Devices. Paper presented at: 2022 IEEE International Conference on E-health Networking, Application & Services (HealthCom)2022.
40. Williams GJ, Al-Baraikan A, Rademakers FE, et al. Wearable technology and the cardiovascular system: the future of patient assessment. The Lancet Digital Health. 2023;5(7):e467-e476.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

41. WANG Miao, SHI Kecan, CHEN Lei, et al. Analysis of the features of lead-type close medical consortium in West China Hospital of Sichuan University.*West China Medical Journal*. 2019; 34(12):1422-1425.
42. Vener DF, Gaies M, Jacobs JP, et al. Clinical Databases and Registries in Congenital and Pediatric Cardiac Surgery, Cardiology, Critical Care, and Anesthesiology Worldwide. *World journal for pediatric & congenital heart surgery.* 2017;8(1):77-87.
43. Pavone N, Burzotta F, Bruno P, et al. Heart Valve Critical Pathway and Heart Valve Clinic: Novel Benchmarks for Modern Management of Valvular Heart Disease. *Critical pathways in cardiology.* 2021;20(3):126-133.
44. Aluru JS, Barsouk A, Saginala K, et al. Valvular Heart Disease Epidemiology. *Med Sci.* 2022;10(2).
45. Bae JY, Fallahi A, Miller W, et al. A call to consider an aortic stenosis screening program. *Trends in cardiovascular medicine.* 2023.
46. Matsushita K, Gao Y, Rubin J, et al. Association of Mild Valvular Lesions With Long-term Cardiovascular Outcomes Among Black Adults. *JAMA network open.* 2022;5(5):e2211946.
47. Chami J, Nicholson C, Strange G, et al. National and regional registries for congenital heart diseases: Strengths, weaknesses and opportunities. *International journal of cardiology.* 2021;338:89-94.
48. Sengupta PP, Shrestha S, Kagiyama N, et al. A Machine-Learning Framework to Identify Distinct Phenotypes of Aortic Stenosis Severity. *JACC Cardiovascular imaging.* 2021;14(9):1707-1720.
49. Rumsfeld JS, Alexander KP, Goff DC, Jr., et al. Cardiovascular health: the importance of measuring patient-reported health status: a scientific statement from the American Heart Association. *Circulation.* 2013;127(22):2233-2249.
50. Makhni EC, Meadows M, Hamamoto JT, et al. Patient Reported Outcomes Measurement Information System (PROMIS) in the upper extremity: the future of outcomes reporting? *Journal of shoulder and elbow surgery.* 2017;26(2):352-357.

Figures

Figure 1 Distribution of West China Hospital and units of 15 medical consortiums
Figure 2 Recruitment process of West China-VHD cohort study
Figure 3 Data management and quality control

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

Tables

Table 1 Summary of Clinical Data Collection

Domain	Type of assessment	Full Lifecycle Comprehensive Management Time Schedule – Inpatients; Outpatients; Community Population																
		Enroll	6m	12m	2y	3y	…	Ny	In-hospital	1m	3m	6m	12m	2y	3y	4y	…	Ny
Biological Sample	Blood	●		●	●	●	●	●	●			●	●	●	●	●	●	●
	Urine	●		●	●	●	●	●	●			●	●	●	●	●	●	●
	Stool	●		●	●	●	●	●	●			●	●	●	●	●	●	●
	Myocardial tissue								●									
	Valves leaflets								●									
Medical Examination	12-ECG	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
	Echocardiography	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
	Cardiac 4D-CT								●			●	●	○	○	○	○	○
Electronic Health Record	Demographic	●							●									
	Perioperative data								●									
	Adverse outcomes	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Functional Capacity	6MWT	●		●	●	●	●	●	●			●	●	●	●	●	●	●
	PFT	●		●	●	●	●	●	●			●	●	●	●	●	●	●
Patient Reported Outcome	KCCQ-12	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
	EQ-5D and EQ-VAS	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
	Lower limb edema	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
	PSQI	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
	HADS	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Wearable Device	Continuous physiological data	○	○	○	○	○	○	○	●	●	●	●	●	●	●	●	●	●

ECG: Electrocardiogram; 4D-CT: 4-Dimensional Computed Tomography; 6MWT: 6-minute Walking Test; PFT: Pulmonary Function Test; KCCQ: The Kansas City Cardiomyopathy Questionnaire;

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

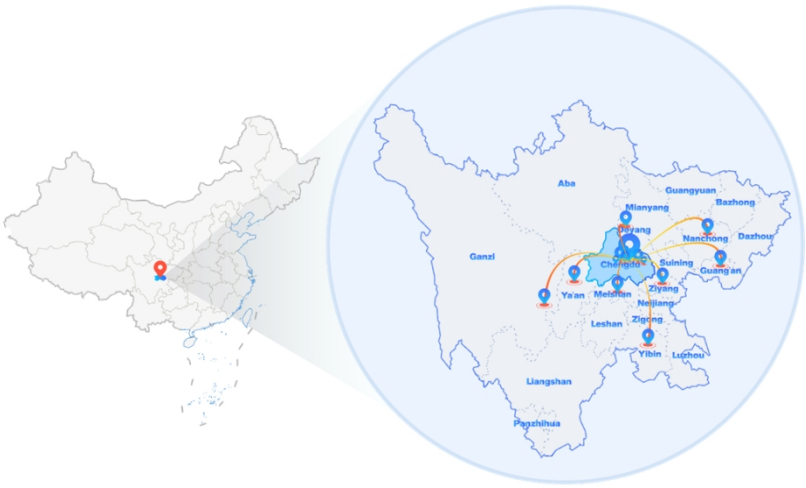
bmjopen-2024-090075 on 3 December 2024. Downloaded from http://bmjopen.bmj.com/ on June 12, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

EQ-5D: EuroQol Five Dimension Scale; EQ-VAS: EuroQol Visual Analogue Scale; PSQI: Pittsburgh Sleep Quality Index; HADS: Hospital Anxiety and Depression Scale. ●Mandatory; ○Available.

For peer review only

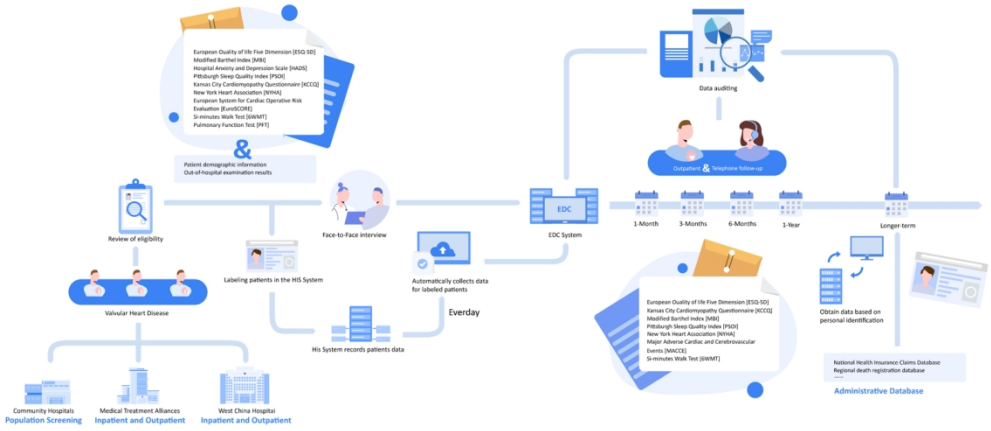
For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

bmjopen-2024-090075 on 30 December 2024. Downloaded from http://bmjopen.bmj.com/ on June 12, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) .
d by copyright, including for uses related to text and data mining, AI training, and similar technologies.



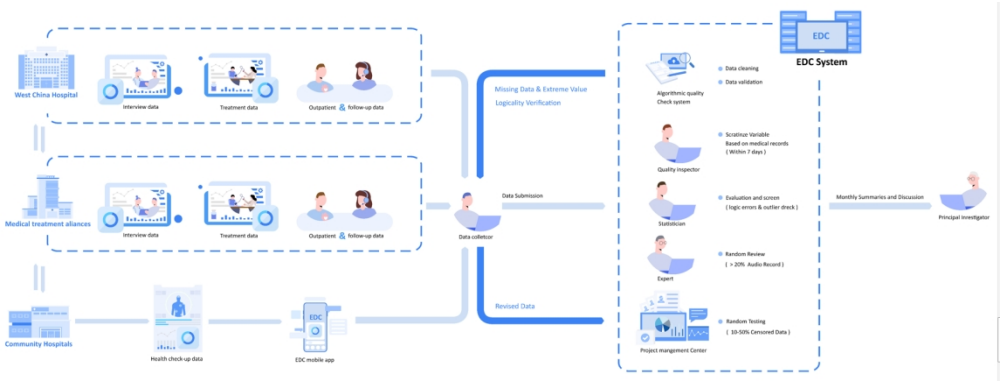
855x481mm (38 x 38 DPI)

BMJ Open: first published as 10.1136/bmjopen-2024-090075 on 3 December 2024. Downloaded from http://bmjopen.bmj.com/ on June 12, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.



1067x471mm (38 x 38 DPI)

BMJ Open: first published as 10.1136/bmjopen-2024-090075 on 3 December 2024. Downloaded from http://bmjopen.bmj.com/ on June 12, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.



1237x469mm (38 x 38 DPI)

BMJ Open: first published as 10.1136/bmjopen-2024-090075 on 3 December 2024. Downloaded from http://bmjopen.bmj.com/ on June 12, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

BMJ Open

Integrated Whole-Life Cycle Accuracy Valvular Heart Disease Epidemiology Cohort Study (iWAVE): protocol for a prospective cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-090075.R1
Article Type:	Protocol
Date Submitted by the Author:	05-Oct-2024
Complete List of Authors:	Liu, Xiang; Sichuan University, Information Technology Center Wang, Yuqiang; West China Hospital of Medicine, Cao, Tingqian; Sichuan University, Department of Integrated Care Management Center Jun, Shi; West China Hospital of Medicine Liu, Lulu; Sichuan University, Department of Cardiovascular Surgery Zhou, Yongzhao; Sichuan University, Department of Integrated Care Management Center Guo, Yingqiang; Sichuan University, Department of Cardiovascular Surgery
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine, Public health, Epidemiology
Keywords:	Valvular heart disease < CARDIOLOGY, Patient Reported Outcome Measures, Quality of Life, Observational Study

SCHOLARONE™
Manuscripts

BMJ Open: first published as 10.1136/bmjopen-2024-090075 on 3 December 2024. Downloaded from http://bmjopen.bmj.com/ on June 12, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Title:

Integrated Whole-Life Cycle Accuracy Valvular Heart Disease Epidemiology Cohort Study (iWAVE): protocol for a prospective cohort study

Author:

Xiang Liu[1,2†], Yuqiang Wang[1,3†], Tingqian Cao[1,4], Jun Shi[1,3], Lulu Liu[1,3], Yongzhao Zhou[4], Yingqiang Guo[1,3*]

[1] Department of Cardiovascular Surgery and National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu, China

[2] Information Technology Center, West China Hospital, Sichuan University, Chengdu, China

[3] Cardiovascular Surgery Research Laboratory, West China Hospital, Sichuan University, Chengdu, China

[4] Department of Integrated Care Management Center, West China Hospital, Sichuan University, Chengdu, China

† These authors contributed equally to the study.

***Corresponding author**:

Yingqiang Guo

Department of Cardiovascular Surgery and National Clinical Research Center for Geriatrics,; Cardiovascular Surgery Research Laboratory, West China Hospital, Sichuan University, Chengdu, China;

Email: drguoyq@wchscu.cn

Word Count: 6670

ABSTRACT

Introduction

Despite the rapid advancements in cardiovascular surgery in China, the prevalence of valvular heart disease (VHD) continues to rise, particularly among the elderly population. In the resource-constrained western regions, the lack of an integrated care management system significantly contributes to the burden of cardiovascular disease. Consequently, a comprehensive cohort data platform that encompasses the entire lifespan of patients with VHD is essential. This prospective cohort study facilitates the examination of risk factor screening, disease progression, diagnostic and treatment strategies, as well as the long-term functional recovery trajectories of patients following valve surgery.

Methods and analysis

The Integrated Whole-Life Cycle Accuracy Valvular Heart Disease Epidemiology Cohort Study (iWAVE) is a prospective cohort study that aims to enroll approximately 10,000 participants, including both patients with VHD and members of the general population, by 2028. Centered at West China Hospital of Sichuan University and conducted in collaboration with 15 medical consortiums and their affiliated community hospitals, this study seeks to assess the disease trajectory of VHD, as well as the risk factors and protective measures that influence its progression and prognosis. The study collects and analyses basic demographic information, peripheral blood and tissue samples, long-term functional follow-up data, and patient-reported

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

outcome questionnaires. Additionally, electronic health records are documented for VHD patients undergoing surgical interventions, along with lifetime endpoint events for the valve clinical study.

Ethics and dissemination

The study protocol was approved by the Biomedical Research Ethics Committee of West China Hospital of Sichuan University (No. 20232422). If a patient volunteers to participate in the study, the following steps are taken: prior to enrollment, a relevant medical history is obtained; subsequently, a patient-specific account is created in the study database to collect clinical data during hospitalization and throughout lifetime follow-up. After hospital discharge, follow-up visits are scheduled at regular intervals in 1 month, 3 months, 6 months, 1 year and annually thereafter. At each follow-up visit, the investigator performs function-related scale assessments. Peripheral venous blood, urine, and stool samples collected are stored in the biospecimen bank of West China Hospital, Sichuan University. Additionally, waste tissue collected during surgery is stored in the biospecimen bank for future measurement of disease-related biomarkers. The results will be disseminated through conference presentations, peer-reviewed publications, and public online platforms.

Key words:

Valvular heart disease; Outcomes; Health-related quality of life; Cohort; Integrated care management system

Strengths and Limitations of This Study

- The iWAVE cohort study utilizes an established integrated care management platform and a well-designed electronic data capture system, facilitating effective disease registration and continuous tracking, which supports high follow-up rates.
- This study monitors patients' progression from high-risk factors to a confirmed diagnosis of VHD, including surgical treatment and ongoing follow-up until an endpoint event occurs, thereby providing valuable longitudinal data to enhance understanding of the disease's development. The cohort represents only the VHD population in western China and may not adequately reflect the characteristics of VHD across the entire Chinese population.
- The study's design limits the analysis of correlations between various medical decisions and long-term patient prognosis; however, incorporating a multicenter cohort may provide a sufficiently large sample size for propensity-matched analyses to investigate these correlations.

INTRODUCTION

Valvular heart disease (VHD), primarily resulting from rheumatic heart disease or degenerative changes, represents an increasing public health concern. Approximately 25 million individuals in China currently experience VHD, with 55.1% affected by rheumatic VHD and 21.3% by degenerative VHD [1]. In recent years, cardiac surgery in China advances rapidly, marked by a significant increase in the number of procedures performed [2]. However, notable economic and educational disparities persist across various regions of the country, resulting in considerable

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

fluctuations in the quality of cardiac surgeries [3]. Unlike the more economically developed eastern regions, which benefit from efficient health resource allocation, the middle- to low-income western regions endure a significant burden of cardiovascular disease due to insufficient health resources and limited access to high-quality healthcare services. Consequently, the burden of cardiovascular disease in western China escalates dramatically over the past decade [1,4].

The Necessitate of the Early Screening and Lifelong Follow-up.

One reason for the poor survival prognosis of VHD patients in China is the lack of early echocardiographic screening and diagnosis among asymptomatic individuals, which indirectly leads to delayed consultations [5]. A recent survey indicates that a significant majority of elderly VHD patients hospitalized in China present with evident symptoms (89.4%); however, only 37% undergo surgical interventions, often due to personal refusal, disease severity, and high surgical risk [6]. Early detection, rational assessment, and optimal referral are crucial for improving VHD prognosis. Therefore, early disease screening and the establishment of medical information registries are necessary for community populations in western China, where medical resources are limited. Moreover, an increasing number of are undergoing cardiac surgery. Although several clinical trials and observational studies demonstrate improvement in postoperative heart function improves over time [7], postoperative functional decline remains common among elderly patients due to comorbidities and frailty[8]. A successful surgery initiates a lifelong journey that may involve potential adverse outcomes, including prosthetic valve failure, stroke, and heart failure readmission. Regular appointments with a cardiologist are essential, as clinical deterioration can occur unnoticed[9]. Quality of life and functional capacity outcomes are increasingly recognized as important indicators of cardiac surgery success. Analyzing functional trajectories through generic measures of functional status can yield valuable insights [10].

Cohort databases significantly enhance our understanding of cardiovascular surgery and play a crucial role in advancing in advancing clinical management and patient care [11]. Notable examples include the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database (ACSD) [12], established in 1989, which encompasses over five million cardiac surgery patients, and the Europe-wide Adult Cardiac Surgery Practice Information Database, initiated in 2002 by the European Association for Cardiothoracic Surgery (EACTS) [13]. In 2013, the Chinese National Center for Cardiovascular Disease (NCCD) and Fu Wai Hospital launched the Chinese Cardiac Surgery Registry (CCSR) [14]. However, these databases predominantly focuses on patients with moderate-to-severe VHD, often overlooking risk factors and epidemiological studies concerning patients with asymptomatic and mild VHD [15]. Furthermore, many cohort databases lack comprehensive data on long-term survival and quality of life improvements [16]. The Chinese healthcare system is primarily oriented towards diagnostics and surgical interventions [17], with less emphasis on primary care and disease management, which are vital for enhancing long-term patient outcomes [18]. Consequently, establishing an early screening and lifelong follow-up system tailored to the characteristics and treatment needs of the Chinese VHD population is essential for improving long-term health outcomes [19].

Establishing a Cohort Study to Enhance Survival Outcomes for Valvular Heart Disease

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Enseignement Superieur (ABES) .
Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Patients in Middle-Low Income Areas of Western China

Western China, encompassing twelve provinces and covering 6.87 million square kilometers including Sichuan Province, exhibits considerable diversity and hosts 56 ethnic minorities, each with unique geographic and climatic conditions. This region, which represents 27.2% of China's population, demonstrates significant genetic diversity and distinct lifestyle choices, such as the Tibetans' adaptation to low oxygen levels on the plateau and the Miao people's sour soup-rich diet[20]. Established in 2009, the West China Hospital Biospecimen Bank of Sichuan University has the capacity to store 10 million samples, supporting biospecimen collection, epidemiological investigations, and follow-ups for natural populations and various disease cohorts. The iWAVE study project, operated by the National Clinical Research Center for Geriatrics at West China Hospital, Sichuan University, leverages the existing integrated care management system, and collaborates with 15 medical consortiums and their affiliated community hospitals in the region to develop a cohort database focused on the whole-life cycle management of VHD patients[19]. As China's aging population increases -projected to reach 395 million individuals aged 65 and older by 2050 - the data gathered from this cohort will enable our understanding of VHD characteristics in Western China and facilitate the establishment of localized standards for early diagnosis, treatment, and rehabilitation[21]. Our goal is to implement a patient-centered approach that encompasses health promotion, disease screening, prevention, diagnosis, treatment, and rehabilitation, ultimately enhancing patients' quality of life. To achieve this, we will collect prospective data, including cardiopulmonary exercise assessments, peripheral blood, myocardial, valve tissue samples, precision medicine tests, imaging data, electronic health records, and we will perform long-term functional follow-ups to evaluate cardiac structure and function.

Aims:

1. Identify outcomes and long-term functional recovery trajectories in VHD patients across multiple dimensions, including age, disease severity, and surgical modality, emphasizing the identification of risk and protective factors that influence individual outcomes throughout the disease lifespan.
2. Analyze postoperative clinical outcomes in VHD patients, such as adverse events during hospitalization, long-term follow-up outcomes, and duration of hospital stays, to provide a comprehensive understanding of postoperative results and identify predictive factors.
3. Develop mortality prediction tools, adapted specifically for the short-term and long-term outcomes in VHD patients within the Chinese population, and compare these tools to the STS score calculator.
4. Establish personalized whole-life cycle follow-up profiles based on patients' clinical characteristics, assess the implementation and efficacy of a integrated care management system for VHD, and evaluate the role of a specialist disease manager in promoting long-term functional recovery.
5. Collect epidemiological data on VHD prevalence within a natural population cohort in Western China, and assess the impact of socio-economic, psychological, physiological factors, along with activity levels and living environments.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

6. Explore the trajectory of VHD development within a natural population cohort by utilizing peripheral blood or tissue samples to identify critical periods of ventricular remodeling and optimal intervention windows.

METHODS AND ANALYSIS

Study design and setting

iWAVE is a prospective, multicenter, observational, population-based cohort study initiated at West China Hospital, West China Tianfu Hospital, and Shang Jin Hospital of West China Hospital. The project progressively expands to include the 15 hospitals within the West China Hospital Medical Consortium and their affiliated community hospitals for ongoing participant recruitment (Figure 1). The National Clinical Medical Research Center for Geriatric Diseases and the Heart Valve Disease Research Center at Sichuan University's West China Hospital manage the study's design and implementation.

Study population

The categorization of participants based on the source population is detailed as follows. 1) Community-based Natural Population Cohort: Eligible participants were permanent residents within the jurisdiction of the West China Hospital Medical Consortium who agree to undergo transthoracic echocardiography at community hospitals. Sonographers conducting the procedures receive standardized training from the Departments of Ultrasound and Cardiology at West China Hospital. Inclusion criteria specify that participants must be 35 years of age or older. Exclusion criteria include an inability to comprehend the questionnaire or refusal to participate in the study. 2) Inpatient and Outpatient Follow-Up Cohort: This group consists of participants from the cardiovascular surgery departments of West China Hospital and 15 associated medical consortiums. Eligibility criteria include patients initially evaluated with moderate or more severe VHD via echocardiography, being of 35 years of age or older, and having the capacity to understand the questionnaire. Exclusion criteria encompass impaired consciousness or death that prevents the completion of the questionnaire, a life expectancy of less than six months, acute aortic dissection, and refusal to participate in the study.

Study procedure

The data elements and definitions for the iWAVE Cohort Study form are meticulously designed, drawing inspiration from the current STS ACSD database template and adapting it to the specific needs of this study. Figure 2 and 3 provide detailed information on the study process.

To streamline data collection and organization, we developed a Chinese Electronic Data Capture (EDC) system. This system requires network connectivity via a computer or handheld mobile device, with each hospital site authorized to access the EDC system using an assigned account. The system accommodates various unit levels, including community hospitals within the medical union, medical union units, and the central hospitals of West China Hospital, Sichuan University. To address the unique characteristics of patient diagnosis and treatment across different levels in the western region of China, specific electronic forms within the EDC system are designated for data collection at each unit level. To comprehensively delineate the characteristics of VHD patients, community hospitals affiliated with the medical consortium primarily gather community-based health examination data from patients. This information

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

For Peer Review Only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

facilitates patient screening and categorization, guiding regular follow-ups within the community based on disease severity. In contrast, medical consortium and West China Hospital, Sichuan University, primarily collect diagnostic and treatment data during hospital visits. The integrated care management system includes patient follow-up components with scheduled follow-ups at 1 month, 3months, 6 months, and 1-year post-discharge, followed by regular annual outpatient follow-ups, addressing instances involving adverse events that require medical attention).

Trained VHD data collectors conduct daily eligibility screenings for patients in outpatient clinics and hospital wards. Upon identifying eligible patients, the EDC system automatically compiles their essential information. This includes the patient registration number, which serves as a unique identifier within the treating hospital; the outpatient visit number for the current visit; the inpatient case number corresponding to the ongoing hospitalization; the patient's ID card number as a distinctive patient identifier; and the phone number as the primary contact method. Within the EDC system, a new account is established for each eligible patient, with these details recorded as essential information. When new VHD patient data is entered into the EDC system, a unique index identifier is automatically generated for the patient. The system then correlates the patient's medical records within the medical consortium units based on the patient's ID card number. It autonomously collects patient treatment data using the registration number, visit number, or case number, thereby constructing comprehensive medical records within the medical consortium.

Continuous follow-up of patients is a crucial aspect of this study, addressing the scarcity of long-term follow-up data for VHD patients both domestically and internationally. Trained physicians conduct ongoing follow-ups, gathering patient-related information through face-to-face interviews utilizing touchscreen questionnaires or paper records. Full-time data collectors execute the follow-up data collection, meticulously verifying and standardizing questionnaire responses before entering them in to the EDC system to ensure accuracy and consistency. The EDC system dispatches follow-up reminders to data collectors one week before each scheduled follow-up (at 1 month, 3months, 6 months, and 1-year post-discharge, among others). We make three attempts to contact patients on different dates and times, depending on the availability of the contact person, as indicated by phone records. All subsequent calls are recorded for verification, and regular quality control assessments are conducted on follow-up results. In cases where patients cannot be contacted, we plan to undertake additional steps to obtain long-term health-related outcomes based on personal information. This involves correlating the patient's ID card number with data from the Chinese Center for Disease Control and Prevention's national disease surveillance system, the cause of death surveillance network report database, the inpatient data identifier from the community hospital in the patient's residential area and regional death registration records. If these follow-up methods are unsuccessful, is the case will be categorized as a loss to follow-up. Notably, participants who are unable to complete follow-up procedures will still be contacted for the subsequent follow-ups unless they actively request to cease communication. The data collected during follow-ups can be linked with patient records in the EDC system using the patient's ID card number as the matching identifier. Ultimately, the patient's timeline for medical and outpatient follow-ups can be organized according to treatment and follow-up dates.

To ensure the scientific rigor of the study, a consulting committee is instituted, comprising

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

experts in cardiac surgery, interventional cardiology, advanced imaging cardiology, echocardiography, heart failure, critical care, cardiac anesthesia, cardiorespiratory physiotherapy, specialist disease management, statistics, computer engineers, and other specialized fields. Additionally, a project management and coordination center is created to oversee and support the iWAVE operation, conduct data quality control, and facilitate regular online and offline data quality control meetings. An independent supervisory committee was also appointed to oversee the entire research process.

Outcome

Primary Outcome:

The long-term goal of this research project is to explore the full life-cycle process of natural populations as they progress from disease risk factors to VHD, undergo surgical treatment, and continue through lifelong follow-up. Primary outcomes are measured using two cohorts:

- Inpatient and Outpatient Follow-Up Cohort: This cohort aims to determine the long-term (5 years and beyond) mortality rate of VHD patients who undergo surgical interventions and are enrolled in the integrated care management system.
- Community-Based Natural Population Cohort: This cohort investigates the incidence of VHD within a natural population in Western China.

Secondary Outcome:

Secondary outcome measures will include electronic health records, patient self-reported outcome questionnaires, and peripheral blood/tissue sample data, all of which may be relevant to the VHD disease course and long-term recovery trajectory. The secondary endpoints of this research project are observational in nature, and an initial exploratory study will be conducted to investigate the following:

- Identify multi-omics predictors (including genomic and miRNA signatures, as well as specific proteins) for the development of left ventricular remodeling in VHD patients.
- Conduct precise medical analyses of the remission of structural heart failure resulting from VHD and the progression of local and systemic complications.
- Statistically analyze the incidence of out-of-hospital long-term adverse outcome events and the corresponding risk factors in VHD patients undergoing surgical intervention.
- Map the trajectory of functional capacity and quality of life recovery in VHD patients following surgical intervention.
- Determine the incidence of adverse outcome events in a community-based natural population cohort of VHD patients who do not receive surgical intervention.

Data Collection

The following data will be collected for all participants in both the inpatient and outpatient follow-up cohorts, as well as the community-based natural population cohort:

1. Basic demographic information and peripheral blood samples.
2. Full-lifecycle medical imaging data.
3. Long-term functional follow-up and patient self-reported outcome questionnaires.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

a. Inpatient and outpatient follow-up cohorts:

i. Peripheral venous blood analyses, including cardiac biomarkers, biochemical indices, coagulation, routine blood cell analyses, endocrine hormone measurements, glycosylated hemoglobin levels, inflammatory factors, and samples for cell-free DNA analysis, miRNA analysis, cytokines, telomere length, metabolomics, proteomics, transcriptomics, and genomics.

ii. Routine biochemical indicators of urine and stool, and samples for precision medicine tests such as microbial sequencing.

iii. Myocardial and/or valvular tissue samples.

iv. 12-lead electrocardiogram, blood pressure, and peripheral oxygen saturation.

v. Echocardiogram and Doppler measurements, cardiac 4-dimensional computed tomography (4D-CT) measurements.

vi. Electronic health record information, including comorbidity information, medication use, surgical risk assessment, surgical operative records, anesthesia monitoring data, critical care records, and in-hospital adverse outcome events.

vii. Valve Clinical Study endpoint events tracked throughout the patient's lifetime.

viii. Functional capacity measures, including six-minute walk test (6MWT), pulmonary function test (PFT), and New York Heart Association classification (NYHA).

ix. Patient self-reported outcome questionnaires: The Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12) questionnaire; EuroQol Five Dimension Scale (EQ-5D) and EuroQol Visual Analogue Scale (EQ-VAS) questionnaires; Lower extremity edema level; Pittsburgh Sleep Quality Index (PSQI); General Anxiety Disorder Scale-7 (GAD-7); Patient Health Questionnaire-9 (PHQ-9).

x. Home wearable devices to capture continuous physiological parameters.

b. Community-based natural population cohorts:

i. Peripheral venous blood analysis, routine biochemical indicators in urine and stool, and sample collection for precision medicine testing.

ii. 12-lead electrocardiogram, blood pressure, and peripheral oxygen saturation.

iii. Echocardiograms and Doppler measurements.

iv. Electronic health record information, including comorbidity information and medication utilization.

v. Major adverse cardiovascular events tracked throughout the patient's lifetime.

vi. Functional capacity measures, including 6MWT, PFT, and NYHA classification.

vii. Patient self-reported outcome questionnaires.

Venous blood, urine, and stool sampling:

Initial peripheral venous blood, urine, and stool samples are collected when patients sign the informed consent and enroll in the cohort study. For the inpatient and outpatient follow-up cohorts, additional peripheral blood samples abtained on the day of discharge. Subsequent routine outpatient follow-up visits, conducted at least once a year at the hospital where the procedure was performed, allow for the collection of peripheral venous blood, urine, and stool specimens. For the community-based natural population cohort, routine physical examination screenings are performed at least annually at the community hospital to collect peripheral venous blood, urine, and stool specimens.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

Myocardial and/or Valve Tissue Sample Collection:
This program is designed for patients undergoing heart valve surgery, either via median sternotomy or transapical catheter valve surgery. Samples of localized myocardial tissue (including the left atrium, left ventricular myocardium, and right atrium) and/or valvular tissue (including aortic, mitral, and tricuspid valve leaflets) are collected without damaging normal tissues. Additionally, whole blood, serum, plasma, fecal matter, urine, and other tissue samples are stored in a biobank for future studies.

Echocardiography and Doppler Measurements:
Experienced echocardiographers assess the extent of a patient's valvular disease and quantify cardiac structural and hemodynamic parameters according to the guidelines fromthe American Society of Echocardiography for the Evaluation of Native Valvular Regurgitation[5] and Rheumatic Heart Disease[22], as well as the joint guidelines from the European Association of Cardiovascular Imaging and the American Society of Echocardiography Assessment of Aortic Valve Stenosis[23].

Cardiac 4D-CT Examination and Measurements:
Patients scheduled for transcatheter aortic valve implantation (TAVI) undergo CT data acquisition and reconstruction in accordance with the TAVI -Expert Consensus Document of the Society of Cardiovascular Computed Tomography[24]. This examination assesses dynamic changes in aortic root geometry and dimensions while providing anatomical information about the vascular system, including the aorta, iliac arteries, and femoral arteries.

Electronic Health Record Information - In-Hospital Adverse Outcome Events
The iWAVE study project framework selects postoperative outcome events that align with those in prominent international databases, such as the STS ASCD[25]. These events include operative mortality, stroke, renal failure, prolonged ventilation, reoperation, composite morbidity and mortality, prolonged postoperative length of stay, short postoperative length of stay and deep sternal wound infection. Although the database primarily represents the US population, which significantly differs from the target population of this study, it is crucial to maintain consistent definitions of outcome events. This consistency facilitates future population-specific analyses, comparisons of VHD management techniques and concepts[26], and the development of risk models tailored to the Chinese VHD population.

Valve Clinical Study endpoint events tracked throughout the patient's lifetime:
The iWAVE study project selects clinical research endpoints developed by the Valve Academic Research Consortium 3 (VARC-3) [27]. These endpoints include mortality, neurologic events, hospitalization (or rehospitalization), bleeding and transfusions, vascular and access-related complications, cardiac structural complications, other procedural or valve-related complications, new conduction disturbances and arrhythmias, acute kidney injury, myocardial infarction, bioprosthetic valve dysfunction, leaflet thickening and reduced motion, clinically significant valve thrombosis, patient-reported outcomes and health status, and composite endpoints. The endpoints and criteria established by VARC ensure consistent reporting, adjudication, and comparison of results across valve devices and treatment strategies.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

Six-Minute Walk Test (6MWT):

The 6MWT is a submaximal exercise assessment tool widely used to evaluate cardiopulmonary function and prognosis in patients, with the six-minute walk distance (6MWD) serving as the primary outcome indicator[28]. Patients perform the 6MWT according to the standardized protocol outlined in the American Thoracic Society guidelines, under the supervision of a cardiopulmonary physical therapist[29]. The test is terminated if any of the following symptoms occur: chest pain, loss of consciousness, intolerable dyspnea, falling, profuse sweating, or pallor.

Pulmonary Function Testing (PFT):

A cardiopulmonary physical therapist conducts PFT using the standard protocols established by the American Thoracic Society and the European Respiratory Society Technical Statement[30]. These tests evaluate the effects of VHD on pulmonary function and airway responsiveness. The patient is positioned appropriately for spirometry, and the test is repeated as needed. The test is terminated if the patient experiences severe dyspnea, marked panic, chest tightness, precordial pain, dizziness, cyanosis, or pallor. Recorded indicators include forced vital capacity (FVC), one-second forced expiratory volume (FEV1), and maximum voluntary ventilation per minute (MVV).

Patient Self-Reported Outcomes:

Patient heart failure symptoms are assessed using the KCCQ-12, the most commonly used tool for evaluating heart failure symptoms[31]. Patients rate the impact of their heart failure symptoms on 12 items, including mood, daily activities, and sleep.

To evaluate patients' health status, the standardized health measurement tool EQ-5D is employed [32]. Widely used globally to determine quality of life, the EQ-5D comprises a descriptive system and predetermined utility values[33]. The descriptive system includes five dimensions: daily activities, self-care, mobility, anxiety/depression, and pain/discomfort, each with five severity levels: extremely, severely, moderately, slightly, and none. A health utility calculator for the Chinese population, available online (www.valueinhealthjournal.com/issues), provides health utility status values ranging from 0 (dead) to 1 (perfectly healthy).

To assess edema, pressure is applied with the thumb for at least 2 seconds over the dorsum of the foot, behind the medial malleolus, and on the lower calf above the medial malleolus. The depth of the indentation and the time required for the skin to return to its original state are recorded and rated on a clinical scale. Patient sleep quality is evaluated using the PSQI, which consists of 19 items that assess subjective sleep quality, time to fall asleep, sleep duration, habitual sleep efficiency, sleep disturbances, and use of sleeping medication[34]. For assessing anxiety and depression, the GAD-7 and PHQ-9 are used to monitor the severity of illness[35,36].

Home Wearable Device to Collect Continuous Dynamic Physiological Parameters:

A medical-grade wearable device, developed in collaboration with an engineering team, continuously and accurately captures dynamic physiological data before, during, and after a patient's walking activity. The physiological data obtained from the wearable device is temporally divided into three segments: the pre-activity resting phase, the activity phase, and the post-activity recovery phase. Automatically calculated according to predefined data

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

preprocessing rules, the parameters include: a) electrocardiographic metrics such as heart rate, duration of each waveform, ST-segment changes, rhythm, and heart rate variability; b) oxygen saturation characteristics; c) triaxial acceleration metrics, including mean, standard deviation, extreme values, root mean square, skewness, kurtosis, gait cycle, activity recognition features, exercise intensity, inclination, and synthetic acceleration; d) adverse events during walking, such as intolerable dyspnea, palpitations, dizziness, chest pain or tightness, fatigue, and hypoxia, along with the total walking distance[37]. The wearable device's capability to capture high-frequency, continuous physiological parameters presents significant potential for personalized health assessment and early warning systems for postoperative patients at home through artificial intelligence (AI)-driven analysis. Designed for remote monitoring, the device facilitates personalized health assessments and early interventions based on continuous data collection and AI analytics[38].

Sample Size

Based on the literature review and the research team's preliminary retrospective data, the 5-year average survival rate for patients with VHD managed using conventional protocols and undergoing surgical interventions is approximately 60%[10]. We anticipate a 30% improvement in this survival rate with the implementation of a novel integrated care management protocol for VHD patients. With a superiority ratio of 1.2, applying a test level of 0.025, a test efficacy of 0.90, and a de-escalation rate of 20%, at least 1,889 VHD inpatients and outpatients need to be enrolled. Furthermore, this study aims to investigate the prevalence of VHD within the broader community. According to survey, the weighted prevalence of VHD among the Chinese population aged 35 years and older is 3.8%[1]. The likelihood of the sample rate obtained during the formal survey differing from the known prevalence by no more than 1% does not exceed 0.05. Considering a deleterious rate of 20%, a minimum of 7,270 patients from the community-based population is required.

The West China Hospital of Sichuan University is one of the largest tertiary hospitals in western China, serving a population that constitutes approximately 6% of the country's total population within its 15 medical consortiums and associated sub-community hospitals[39]. Therefore, we plan to enroll at least 10,000 patients over a 5-year period (October 1, 2023, to October 1, 2028) to achieve the objectives of the prospective cohort study.

Data management and monitoring

The information stored in the iWAVE Registry Database is unalterable and can only be accessed for query analysis through database views. The EDC system provides standardized forms for VHD follow-ups, available in both mobile and personal computer versions. Trained data collectors are authorized to conduct follow-ups and collect data exclusively within the hospital's internal network environment, using tablets or physician workstations. Data integration occurs through a dedicated network channel in the medical cloud to ensure data security.

All collected data undergo daily synchronization, where information from the hospital's electronic health record system is automatically integrated with the EDC system. This synchronization retrieves comprehensive data about participants' medical management, laboratory test results, and, if applicable, surgical procedures throughout the research period.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

To establish a connection between health records in a fully covered participant management database for long-term medical or mortality records one year after recruitment and beyond, an annual linkage is implemented (Figure 2).

The EDC system data collection form template is developed by the Heart Valve Team at West China Hospital, Sichuan University. All units within the medical consortium, including community hospitals, adhere to this standardized template for data collection. Before data collection begins, researchers and data collectors undergo comprehensive training covering key elements, definitions, and the data input system. The Project Management Coordination Center conducts regular meetings to provide feedback on data quality control reports and implements retraining as needed. Additionally, there is a strong emphasis on maintaining the stability of on-site team members. When there are changes on-site researchers, coordinators, or data collectors, prompt training for new staff becomes imperative.

Participating sites ensure the reporting of all eligible cases to iWAVE, with specific methods outlined below. For sites utilizing electronic medical records, an electronic query algorithm is employed to identify patients with VHD by searching data fields that are most likely to indicate relevant events among all patient records involved in cardiovascular surgery. These events may include conditions such as "rheumatic heart disease", "degenerative heart disease", "valvular stenosis", " valvular regurgitation" among others. Coordinators subsequently evaluate compliance with inclusion criteria based on electronic medical records. In cases where electronic medical records are not used or lack statistical functionality - such as when patients present external examination reports or hospital records - coordinators manually review the patients' external paper records. The accuracy and completeness of reported data are ensured through a multifaceted approach. Firstly, the EDC system incorporates data input checks to mitigate errors and enhance the precision of data collection. An algorithmic quality check system automatically prompts notifications for researchers to rectify or review data deviations from predefined rules. Secondly, quality inspectors meticulously examine each variable based on medical records within seven days of data submission. In incorrect, suspicious, or incomplete data are identified during ongoing audits, researchers reporting on VHD patients must correct or complete records and clarify any missing or dubious data elements. Inspectors summarize the monthly progress of data collection and quality measures and engage in regular discussions with the principal investigator. Thirdly, statisticians routinely evaluate and screen the collected data, including checks for logic errors and outliers. Fourthly, the project management center conducts random testing on 10-50% of the data weekly to examine extreme values or missing entries. Fifthly, the project management center deploys a coordinator to hospital wards and outpatient clinics every 3-6 months for on-site checks, ensuring the continuity, completeness, and accuracy of reported data. Lastly, experts randomly review more than 20% of the audio recordings from the entire interview process to ensure the quality of baseline and subsequent data. In cases of disagreement, data collectors and quality inspectors collaboratively reassess the data (Figure 4).

Data Security

First, the EDC system allows access exclusively within the confines of the hospital's internal network, with access permissions tailored to the specific responsibilities of individual researchers. Each researcher is assigned a unique account, and user authentication is achieved

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

through secure passwords, thereby reducing the risk of unauthorized access to the EDC system. In accordance with ethical standards, the EDC system employs anonymization and de-identification processes for reported data. All data transfers are securely conducted within encrypted tunnels and stored in the database of the West China Hospital, Sichuan University Information Center. To minimize the risk of data loss, routine backups are systematically performed for all storage.

Statistic and Analysis

Data are presented as percentages for categorical variables and as mean ± standard deviation (SD) or median (25th to 75th percentile) for continuous variables. The distribution of continuous variables is examined using the Kolmogorov-Smirnov test. Comparisons are made using the Student's t-test or Mann-Whitney U test for continuous variables, and the Chi-Square or Fisher's exact test for categorical variables, as appropriate. Linear mixed-effects models are employed to assess changes in clinical parameters (e.g., echocardiographic measurements, indicators of functional capacity) from the time of surgical intervention to long-term follow-up.

Survival analyses are performed using the Kaplan-Meier method to report annual event rates. Model survival functions are estimated using risk ratios associated with predetermined key covariates, adjusted for age, gender, and other potential confounders, including comorbidities and relevant echocardiographic characteristics. The influence of prognostic factors on patients with VHD is explored through Multivariate Cox proportional hazards regression modeling, quantifying the degree of influence via hazard ratios with 95% confidence intervals (CIs). The selection of variables for the model is based on their clinical importance and includes process variables such as VHD-specific characteristics, preoperative assessments, surgery-related information, and intensive care management. Independent predictors are selected using Stata's Lasso technique with cross-validation.

Binary logistic regression, based on L1 and L2 regularization, is applied with the occurrence of the outcome event as the dependent variable. The coefficients from the logistic regression model rank the importance of each parameter, constructing a feature screening model based on the importance of the parameters and the model's predictive power. The best subset of features is determined by iterating through the extracted features for selection until stability in the feature set is achieved. Five-fold cross-validation is used to generate the training and validation sets, where the training set builds the model and the validation set confirms the model's capabilities. We experiment with the selected features using various machine learning models, including logistic regression, support vector machine, linear discriminant analysis, k-nearest neighbors, and random forest classifiers, employing five-fold cross-validation for training. The predictive power of the models is assessed by calculating the area under the receiver operating characteristic curve. Statistical analyses will be conducted using R version 3.6.2. A two-tailed P-value < 0.05 will be considered statistically significant.

Patient and Public Involvement

Patients and the public are not involved in the design, recruitment, or conduct of this study. While we do not plan to inform every individual participant of the study results,
we will disseminate the findings to the public through community outreach and public

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

engagement initiatives.

Ethics and Dissemination

The study was approved by the Biomedical Research Ethics Committee of West China Hospital of Sichuan University (No. 20232422). All research organizations contributing data for the iWAVE study comply with this ethical approval, and any modifications to the study protocol will be submitted for further ethical review. All participants are required to provide written informed consent, and patient data will be stored in de-identified form in the Information Center of West China Hospital of Sichuan University. All protocols will be conducted in compliance with the Declaration of Helsinki. Access to the study data will be restricted to researchers and ethics committees associated with the study. The results will be disseminated in various formats, including conference abstracts, posters, presentations, and peer-reviewed scientific journals. All results presented in this study are cohort data, ensuring that participants cannot be individually identified. Additionally, the findings will be reported to local governments and health and wellness committees to inform policy development, as well as to medical research centers and units that participated in and supported the cohort study.

DISCUSSION

To the best of our knowledge, this is the first cohort study conducted across multiple medical consortiums led by a regional center hospital in Western China. It focuses on the diagnosis, treatment, and prognostic outcomes in a population with VHD in the region, providing comprehensive data on risk factors, diagnostic and therapeutic management, physical status, and whole-life cycle follow-up experiences.

Large multicenter disease cohort databases capture heterogeneous samples from the population due to their extensive sample size, thereby reflecting real-world clinical effectiveness rather than the clinical efficacy observed under ideal conditions. These databases also enhance understanding of diverse care delivery methods and outcomes, as well as inter-center variations. Consequently, they can support quality improvement efforts and inform health policy initiatives[40].

Effective management of VHD in adults requires continuous monitoring as patients transition from disease screening registries to whole-life cycle follow-up[41]. To date, most studies focus on the association between moderate and severe VHD and clinical events, with limited understanding of the factors influencing the progression of mild VHD[42,43]. Matsushita's 25-year follow-up of mild VHD conditions, such as aortic atherosclerosis and mild aortic regurgitation, reveals that each mild VHD lesion is independently associated with at least one adverse cardiovascular outcome[44]. Given the low prevalence of cardiac screening and the significant number of patients who are never formally referred to a cardiologist[15], more effective data registration and linkage are crucial to prevent patients from "slipping through the cracks"[45]. This is especially true for VHD patients in low- and middle-income regions of Western China, who often travel long distances to large medical centers for treatment. The widespread use of diagnostic cardiac imaging, artificial intelligence algorithms for automated image interpretation, and optimized referral pathways may enhance patients' access to sustained high-quality care throughout their lives [46].

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

The American Heart Association released a statement titled "The Importance of Measuring Patient-Reported Health Status," which identifies three key domains: symptom burden, functional status, and health-related quality of life[47]. Long-term or lifelong patient-reported outcomes are more significant than those recorded over shorter periods in conventional databases, as they more accurately define treatment success[48]. Patients undergoing valvular surgical interventions face long-term risks such as prosthetic valve failure, bleeding, embolism, and readmission for heart failure, which impose a substantial healthcare burden[42]. Thus, it is essential to link administrative databases - such as national mortality surveillance databases, community hospital records, and health insurance data - with existing cohort databases to collect prognostic and health data [19]. This approach can enhance longitudinal follow-up, survival rates, and overall quality of life in the growing and aging VHD population.

Although national databases for cardiac surgery have long been established internationally, there are notable in population and disease characteristics, as well as healthcare public service systems, among China, Europe, and the United States [14 26]. Therefore, the iWAVE cohort database accounts for the unique population characteristics of Western China, focusing on screening variables related to the diagnosis, treatment, and prognosis of VHD[20]. This database aims to facilitate continuous monitoring of VHD throughout the lifespan of the population in Western China, enhancing the roles and responsibilities of government, hospitals, clinicians, and public health organizations to create a model of accessible and affordable lifelong care for middle- to low-income VHD patients in the region.

Limitation:

This study presents several limitations. First, the medical centers involved are confined to Western China, resulting in a cohort that only represents the VHD population in that region and fails to capture the broader characteristics of VHD across China. However, as the study progresses, we aim to broaden the inclusion criteria to encompass more large medical centers in non-Western China, thereby diversifying the geographic distribution of the study population over time. Second, the current biomarkers lack specificity in predicting VHD disease progression, and with the ongoing advancement of transcatheter valve interventions, obtaining patient biospecimens becomes increasingly challenging. Therefore, we plan to collect peripheral venous blood samples, urine and stool samples from a community-based natural population cohort, as well as samples of valvular and/or myocardial tissue from patients who undergo median open-heart surgery at the medical centers involved in this study, to explore the microscopic mechanisms of VHD disease. Third, the design of the cohort study limits our ability to implement varied medical interventions for conducting long-term prognostic correlation analyses. Nonetheless, incorporating a multicenter cohort population could provide a sufficiently large sample size for propensity-matched analyses aimed at exploring the relationship between target variables and outcome events. Finally, significant time and resources were dedicated during the pre-study phase to ensure the accuracy and completeness of the data. In future sustainability studies, the iWAVE cohort study is committed to streamlining the data reporting process and automating data collection.

A descriptive analysis report based on the iWAVE cohort study provides a comprehensive overview of the incidence, demographics, care pathways, and whole-life cycle follow-up of

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

VHD in the population of Western China. This report identifies risk-modifying factors that influence outcomes, establishes benchmarks among cardiac centers, and proposes system-wide strategies aimed at improving the survival of patients with VHD. The iWAVE database enables continuous monitoring of the entire lifespan of VHD patients within this population. Additionally, the database assists both the public and government in prioritizing primary prevention and lifelong follow-up of VHD patients. Successful outcomes may motivate other cardiovascular medical centers across the country to participate, potentially establishing a national platform for monitoring cardiovascular surgical care in Western China, facilitating research projects, establishing benchmarking standards, and identifying areas for potential quality improvement.

Acknowledgements

We gratefully acknowledge the contributions of all hospitals, principal investigators, healthcare professionals, researchers, and patients involved in the iWAVE cohort study. We also extend our thanks to the Integrated Care Management Centre of West China Hospital of Sichuan University for their support in providing a whole-life cycle management system. Additionally, we appreciate the efforts of the Information Centre of Sichuan University for their contributions in supplying medical electronic case records, developing the EDC system, and enhancing data analysis and quality control.

Funding

This work was supported by National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University (No. Z2024YY001)

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability

We invite national and international collaborations for projects concerning various aspects, including but not limited to disease screening strategies, diagnostic and therapeutic decisions, and long-term functional trajectories. Researchers are encouraged to apply for data access by contacting the Chief Investigator (YQ-G) at drguoyq@wchscu.cn, providing details of the study objectives and proposals.

Author Contributions

All authors contributed to the conception or design of the work. Yuqiang Wang, Xiang Liu and Tingqian Cao contributed to the acquisition, analysis, or interpretation of data for the work. Jun Shi contributed to analysis for the work. Lulu Liu contributed to the interpretation of data for the work. Yuqiang Wang and Xiang Liu drafted the manuscript. Yongzhao Zhou and Yingqiang Guo critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy. Guarantor is Yuqiang Wang.

Reference:

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

1. Yang Y, Wang Z, Chen Z, et al. Current status and etiology of valvular heart disease in China: a population-based survey. *BMC Cardiovasc Disord.* 2021;21(1):339.
2. MA L, WANG Z, FAN J, et al. Interpretation of Report on Cardiovascular Health and Diseases in China 2022. *Chinese General Practice.* 2023;26(32):3975.
3. Jiang L, Krumholz HM, Li X, et al. Achieving best outcomes for patients with cardiovascular disease in China by enhancing the quality of medical care and establishing a learning health-care system. *Lancet* 2015;386(10002):1493-505.
4. Liqin L, Xu Z, Lanyu Z, et al. Degree of Coordination between Primary Care Resource Allocation and Economic Development in Eastern. Central and Western China. *Chinese General Practice*. 2021, 24(22): 2777-2784.
5. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography* 2017;30(4):303-71.
6. Xu H, Liu Q, Cao K, et al. Distribution, Characteristics, and Management of Older Patients With Valvular Heart Disease in China: China-DVD Study. *JACC Asia* 2022;2(3):354-65.
7. Çelik M, Durko AP, Bekkers JA, et al. Outcomes of surgical aortic valve replacement over three decades. *The Journal of thoracic and cardiovascular surgery* 2022;164(6):1742-51.e8.
8. Messika-Zeitoun D, Baumgartner H, Burwash IG, et al. Unmet needs in valvular heart disease. *European heart journal* 2023;44(21):1862-73.
9. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease: Developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Revista espanola de cardiologia.* 2022;75(6):524.
10. Praz F, Beyersdorf F, Haugaa K, et al. Valvular heart disease: from mechanisms to management. *Lancet.* 2024;403(10436):1576-89.
11. Saxena A, Newcomb AE, Dhurandhar V, et al. Application of Clinical Databases to Contemporary Cardiac Surgery Practice: Where are We now? *Heart, lung & circulation.* 2016;25(3):237-42.
12. Shahian DM, Jacobs JP, Edwards FH, et al. The society of thoracic surgeons national database. *Heart.* 2013;99(20):1494-501.
13. Head SJ, Howell NJ, Osnabrugge RL, et al. The European association for cardio-thoracic surgery (EACTS) database: an introduction. *European Journal of Cardio-Thoracic Surgery.* 2013;44(3):e175-e80.
14. Rao C, Zhang H, Gao H, et al. The Chinese Cardiac Surgery Registry: Design and Data Audit. *The Annals of thoracic surgery.* 2016;101(4):1514-20.
15. Puri R, Dykun I, Kalra A. The Spectrum of Valvular Heart Disease and the Importance of "Mild". *JAMA network open.* 2022;5(5):e2211955.
16. Charles EJ, Mehaffey JH, Hawkins RB, et al. Meaningful Patient-centered Outcomes 1 Year Following Cardiac Surgery. *Annals of surgery.* 2021;273(6):e247-e54.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

17. Davidson LJ, Davidson CJ. Transcatheter Treatment of Valvular Heart Disease: A Review. *Jama.* 2021;325(24):2480-94.
18. Su Z, Zhang Y, Cai X, et al. Improving long-term care and outcomes of congenital heart disease: fulfilling the promise of a healthy life. *The Lancet Child & adolescent health.* 2023;7(7):502-18.
19. Wang Y, Cao T, Shi J, et al. Design and Application of Comprehensive Management System For Patients with Chronic Aortic Valve Disease-A Perspective From West China Hospital. *Current problems in cardiology.* 2023;49(1 Pt B):102169.
20. Zhao X, Hong F, Yin J, et al. Cohort Profile: the China Multi-Ethnic Cohort (CMEC) study. *International journal of epidemiology.* 2021;50(3):721-211. doi: 10.1093/ije/dyaa185
21. Chen X, Giles J, Yao Y, et al. The path to healthy ageing in China: a Peking University-Lancet Commission. *Lancet.* 2022;400(10367):1967-2006.
22. Pandian NG, Kim JK, Arias-Godinez JA, et al. Recommendations for the Use of Echocardiography in the Evaluation of Rheumatic Heart Disease: A Report from the American Society of Echocardiography. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography.* 2023;36(1):3-28.
23. Baumgartner H, Hung J, Bermejo J, et al. Recommendations on the Echocardiographic Assessment of Aortic Valve Stenosis: A Focused Update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography.* 2017;30(4):372-92.
24. Blanke P, Weir-McCall JR, Achenbach S, et al. Computed tomography imaging in the context of transcatheter aortic valve implantation (TAVI) / transcatheter aortic valve replacement (TAVR): An expert consensus document of the Society of Cardiovascular Computed Tomography. *Journal of cardiovascular computed tomography.* 2019;13(1):1-20.
25. Shahian DM, Jacobs JP, Badhwar V, et al. The Society of Thoracic Surgeons 2018 Adult Cardiac Surgery Risk Models: Part 1-Background, Design Considerations, and Model Development. *The Annals of thoracic surgery.* 2018;105(5):1411-18.
26. Lin H, Gong J, Wu Y, et al. A Comparative Study on Surgical Treatment of Valvular Heart Disease between High-Volume Cardiac Centers in China and STS Data. *Journal of cardiovascular development and disease.* 2022;9(7)
27. Généreux P, Piazza N, Alu MC, et al. Valve Academic Research Consortium 3: updated endpoint definitions for aortic valve clinical research. *European heart journal.* 2021;42(19):1825-57.
28. Agarwala P, Salzman SH. Six-Minute Walk Test: Clinical Role, Technique, Coding, and Reimbursement. *Chest.* 2020;157(3):603-11.
29. ATS statement: guidelines for the six-minute walk test. *American journal of respiratory and critical care medicine.* 2002;166(1):111-7.
30. Graham BL, Steenbruggen I, Miller MR, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. *American journal of respiratory and critical care medicine.* 2019;200(8):e70-e88.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Enseignement Superieur (ABES) .

31. Spertus JA, Jones PG. Development and Validation of a Short Version of the Kansas City Cardiomyopathy Questionnaire. *Circulation Cardiovascular quality and outcomes.* 2015;8(5):469-76.
32. Luo N, Liu G, Li M, et al. Estimating an EQ-5D-5L Value Set for China. *Value Health.* 2017;20(4):662-69.
33. Wisløff T, Hagen G, Hamidi V, et al. Estimating QALY gains in applied studies: a review of cost-utility analyses published in 2010. *Pharmacoeconomics.* 2014;32(4):367-75.
34. Buysse DJ, Reynolds III CF, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry research*. 1989;28(2):193-213.
35. Zhang C, Wang T, Zeng P, et al. Reliability, Validity, and Measurement Invariance of the General Anxiety Disorder Scale Among Chinese Medical University Students. *Frontiers in psychiatry.* 2021;12:648755.
36. Wang W, Bian Q, Zhao Y, et al. Reliability and validity of the Chinese version of the Patient Health Questionnaire (PHQ-9) in the general population. *General hospital psychiatry.* 2014;36(5):539-44.
37. Wang J, Yang Z, Wang Y, et al. A Quantitative Approach and Preliminary Application in Healthy Subjects and Patients with Valvular Heart Disease for 24-h Breathing Patterns Analysis Using Wearable Devices. *2022 IEEE International Conference on E-health Networking, Application & Services (HealthCom)2022*.
38. Williams GJ, Al-Baraikan A, Rademakers FE, et al. Wearable technology and the cardiovascular system: the future of patient assessment. *The Lancet Digital Health*. 2023;5(7):e467-e76.
39. WANG Miao, SHI Kecan, CHEN Lei, et al. Analysis of the features of lead-type close medical consortium in West China Hospital of Sichuan University.*West China Medical Journal*. 2019; 34(12):1422-1425.
40. Vener DF, Gaies M, Jacobs JP, et al. Clinical Databases and Registries in Congenital and Pediatric Cardiac Surgery, Cardiology, Critical Care, and Anesthesiology Worldwide. *World journal for pediatric & congenital heart surgery.* 2017;8(1):77-87.
41. Pavone N, Burzotta F, Bruno P, et al. Heart Valve Critical Pathway and Heart Valve Clinic: Novel Benchmarks for Modern Management of Valvular Heart Disease. *Critical pathways in cardiology.* 2021;20(3):126-33.
42. Aluru JS, Barsouk A, Saginala K, et al. Valvular Heart Disease Epidemiology. *Med Sci.* 2022;10(2)
43. Bae JY, Fallahi A, Miller W, et al. A call to consider an aortic stenosis screening program. *Trends in cardiovascular medicine.* 2023
44. Matsushita K, Gao Y, Rubin J, et al. Association of Mild Valvular Lesions With Long-term Cardiovascular Outcomes Among Black Adults. *JAMA network open.* 2022;5(5):e2211946.
45. Chami J, Nicholson C, Strange G, et al. National and regional registries for congenital heart diseases: Strengths, weaknesses and opportunities. *International journal of cardiology.* 2021;338:89-94.
46. Sengupta PP, Shrestha S, Kagiyama N, et al. A Machine-Learning Framework to Identify Distinct Phenotypes of Aortic Stenosis Severity. *JACC Cardiovascular imaging.*

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

2021;14(9):1707-20.
47. Rumsfeld JS, Alexander KP, Goff DC, Jr., et al. Cardiovascular health: the importance of measuring patient-reported health status: a scientific statement from the American Heart Association. *Circulation.* 2013;127(22):2233-49.
48. Makhni EC, Meadows M, Hamamoto JT, et al. Patient Reported Outcomes Measurement Information System (PROMIS) in the upper extremity: the future of outcomes reporting? *Journal of shoulder and elbow surgery.* 2017;26(2):352-57.

Figures

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

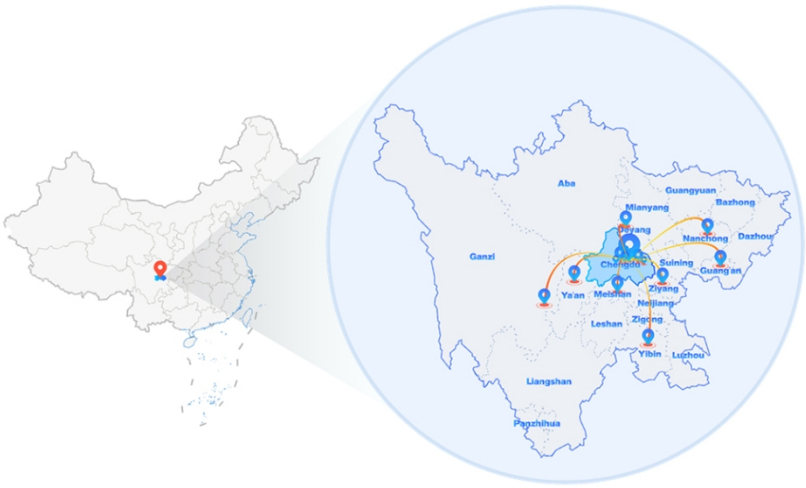


Figure 1

101x57mm (300 x 300 DPI)

BMJ Open: first published as 10.1136/bmjopen-2024-090075 on 3 December 2024. Downloaded from http://bmjopen.bmj.com/ on June 12, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

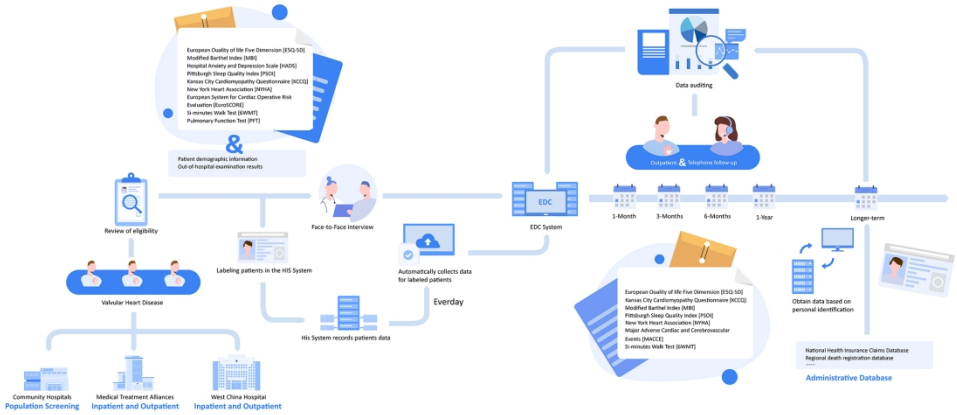


Figure 2

203x108mm (300 x 300 DPI)

BMJ Open: first published as 10.1136/bmjopen-2024-090075 on 3 December 2024. Downloaded from http://bmjopen.bmj.com/ on June 12, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Domain	Type of assessment	The Whole-Life Cycle Comprehensive Management Time Schedule – Inpatients; Outpatients; Community Population															
		Enroll	6m	12m	2y	3y	...	Ny	In-hospital	1m	3m	6m	12m	2y	3y	4y	...	Ny
Biological Sample	Blood	●		●	●	●	●	●	●			○	●	●	●	●	●	●
	Urine	●		●	●	●	●	●	●			○	●	●	●	●	●	●
	Stool	●		●	●	●	●	●	●			○	●	●	●	●	●	●
	Myocardial tissue								●									
	Valves leaflets																	
Medical Examination	12-ECG	●	●	●	●	●	●	●	●	●	○	●	●	●	●	●	●	●
	Echocardiography	●	●	●	●	●	●	●	●	●	○	●	●	●	●	●	●	●
	Cardiac 4D-CT								●			●	○	○	○	○	○	○
Electronic Health Record	Demographic	●							●									
	Perioperative data								●									
	Adverse outcomes	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Functional Capacity	6MWT	●	○	●	●	●	●	●	●	●	○	○	●	●	●	●	●	●
	PFT	●	○	●	●	●	●	●	●	●	○	○	●	●	●	●	●	●
Patient Reported Outcome	KCCQ-12	●	○	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
	EQ-5D and EQ-VAS	●	○	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
	Lower limb edema	●	○	●	●	●	●	●	●	●	○	●	●	●	●	●	●	●
	PSQI	●	○	●	●	●	●	●	●	●	○	●	●	●	●	●	●	●
	HADS	●	○	●	●	●	●	●	●	●	○	●	●	●	●	●	●	●
Wearable Device	Continuous physiological data	○	○	○	○	○	○	○	●	●	○	○	○	○	○	○	○	○

ECG: Electrocardiogram; 4D-CT: 4-Dimensional Computed Tomography; 6MWT: 6-minute Walking Test; PFT: Pulmonary Function Test; KCCQ: The Kansas City Cardiomyopathy Questionnaire; EQ-5D: EuroQol Five Dimension Scale; EQ-VAS: EuroQol Visual Analogue Scale; PSQI: Pittsburgh Sleep Quality Index; HADS: Hospital Anxiety and Depression Scale. ●Mandatory; ○Available.

Figure 3

203x105mm (300 x 300 DPI)

BMJ Open: first published as 10.1136/bmjopen-2024-090075 on 3 December 2024. Downloaded from http://bmjopen.bmj.com/ on June 12, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

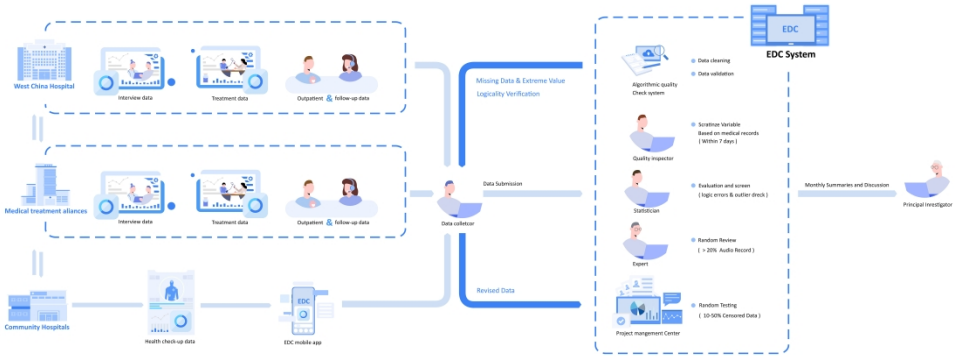


Figure4

680x297mm (300 x 300 DPI)

BMJ Open: first published as 10.1136/bmjopen-2024-090075 on 3 December 2024. Downloaded from http://bmjopen.bmj.com/ on June 12, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

BMJ Open

Integrated Whole-Life Cycle Accuracy Valvular Heart Disease Epidemiology Cohort Study (iWAVE): protocol for a prospective cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-090075.R2
Article Type:	Protocol
Date Submitted by the Author:	05-Nov-2024
Complete List of Authors:	Liu, Xiang; Sichuan University, Information Technology Center Wang, Yuqiang; West China Hospital of Medicine, Cao, Tingqian; Sichuan University, Department of Integrated Care Management Center Jun, Shi; West China Hospital of Medicine Liu, Lulu; Sichuan University, Department of Cardiovascular Surgery Zhou, Yongzhao; Sichuan University, Department of Integrated Care Management Center Guo, Yingqiang; Sichuan University, Department of Cardiovascular Surgery
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine, Public health, Epidemiology
Keywords:	Valvular heart disease < CARDIOLOGY, Patient Reported Outcome Measures, Quality of Life, Observational Study

SCHOLARONE™
Manuscripts

BMJ Open: first published as 10.1136/bmjopen-2024-090075 on 3 December 2024. Downloaded from http://bmjopen.bmj.com/ on June 12, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Integrated Whole-Life Cycle Accuracy Valvular Heart Disease Epidemiology Cohort Study (iWAVE): protocol for a prospective cohort study

Xiang Liu[1,2†], Yuqiang Wang[1,3†], Tingqian Cao[1,4], Jun Shi[1,3], Lulu Liu[1,3], Yongzhao Zhou[4], Yingqiang Guo[1,3*]

[1] Department of Cardiovascular Surgery and National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu, China
[2] Information Technology Center, West China Hospital, Sichuan University, Chengdu, China
[3] Cardiovascular Surgery Research Laboratory, West China Hospital, Sichuan University, Chengdu, China
[4] Department of Integrated Care Management Center, West China Hospital, Sichuan University, Chengdu, China
† These authors contributed equally to the study.

***Correspondence to:**
Yingqiang Guo
Department of Cardiovascular Surgery and National Clinical Research Center for Geriatrics; Cardiovascular Surgery Research Laboratory, West China Hospital, Sichuan University, Chengdu, China
Email: drguoyq@wchscu.cn

Word count: 6372

ABSTRACT

Introduction

Despite the rapid advancements in cardiovascular surgery in China, the prevalence of valvular heart disease (VHD) continues to rise, particularly among the elderly population. In the resource-constrained western regions, the lack of an integrated care management system significantly contributes to the burden of cardiovascular disease. Consequently, a comprehensive cohort data platform that encompasses the entire lifespan of patients with VHD is essential. This prospective cohort study aims to facilitate the examination of risk factor screening, disease progression, diagnostic and treatment strategies, and the long-term functional recovery trajectories of patients following valve surgery.

Methods and analysis

The Integrated Whole-Life Cycle Accuracy Valvular Heart Disease Epidemiology Cohort Study (iWAVE) is a prospective cohort study that plans to enrol approximately 10,000 participants, including both patients with VHD and members of the general population, by 2028. Lead by West China Hospital of Sichuan University, it will be conducted in collaboration with 15 medical consortiums and their affiliated community hospitals. This study seeks to assess the disease trajectory of VHD, as well as the risk factors and protective measures that influence its progression and prognosis. This study will collect and analyse basic demographic information, peripheral blood and tissue samples, long-term functional follow-up data, and patient-reported outcome questionnaires. Additionally, electronic health records will be used to document VHD

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

patients undergoing surgical interventions, along with lifetime endpoint events for the valve clinical study.

Ethics and dissemination

The study protocol was approved by the Biomedical Research Ethics Committee of West China Hospital of Sichuan University (No. 20232422). All participants will be required to provide written informed consent. The study findings will be disseminated via publications in peer-reviewed journals and presentations at scientific conferences.

Keywords:

Valvular heart disease; Outcomes; Health-related quality of life; Cohort; Integrated care management system

Strengths and limitations of this study

- The iWAVE cohort study will utilize an established integrated care platform and a well-designed electronic data capture system, facilitating effective disease registration and continuous tracking, which will support high follow-up rates.
- This study will monitor patients' progression from high-risk factors to a confirmed diagnosis of VHD, including surgical treatment and ongoing follow-up until an endpoint event occurs, thereby providing valuable longitudinal data to enhance the understanding of the development of VHD.
- The cohort represents only the VHD population in western China and may not adequately reflect the characteristics of VHD across the entire Chinese population.
- The study design limits the analysis of correlations between various medical decisions and long-term patient prognosis; however, incorporating a multicentre cohort may provide a sufficiently large sample size for propensity score-matched analyses to investigate these correlations.

INTRODUCTION

Valvular heart disease (VHD), which primarily results from rheumatic heart disease or degenerative changes, represents an increasing public health concern. Approximately 25 million individuals in China currently experience VHD, with 55.1% affected by rheumatic VHD and 21.3% affected by degenerative VHD [1]. In recent years, cardiac surgery in China has advanced rapidly, marked by a significant increase in the number of procedures performed [2]. However, notable economic and educational disparities persist across various regions of the country, resulting in considerable fluctuations in the quality of cardiac surgeries [3]. Unlike the more economically developed eastern regions, which benefit from efficient health resource allocation, the middle- to low-income western regions endure a significant burden of cardiovascular disease because of insufficient health resources and limited access to high-quality health care services. Consequently, the burden of cardiovascular disease in western China has increased dramatically over the past decade [1,4].

One reason for the poor survival of VHD patients in China is the lack of early echocardiographic screening and diagnosis among asymptomatic individuals, which indirectly leads to delayed consultations [5]. A recent survey indicated that a significant majority of elderly VHD patients hospitalized in China present with evident symptoms (89.4%); however, only 37%

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

undergo surgical interventions, often due to personal refusal, disease severity, and high surgical risk [6]. Early detection, rational assessment, and optimal referral are crucial for improving VHD outcomes. Therefore, early disease screening and the establishment of medical information registries are necessary for community populations in western China, where medical resources are limited. Moreover, an increasing number of patients are undergoing cardiac surgery. Although several clinical trials and observational studies have demonstrated that postoperative heart function improves over time [7], postoperative functional decline remains common among elderly patients due to comorbidities and frailty [8]. Successful surgery initiates a lifelong journey that may involve potential adverse outcomes, including prosthetic valve failure, stroke, and heart failure readmission. Regular appointments with a cardiologist are essential, as clinical deterioration can occur unnoticed [9]. Quality of life and functional capacity outcomes are increasingly recognized as important indicators of cardiac surgery success. Analysing functional trajectories through generic measures of functional status can yield valuable insights [10].

Cohort databases significantly enhance our understanding of cardiovascular surgery and play a crucial role in advancing clinical management and patient care [11]. Notable examples include the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database (ACSD) [12], established in 1989, which encompasses over five million cardiac surgery patients, and the Europe-wide Adult Cardiac Surgery Practice Information Database, initiated in 2002 by the European Association for Cardiothoracic Surgery (EACTS) [13]. In 2013, the Chinese National Center for Cardiovascular Disease (NCCD) and Fu Wai Hospital launched the Chinese Cardiac Surgery Registry (CCSR) [14]. However, these databases predominantly focus on patients with moderate-to-severe VHD, often overlooking risk factors and epidemiological studies concerning patients with asymptomatic and mild VHD [15]. Furthermore, many cohort databases lack comprehensive data on long-term survival and quality of life improvements [16]. The Chinese health care system is primarily oriented towards diagnostics and surgical interventions [17], with less emphasis on primary care and disease management, which are vital for enhancing long-term patient outcomes [18]. Consequently, establishing an early screening and lifelong follow-up system tailored to the characteristics and treatment needs of the Chinese VHD population is essential for improving long-term health outcomes [19].

Western China, which encompasses twelve provinces and covers 6.87 million square kilometres, including Sichuan Province, exhibits considerable diversity, with unique geographic and climatic conditions, and hosts 56 ethnic minorities. This region, which represents 27.2% of China's population, has significant genetic diversity and distinct lifestyle choices, such as the Tibetans' adaptation to low oxygen levels on the plateau and the Miao people's sour soup-rich diet [20]. Established in 2009, the West China Hospital Biospecimen Bank of Sichuan University has the capacity to store 10 million samples, supporting biospecimen collection, epidemiological investigations, and follow-ups for natural populations and various disease cohorts. The iWAVE study project, which is being operated by the National Clinical Research Center for Geriatrics at West China Hospital, Sichuan University, is leveraging the existing integrated care management system and collaborating with 15 medical consortiums and their affiliated community hospitals in the region to develop a cohort database focused on the whole-life cycle management of VHD patients [19]. As China's ageing population increases—projected to reach 395 million individuals aged 65 and older by 2050—the data gathered from

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

this cohort will improve our understanding of VHD characteristics in Western China and facilitate the establishment of localized standards for early diagnosis, treatment, and rehabilitation [21]. Our goal is to implement a patient-centred approach that encompasses health promotion, disease screening, prevention, diagnosis, treatment, and rehabilitation, ultimately increasing patients' quality of life. To achieve this goal, we will collect prospective data, including cardiopulmonary exercise assessments; peripheral blood, myocardial, and valve tissue samples; medical test results; imaging data; and electronic health records, and we will perform long-term functional follow-ups to evaluate cardiac structure and function.

Aims

1. The outcomes and long-term functional recovery trajectories of VHD patients across multiple dimensions, including age, disease severity, and surgical modality, will be collected, and the risk and protective factors that influence individual outcomes throughout the disease lifespan will be identified.
2. Postoperative clinical outcomes of VHD patients, such as adverse events during hospitalization, long-term follow-up outcomes, and duration of hospital stay, will be analysed to provide a comprehensive understanding of postoperative results and identify predictive factors.
3. Mortality prediction tools adapted specifically for short-term and long-term outcomes in VHD patients within the Chinese population will be developed, and these tools will be compared with the STS score calculator.
4. Personalized whole-life cycle follow-up profiles will be established on the basis of patients' clinical characteristics, the implementation and efficacy of an integrated care management system for VHD will be assessed, and the role of a specialist disease manager in promoting long-term functional recovery will be evaluated.
5. Epidemiological data on VHD prevalence within a natural population cohort in Western China will be collected, and the impacts of socioeconomic, psychological, and physiological factors, along with activity levels and living environments, will be assessed.
6. The trajectory of VHD development within a natural population cohort will be explored by utilizing peripheral blood or tissue samples to identify critical periods of ventricular remodelling and optimal intervention windows.

METHODS AND ANALYSIS

Study design and setting

iWAVE is a prospective, multicentre, observational, population-based cohort study initiated at West China Hospital, West China Tianfu Hospital, and Shang Jin Hospital of West China Hospital. The project will progressively expand to include the 15 hospitals within the West China Hospital Medical Consortium and their affiliated community hospitals for ongoing participant recruitment (Figure 1). The National Clinical Medical Research Center for Geriatric Diseases and the Heart Valve Disease Research Center at Sichuan University's West China Hospital will manage the study's design and implementation.

Study population

The categorization of participants on the basis of the source population is detailed below. 1)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

Community-based Natural Population Cohort: Eligible participants are permanent residents within the jurisdiction of the West China Hospital Medical Consortium who agree to undergo transthoracic echocardiography at community hospitals. Sonographers conducting the procedures will receive standardized training from the Departments of Ultrasound and Cardiology at West China Hospital. The inclusion criterion is that the participants must be 35 years of age or older. The exclusion criteria include an inability to comprehend the questionnaire or refusal to participate in the study. 2) Inpatient and Outpatient Follow-Up Cohort: This group consists of participants from the cardiovascular surgery departments of West China Hospital and 15 associated medical consortiums. The eligibility criteria include patients initially evaluated with moderate or more severe VHD via echocardiography, being 35 years of age or older, and having the capacity to understand the questionnaire. The exclusion criteria include impaired consciousness or death that prevents the completion of the questionnaire, a life expectancy of less than six months, acute aortic dissection, and refusal to participate in the study.

Study procedure

The data elements and definitions for the iWAVE Cohort Study form were meticulously designed, drawing inspiration from the current STS ACSD database template and adapting it to the specific needs of this study. Figures 2 and 3 provide detailed information on the study process.

To streamline data collection and organization, we developed a Chinese electronic data capture (EDC) system. This system requires network connectivity via a computer or handheld mobile device, with each hospital site authorized to access the EDC system via an assigned account. The system accommodates various unit levels, including community hospitals within medical unions, medical union units, and the central hospitals of West China Hospital, Sichuan University. To address the unique characteristics of patient diagnosis and treatment across different levels in the western region of China, specific electronic forms within the EDC system will be designated for data collection at each unit level. To comprehensively delineate the characteristics of VHD patients, community hospitals affiliated with the medical consortium will primarily gather community-based health examination data from patients. This information will facilitate patient screening and categorization, guiding regular follow-ups within the community on the basis of disease severity. In contrast, the medical consortium and West China Hospital, Sichuan University, will primarily collect diagnostic and treatment data during hospital visits. The integrated care management system will include patient follow-up components with scheduled follow-ups at 1 month, 3 months, 6 months, and 1 year post-discharge, followed by regular annual outpatient follow-ups, addressing instances involving adverse events that require medical attention.

Trained VHD data collectors will conduct daily eligibility screenings for patients in outpatient clinics and hospital wards. Upon identifying eligible patients, the EDC system will automatically compile their essential information. This includes the patient registration number, which serves as a unique identifier within the treating hospital; the outpatient visit number for the current visit; the inpatient case number corresponding to the ongoing hospitalization; the patient's ID card number as a distinctive patient identifier; and the phone number as the primary contact method. Within the EDC system, a new account is established for each eligible patient,

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

with these details recorded as essential information. When new VHD patient data are entered into the EDC system, a unique index identifier is automatically generated for the patient. The system then correlates the patient's medical records within the medical consortium units on the basis of the patient's ID card number. It autonomously collects patient treatment data using the registration number, visit number, or case number, thereby constructing comprehensive medical records within the medical consortium.

Continuous follow-up of patients is a crucial aspect of this study, addressing the scarcity of long-term follow-up data for VHD patients both domestically and internationally. Trained physicians will conduct ongoing follow-ups and gather patient-related information through face–to–face interviews via touchscreen questionnaires or paper records. Full-time data collectors execute the follow-up data collection, meticulously verifying and standardizing questionnaire responses before entering them into the EDC system to ensure accuracy and consistency. The EDC system dispatches follow-up reminders to data collectors one week before each scheduled follow-up (at 1 month, 3 months, 6 months, and 1 year post-discharge, among others). We will make three attempts to contact patients on different dates and times, depending on the availability of the contact person, as indicated by phone records. All subsequent calls will be recorded for verification, and regular quality control assessments will be conducted on the follow-up results. In cases where patients cannot be contacted, we plan to undertake additional steps to obtain long-term health-related outcomes on the basis of personal information. This involves correlating the patient's ID card number with data from the Chinese Center for Disease Control and Prevention's national disease surveillance system, the cause of death surveillance network report database, the inpatient data identifier from the community hospital in the patient's residential area, and regional death registration records. If these follow-up methods are unsuccessful, the case will be categorized as a loss to follow-up. Notably, participants who are unable to complete follow-up procedures will still be contacted for subsequent follow-ups unless they actively request the cessation of communication. The data collected during follow-up can be linked with patient records in the EDC system using the patient's ID card number as the matching identifier. Ultimately, the patient's timeline for medical and outpatient follow-ups can be organized according to treatment and follow-up dates.

To ensure the scientific rigor of the study, a consulting committee comprising experts in cardiac surgery, interventional cardiology, advanced imaging cardiology, echocardiography, heart failure, critical care, cardiac anaesthesia, cardiorespiratory physiotherapy, specialist disease management, statistics, computer engineers, and other specialized fields was established. Additionally, a project management and coordination centre was created to oversee and support the iWAVE operation, conduct data quality control, and facilitate regular online and offline data quality control meetings. An independent supervisory committee was also appointed to oversee the entire research process.

Outcomes

Primary outcomes

The long-term goal of this research project is to explore the full life cycle process of natural populations as they progress from disease risk factors to VHD, undergo surgical treatment, and continue through lifelong follow-up. Primary outcomes will be measured in two cohorts:

- Inpatient and outpatient follow-up cohort: This cohort aims to determine the long-term (5

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

years and beyond) mortality rate of VHD patients who undergo surgical interventions and are enrolled in the integrated care management system.

- Community-Based Natural Population Cohort: This cohort will investigate the incidence of VHD within a natural population in Western China.

Secondary outcomes

The secondary endpoints of this research project are observational, and an initial exploratory study will be conducted to investigate the following:

- Explore and identify multiomics predictors (including genomic and miRNA signatures, as well as specific proteins) for the development of left ventricular remodelling in VHD patients.
- To determine the incidence of short-term (1-, 3-, and 6-month) and long-term (more than 1 year) adverse events in patients undergoing surgery on the basis of the 'Valve Academic Research Consortium 3 (VARC-3) endpoint events' and to identify the corresponding protective factors and risk factors.
- To assess the long-term functional trajectories of VHD patients by analysing changes in patient self-reported outcomes and functional capacity measures.

Data collection

The following data will be collected for all participants in both the inpatient and outpatient follow-up cohorts, as well as the community-based natural population cohort:

1. Basic demographic information and peripheral blood samples.
2. Full-lifecycle medical imaging data.
3. Long-term functional follow-up and patient self-reported outcome questionnaires.

a. Inpatient and outpatient follow-up cohorts:

i. Peripheral venous blood parameters, including cardiac biomarkers, biochemical indices, coagulation, routine blood cell analyses, endocrine hormone measurements, glycosylated haemoglobin levels, inflammatory factors, and samples for cell-free DNA analysis, miRNA analysis, cytokines, telomere length, metabolomics, proteomics, transcriptomics, and genomics.

ii. Routine biochemical indicators of urine and stool and samples for precision medicine tests, such as microbial sequencing.

iii. Myocardial and/or valvular tissue samples.

iv. Blood pressure, 12-lead electrocardiogram, and peripheral oxygen saturation.

v. Echocardiogram and Doppler measurements and cardiac 4-dimensional computed tomography (4D-CT) measurements.

vi. Electronic health record information, including comorbidity information, medication use, surgical risk assessment, surgical operative records, anaesthesia monitoring data, critical care records, and in-hospital adverse outcome events.

vii. Valve clinical study endpoint events tracked throughout the patient's lifetime.

viii. Functional capacity measures, including the six-minute walk test (6MWT), pulmonary function test (PFT), and New York Heart Association (NYHA) classification.

ix. Patient self-reported outcome questionnaires: The Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12) questionnaire; EuroQol Five Dimension Scale (EQ-5D) and EuroQol Visual Analogue Scale (EQ-VAS) questionnaires; lower extremity oedema level;

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

Pittsburgh Sleep Quality Index (PSQI); General Anxiety Disorder Scale-7 (GAD-7); Patient Health Questionnaire-9 (PHQ-9).

x. Home wearable devices to capture continuous physiological parameters.

b. Community-based natural population cohorts:

i. Peripheral venous blood analysis, routine biochemical indicators in urine and stool, and sample collection for precision medical testing.

ii. Blood pressure, 12-lead electrocardiogram, and peripheral oxygen saturation.

iii. Echocardiograms and Doppler measurements.

iv. Electronic health record information, including comorbidity information and medication utilization.

v. Major adverse cardiovascular events tracked throughout the patient's lifetime.

vi. Functional capacity measures, including the 6MWT, PFT, and NYHA classification.

vii. Patient self-reported outcome questionnaires.

Venous blood, urine, and stool sampling:

Initial peripheral venous blood, urine, and stool samples will be collected when patients provide informed consent and enrol in the cohort study. For the inpatient and outpatient follow-up cohorts, additional peripheral blood samples will be obtained on the day of discharge. Subsequent routine outpatient follow-up visits will be conducted at least once a year at the hospital where the procedure was performed, allowing for the collection of peripheral venous blood, urine, and stool samples. For the community-based natural population cohort, routine physical examination screenings will be performed at least annually at the community hospital to collect peripheral venous blood, urine, and stool samples.

Myocardial and/or valve tissue sample collection:

This program is designed for patients undergoing heart valve surgery, either via median sternotomy or transapical catheter valve surgery. Samples of localized myocardial tissue (including the left atrium, left ventricular myocardium, and right atrium) and/or valvular tissue (including the aortic, mitral, and tricuspid valve leaflets) will be collected without damaging normal tissues. Additionally, whole blood, serum, plasma, faecal matter, urine, and other tissue samples will be stored in a biobank for future studies.

Echocardiography and Doppler measurements:

Experienced echocardiographers will assess the extent of a patient's valvular disease and quantify their cardiac structural and haemodynamic parameters according to the guidelines from the American Society of Echocardiography for the Evaluation of Native Valvular Regurgitation [5] and Rheumatic Heart Disease [22], as well as the joint guidelines from the European Association of Cardiovascular Imaging and the American Society of Echocardiography Assessment of Aortic Valve Stenosis [23].

Cardiac 4D-CT examination and measurements:

Patients scheduled for transcatheter aortic valve implantation (TAVI) will undergo CT data acquisition and reconstruction in accordance with the TAVI Expert Consensus Document of the Society of Cardiovascular Computed Tomography [24]. This examination assesses dynamic

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

changes in aortic root geometry and dimensions while providing anatomical information about the vascular system, including the aorta, iliac arteries, and femoral arteries.

Electronic health record information—in-hospital adverse outcome events:
The iWAVE study project framework selected postoperative outcome events that align with those in prominent international databases, such as the STS ASCD [25]. These events include operative mortality, stroke, renal failure, prolonged ventilation, reoperation, composite morbidity and mortality, prolonged postoperative length of stay, short postoperative length of stay and deep sternal wound infection. Although the database primarily represents the US population, which significantly differs from the target population of this study, it is crucial to maintain consistent definitions of outcome events. This consistency will facilitate future population-specific analyses, comparisons of VHD management techniques and concepts [26], and the development of risk models tailored to the Chinese VHD population.

Valve clinical study endpoint events tracked throughout the patient's lifetime:
The iWAVE study project selected clinical research endpoints developed by the Valve Academic Research Consortium 3 (VARC-3) [27]. These endpoints include mortality, neurologic events, hospitalization (or rehospitalization), bleeding and transfusions, vascular and access-related complications, cardiac structural complications, other procedural or valve-related complications, new conduction disturbances and arrhythmias, acute kidney injury, myocardial infarction, bioprosthetic valve dysfunction, leaflet thickening and reduced motion, clinically significant valve thrombosis, patient-reported outcomes and health status, and composite endpoints. The endpoints and criteria established by the VARC will ensure consistent reporting, adjudication, and comparison of results across valve devices and treatment strategies.

Six-minute walk test (6MWT):
The 6MWT is a submaximal exercise assessment tool widely used to evaluate cardiopulmonary function and prognosis in patients, with the six-minute walk distance (6MWD) serving as the primary outcome indicator [28]. Patients perform the 6MWT according to the standardized protocol outlined in the American Thoracic Society guidelines under the supervision of a cardiopulmonary physical therapist [29]. The test is terminated if any of the following symptoms occur: chest pain, loss of consciousness, intolerable dyspnoea, falling, profuse sweating, or pallor.

Pulmonary function testing (PFT):
A cardiopulmonary physical therapist will conduct PFT using the standard protocols established by the American Thoracic Society and the European Respiratory Society Technical Statement [30]. These tests evaluate the effects of VHD on pulmonary function and airway responsiveness. The patient is positioned appropriately for spirometry, and the test is repeated as needed. The test is terminated if the patient experiences severe dyspnoea, marked panic, chest tightness, precordial pain, dizziness, cyanosis, or pallor. The recorded indicators include forced vital capacity (FVC), one-second forced expiratory volume (FEV1), and maximum voluntary ventilation per minute (MVV).

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

Patient self-reported outcomes:

Patient heart failure symptoms will be assessed using the KCCQ-12, the most commonly used tool for evaluating heart failure symptoms [31]. Patients rate the impact of their heart failure symptoms on 12 items, including mood, daily activities, and sleep.

To evaluate patients' health status, the standardized health measurement tool EQ-5D will be employed [32]. Widely used globally to determine quality of life, the EQ-5D comprises a descriptive system and predetermined utility values [33]. The descriptive system includes five dimensions, namely, daily activities, self-care, mobility, anxiety/depression, and pain/discomfort, each with five severity levels: extremely, severely, moderately, slightly, and none. A health utility calculator for the Chinese population, available online (www.valueinhealthjournal.com/issues), provides health utility status values ranging from 0 (dead) to 1 (perfectly healthy).

To assess oedema, pressure will be applied with the thumb for at least 2 seconds over the dorsum of the foot, behind the medial malleolus, and on the lower calf above the medial malleolus. The depth of the indentation and the time required for the skin to return to its original state will be recorded and rated on a clinical scale. Patient sleep quality will be evaluated using the PSQI, which consists of 19 items that assess subjective sleep quality, time to fall asleep, sleep duration, habitual sleep efficiency, sleep disturbances, and the use of sleeping medication [34]. To assess anxiety and depression, the GAD-7 and PHQ-9 will be used to monitor the severity of illness [35,36].

Home wearable device to collect continuous dynamic physiological parameters:

A medical-grade wearable device, developed in collaboration with an engineering team, will continuously and accurately capture dynamic physiological data before, during, and after a patient's walking activity. The physiological data obtained from the wearable device are temporally divided into three segments: the pre-activity resting phase, the activity phase, and the post-activity recovery phase. Automatically calculated according to predefined data preprocessing rules, the parameters include a) electrocardiographic metrics such as heart rate, duration of each waveform, ST-segment changes, rhythm, and heart rate variability; b) oxygen saturation characteristics; c) triaxial acceleration metrics, including the mean, standard deviation, extreme values, root mean square, skewness, kurtosis, gait cycle, activity recognition features, exercise intensity, inclination, and synthetic acceleration; and d) adverse events during walking, such as intolerable dyspnoea, palpitations, dizziness, chest pain or tightness, fatigue, and hypoxia, along with the total walking distance [37]. The ability of wearable devices to capture high-frequency, continuous physiological parameters presents significant potential for personalized health assessment and early warning systems for postoperative patients at home through artificial intelligence (AI)-driven analysis. Designed for remote monitoring, the device facilitates personalized health assessments and early interventions on the basis of continuous data collection and AI analytics [38].

Sample size

On the basis of the literature review and the research team's preliminary retrospective data, the 5-year average survival rate for patients with VHD managed via conventional protocols and who are undergoing surgical interventions is approximately 60% [10]. We anticipate a 30%

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

improvement in this survival rate with the implementation of a novel integrated care management protocol for VHD patients. With a superiority ratio of 1.2, a test level of 0.025, a test efficacy of 0.90, and a de-escalation rate of 20%, at least 1,889 VHD inpatients and outpatients need to be enrolled. Furthermore, this study aims to investigate the prevalence of VHD within the broader community. According to a survey, the weighted prevalence of VHD among the Chinese population aged 35 years and older is 3.8% [1]. The likelihood of the sample rate obtained during the formal survey differing from the known prevalence by no more than 1% does not exceed 0.05. Considering a deleterious rate of 20%, a minimum of 7,270 patients from the community-based population is required.

The West China Hospital of Sichuan University is one of the largest tertiary hospitals in western China, serving a population that constitutes approximately 6% of the country's total population within its 15 medical consortiums and associated subcommunity hospitals [39]. Therefore, we plan to enrol at least 10,000 patients over a 5-year period (October 1, 2023, to October 1, 2028) to achieve the objectives of this prospective cohort study.

Data management and monitoring

The information stored in the iWAVE Registry Database is unalterable and can only be accessed for query analysis through database views. The EDC system provides standardized forms for VHD follow-ups and is available in both mobile and personal computer versions. Trained data collectors will be authorized to conduct follow-ups and collect data exclusively within the hospital's internal network environment, using tablets or physician workstations. Data integration will occur through a dedicated network channel in the medical cloud to ensure data security.

All collected data will undergo daily synchronization, where information from the hospital's electronic health record system will be automatically integrated with the EDC system. This synchronization will retrieve comprehensive data about participants' medical management, laboratory test results, and, if applicable, surgical procedures throughout the research period. To establish a connection between health records in a fully covered participant management database for long-term medical or mortality records one year after recruitment and beyond, an annual linkage will be implemented (Figure 2).

The EDC system data collection form template was developed by the Heart Valve Team at West China Hospital, Sichuan University. All units within the medical consortium, including community hospitals, will adhere to this standardized template for data collection. Before data collection begins, researchers and data collectors will undergo comprehensive training covering key elements, definitions, and the data input system. The Project Management Coordination Center will conduct regular meetings to provide feedback on data quality control reports and implement retraining as needed. Additionally, there will be a strong emphasis on maintaining the stability of the onsite team members. When there are changes in onsite researchers, coordinators, or data collectors, prompt training for new staff becomes imperative.

Participating sites will ensure the reporting of all eligible cases to iWAVE, with the specific methods outlined below. For sites utilizing electronic medical records, an electronic query algorithm will be employed to identify patients with VHD by searching for data fields that are most likely to indicate relevant events among all patient records involved in cardiovascular surgery. These events may include conditions such as "rheumatic heart disease",

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

"degenerative heart disease", "valvular stenosis", and "valvular regurgitation". Coordinators will subsequently evaluate compliance with the inclusion criteria on the basis of the electronic medical records. In cases where electronic medical records are not used or lack statistical functionality, such as when patients present external examination reports or hospital records, the coordinators will manually review the patients' external paper records. The accuracy and completeness of the reported data will be ensured through a multifaceted approach. First, the EDC system incorporates data input checks to mitigate errors and enhance the precision of data collection. An algorithmic quality check system automatically prompts notifications for researchers to rectify or review data deviations from predefined rules. Second, quality inspectors will meticulously examine each variable on the basis of medical records within seven days of data submission. If incorrect, suspicious, or incomplete data are identified during ongoing audits, researchers reporting on VHD patients must correct or complete the records and clarify any missing or dubious data elements. The inspectors will summarize the monthly progress of data collection and quality measures and engage in regular discussions with the principal investigator. Third, statisticians will routinely evaluate and screen the collected data, including checks for logic errors and outliers. Fourth, the project management centre will conduct random testing on 10–50% of the data weekly to examine extreme values or missing entries. Fifth, the project management centre will deploy a coordinator to hospital wards and outpatient clinics every 3–6 months for onsite checks, ensuring the continuity, completeness, and accuracy of the reported data. Finally, the experts will randomly review more than 20% of the audio recordings from the entire interview process to ensure the quality of the baseline and subsequent data. In cases of disagreement, the data collectors and quality inspectors will collaboratively reassess the data (Figure 4).

Data security

The EDC system allows access exclusively within the confines of the hospital's internal network, with access permissions tailored to the specific responsibilities of individual researchers. Each researcher is assigned a unique account, and user authentication is achieved through secure passwords, thereby reducing the risk of unauthorized access to the EDC system. In accordance with ethical standards, the EDC system employs anonymization and deidentification processes for reported data. All data transfers are securely conducted within encrypted tunnels and stored in the database of West China Hospital, Sichuan University Information Center. To minimize the risk of data loss, routine backups are systematically performed for all storage.

Statistical analysis

Data will be presented as percentages for categorical variables and as the means ± standard deviations (SDs) or medians (25th to 75th percentiles) for continuous variables. The distribution of continuous variables will be examined via the Kolmogorov–Smirnov test. Comparisons will be made using Student's t test or the Mann–Whitney U test for continuous variables and the chi–square test or Fisher's exact test for categorical variables, as appropriate. Linear mixed-effects models will be employed to assess changes in clinical parameters (e.g., echocardiographic measurements, indicators of functional capacity) from the time of surgical intervention to long-term follow-up.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

Survival analyses will be performed using the Kaplan–Meier method to report annual event rates. Model survival functions will be estimated using risk ratios associated with predetermined key covariates adjusted for age, sex, and other potential confounders, including comorbidities and relevant echocardiographic characteristics. The influence of prognostic factors on patients with VHD will be explored through multivariate Cox proportional hazards regression modelling, with the degree of influence quantified via hazard ratios with 95% confidence intervals (CIs). The selection of variables for the model will be based on their clinical importance and will include process variables such as VHD-specific characteristics, preoperative assessments, surgery-related information, and intensive care management. Independent predictors will be selected using Stata's Lasso technique with cross-validation.

Binary logistic regression, which is based on L1 and L2 regularization, will be applied with the occurrence of the outcome event as the dependent variable. The coefficients from the logistic regression model rank the importance of each parameter, constructing a feature screening model on the basis of the importance of the parameters and the model's predictive power. The best subset of features will be determined by iterating through the extracted features for selection until stability in the feature set is achieved. Fivefold cross-validation will be used to generate the training and validation sets, where the training set builds the model and the validation set confirms the model's capabilities. We will experiment with the selected features using various machine learning models, including logistic regression, support vector machine, linear discriminant analysis, k-nearest neighbours, and random forest classifiers, and employ fivefold cross-validation for training. The predictive power of the models will be assessed by calculating the area under the receiver operating characteristic curve. Statistical analyses will be conducted using R version 3.6.2. A two-tailed P value < 0.05 will be considered statistically significant.

Patient and public involvement

Patients and the public are not involved in the design, recruitment, or conduct of this study. While we do not plan to inform every individual participant of the study results, we will disseminate the findings to the public through community outreach and public engagement initiatives.

ETHICS AND DISSEMINATION

This study was approved by the Biomedical Research Ethics Committee of West China Hospital of Sichuan University (No. 20232422). All research organizations contributing data for the iWAVE study will comply with this ethical approval, and any modifications to the study protocol will be submitted for further ethical review. All participants will be required to provide written informed consent, and patient data will be stored in deidentified form at the Information Center of West China Hospital of Sichuan University. All protocols will be conducted in compliance with the Declaration of Helsinki. Access to the study data will be restricted to researchers and ethics committees associated with the study.

The results will be disseminated in various formats, including conference abstracts, posters, presentations, and peer-reviewed scientific journals. All of the results generated in this study will be cohort data, ensuring that participants cannot be individually identified. Additionally, the findings will be reported to local governments and health and wellness committees to inform

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

policy development, as well as to medical research centres and units that participate in and support the cohort study.

DISCUSSION

To the best of our knowledge, this is the first cohort study conducted across multiple medical consortiums led by a regional centre hospital in Western China. It focuses on the diagnosis, treatment, and prognostic outcomes in a population with VHD in the region, providing comprehensive data on risk factors, diagnostic and therapeutic management, physical status, and whole-life cycle follow-up experiences.

Although national databases for cardiac surgery have long been established internationally, there are notable differences in population and disease characteristics, as well as health care public service systems, among China, Europe, and the United States [14,26]. Therefore, the iWAVE cohort database accounts for the unique population characteristics of Western China and focuses on screening variables related to the diagnosis, treatment, and prognosis of VHD [20]. The iWAVE database will enable continuous monitoring of the entire lifespan of VHD patients within this population. A series of analysis reports based on the iWAVE cohort study will provide a comprehensive overview of the incidence, demographics, care pathways, and whole-life cycle follow-up of VHD in the population of Western China. This report will identify risk-modifying factors that influence outcomes, establish benchmarks among cardiac centres, and propose system-wide strategies aimed at improving the survival of patients with VHD. Additionally, the database is promising for assisting both the public and the government in prioritizing primary prevention and lifelong follow-up of VHD patients. Successful outcomes may motivate other cardiovascular medical centres across the country to participate, potentially establishing a national platform for monitoring cardiovascular surgical care in Western China, facilitating research projects, establishing benchmarking standards, and identifying areas for potential quality improvement.

This study has several limitations. First, the medical centres involved are confined to Western China, resulting in a cohort that represents only the VHD population in that region and fails to capture the broader characteristics of VHD across China. However, as the study progresses, we aim to broaden the inclusion criteria to encompass more large medical centres in non-Western China, thereby diversifying the geographic distribution of the study population over time. Second, the current biomarkers lack specificity in predicting VHD disease progression, and with the ongoing advancement of transcatheter valve interventions, obtaining patient biospecimens has become increasingly challenging. Therefore, we plan to collect peripheral venous blood samples and urine and stool samples from a community-based natural population cohort, as well as samples of valvular and/or myocardial tissue from patients who undergo median open-heart surgery at the medical centres involved in this study, to explore the microscopic mechanisms of VHD disease. Third, the design of the cohort study limits our ability to implement various medical interventions for conducting long-term prognostic correlation analyses. Nonetheless, incorporating a multicentre cohort population could provide a sufficiently large sample size for propensity score-matched analyses aimed at exploring the relationships between target variables and outcome events. Finally, significant time and resources were dedicated during the prestudy phase to ensure the accuracy and completeness

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

of the data. In future sustainability studies, the iWAVE cohort study is committed to streamlining the data reporting process and automating data collection.

Acknowledgements

We gratefully acknowledge the contributions of all hospitals, principal investigators, healthcare professionals, researchers, and patients involved in the iWAVE cohort study. We also extend our thanks to the Integrated Care Management Centre of West China Hospital of Sichuan University for their support in providing a whole-life cycle management system. Additionally, we appreciate the efforts of the Information Centre of Sichuan University for their contributions in supplying medical electronic case records, developing the EDC system, and enhancing data analysis and quality control.

Funding

This work was supported by National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University (No. Z2024YY001)

Competing interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability statement

We invite national and international collaborations for projects concerning various aspects, including but not limited to disease screening strategies, diagnostic and therapeutic decisions, and long-term functional trajectories. Researchers are encouraged to apply for data access by contacting the Chief Investigator (YQ-G) at drguoyq@wchscu.cn, providing details of the study objectives and proposals.

Contributors

All authors contributed to the conception or design of the work. Yuqiang Wang, Xiang Liu and Tingqian Cao contributed to the acquisition, analysis, or interpretation of data for the work. Jun Shi contributed to analysis for the work. Lulu Liu contributed to the interpretation of data for the work. Yuqiang Wang and Xiang Liu drafted the manuscript. Yongzhao Zhou and Yingqiang Guo critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work, ensuring integrity and accuracy.

References

1. Yang Y, Wang Z, Chen Z, et al. Current status and etiology of valvular heart disease in China: a population-based survey. *BMC Cardiovasc Disord.* 2021;21(1):339.
2. MA L, WANG Z, FAN J, et al. Interpretation of Report on Cardiovascular Health and Diseases in China 2022. *Chinese General Practice.* 2023;26(32):3975.
3. Jiang L, Krumholz HM, Li X, et al. Achieving best outcomes for patients with cardiovascular disease in China by enhancing the quality of medical care and establishing a learning health-care system. *Lancet* 2015;386(10002):1493-505.
4. Liqin L, Xu Z, Lanyu Z, et al. Degree of Coordination between Primary Care Resource

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

Allocation and Economic Development in Eastern. Central and Western China. *Chinese General Practice*. 2021, 24(22): 2777-2784.

5. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography* 2017;30(4):303-71.
6. Xu H, Liu Q, Cao K, et al. Distribution, Characteristics, and Management of Older Patients With Valvular Heart Disease in China: China-DVD Study. *JACC Asia* 2022;2(3):354-65.
7. Çelik M, Durko AP, Bekkers JA, et al. Outcomes of surgical aortic valve replacement over three decades. *The Journal of thoracic and cardiovascular surgery* 2022;164(6):1742-51.e8.
8. Messika-Zeitoun D, Baumgartner H, Burwash IG, et al. Unmet needs in valvular heart disease. *European heart journal* 2023;44(21):1862-73.
9. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease: Developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Revista espanola de cardiologia.* 2022;75(6):524.
10. Praz F, Beyersdorf F, Haugaa K, et al. Valvular heart disease: from mechanisms to management. *Lancet.* 2024;403(10436):1576-89.
11. Saxena A, Newcomb AE, Dhurandhar V, et al. Application of Clinical Databases to Contemporary Cardiac Surgery Practice: Where are We now? *Heart, lung & circulation.* 2016;25(3):237-42.
12. Shahian DM, Jacobs JP, Edwards FH, et al. The society of thoracic surgeons national database. *Heart.* 2013;99(20):1494-501.
13. Head SJ, Howell NJ, Osnabrugge RL, et al. The European association for cardio-thoracic surgery (EACTS) database: an introduction. *European Journal of Cardio-Thoracic Surgery.* 2013;44(3):e175-e80.
14. Rao C, Zhang H, Gao H, et al. The Chinese Cardiac Surgery Registry: Design and Data Audit. *The Annals of thoracic surgery.* 2016;101(4):1514-20.
15. Puri R, Dykun I, Kalra A. The Spectrum of Valvular Heart Disease and the Importance of "Mild". *JAMA network open.* 2022;5(5):e2211955.
16. Charles EJ, Mehaffey JH, Hawkins RB, et al. Meaningful Patient-centered Outcomes 1 Year Following Cardiac Surgery. *Annals of surgery.* 2021;273(6):e247-e54.
17. Davidson LJ, Davidson CJ. Transcatheter Treatment of Valvular Heart Disease: A Review. *Jama.* 2021;325(24):2480-94.
18. Su Z, Zhang Y, Cai X, et al. Improving long-term care and outcomes of congenital heart disease: fulfilling the promise of a healthy life. *The Lancet Child & adolescent health.* 2023;7(7):502-18.
19. Wang Y, Cao T, Shi J, et al. Design and Application of Comprehensive Management System For Patients with Chronic Aortic Valve Disease-A Perspective From West China Hospital. *Current problems in cardiology.* 2023;49(1 Pt B):102169.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

For peer review only

Enseignement Superieur (ABES) .
Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

20. Zhao X, Hong F, Yin J, et al. Cohort Profile: the China Multi-Ethnic Cohort (CMEC) study. *International journal of epidemiology.* 2021;50(3):721-21l. doi: 10.1093/ije/dyaa185
21. Chen X, Giles J, Yao Y, et al. The path to healthy ageing in China: a Peking University-Lancet Commission. *Lancet.* 2022;400(10367):1967-2006.
22. Pandian NG, Kim JK, Arias-Godinez JA, et al. Recommendations for the Use of Echocardiography in the Evaluation of Rheumatic Heart Disease: A Report from the American Society of Echocardiography. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography.* 2023;36(1):3-28.
23. Baumgartner H, Hung J, Bermejo J, et al. Recommendations on the Echocardiographic Assessment of Aortic Valve Stenosis: A Focused Update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography.* 2017;30(4):372-92.
24. Blanke P, Weir-McCall JR, Achenbach S, et al. Computed tomography imaging in the context of transcatheter aortic valve implantation (TAVI) / transcatheter aortic valve replacement (TAVR): An expert consensus document of the Society of Cardiovascular Computed Tomography. *Journal of cardiovascular computed tomography.* 2019;13(1):1-20.
25. Shahian DM, Jacobs JP, Badhwar V, et al. The Society of Thoracic Surgeons 2018 Adult Cardiac Surgery Risk Models: Part 1-Background, Design Considerations, and Model Development. *The Annals of thoracic surgery.* 2018;105(5):1411-18.
26. Lin H, Gong J, Wu Y, et al. A Comparative Study on Surgical Treatment of Valvular Heart Disease between High-Volume Cardiac Centers in China and STS Data. *Journal of cardiovascular development and disease.* 2022;9(7)
27. Généreux P, Piazza N, Alu MC, et al. Valve Academic Research Consortium 3: updated endpoint definitions for aortic valve clinical research. *European heart journal.* 2021;42(19):1825-57.
28. Agarwala P, Salzman SH. Six-Minute Walk Test: Clinical Role, Technique, Coding, and Reimbursement. *Chest.* 2020;157(3):603-11.
29. ATS statement: guidelines for the six-minute walk test. *American journal of respiratory and critical care medicine.* 2002;166(1):111-7.
30. Graham BL, Steenbruggen I, Miller MR, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. *American journal of respiratory and critical care medicine.* 2019;200(8):e70-e88.
31. Spertus JA, Jones PG. Development and Validation of a Short Version of the Kansas City Cardiomyopathy Questionnaire. *Circulation Cardiovascular quality and outcomes.* 2015;8(5):469-76.
32. Luo N, Liu G, Li M, et al. Estimating an EQ-5D-5L Value Set for China. *Value Health.* 2017;20(4):662-69.
33. Wisløff T, Hagen G, Hamidi V, et al. Estimating QALY gains in applied studies: a review of cost-utility analyses published in 2010. *Pharmacoeconomics.* 2014;32(4):367-75.
34. Buysse DJ, Reynolds III CF, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Superieur (ABES) .

instrument for psychiatric practice and research. *Psychiatry research*. 1989;28(2):193-213.

35. Zhang C, Wang T, Zeng P, et al. Reliability, Validity, and Measurement Invariance of the General Anxiety Disorder Scale Among Chinese Medical University Students. *Frontiers in psychiatry*. 2021;12:648755.
36. Wang W, Bian Q, Zhao Y, et al. Reliability and validity of the Chinese version of the Patient Health Questionnaire (PHQ-9) in the general population. *General hospital psychiatry*. 2014;36(5):539-44.
37. Wang J, Yang Z, Wang Y, et al. A Quantitative Approach and Preliminary Application in Healthy Subjects and Patients with Valvular Heart Disease for 24-h Breathing Patterns Analysis Using Wearable Devices. *2022 IEEE International Conference on E-health Networking, Application & Services (HealthCom)2022*.
38. Williams GJ, Al-Baraikan A, Rademakers FE, et al. Wearable technology and the cardiovascular system: the future of patient assessment. *The Lancet Digital Health*. 2023;5(7):e467-e76.
39. WANG Miao, SHI Kecan, CHEN Lei, et al. Analysis of the features of lead-type close medical consortium in West China Hospital of Sichuan University.*West China Medical Journal*. 2019; 34(12):1422-1425.

FIGURES

Figure 1. Distribution of West China Hospital and units of the 15 participating medical consortiums

Figure 2. Recruitment process of the iWAVE cohort study

Figure 3. Summary of clinical data collection

Figure 4. Data management and quality control

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Superieur (ABES) .

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

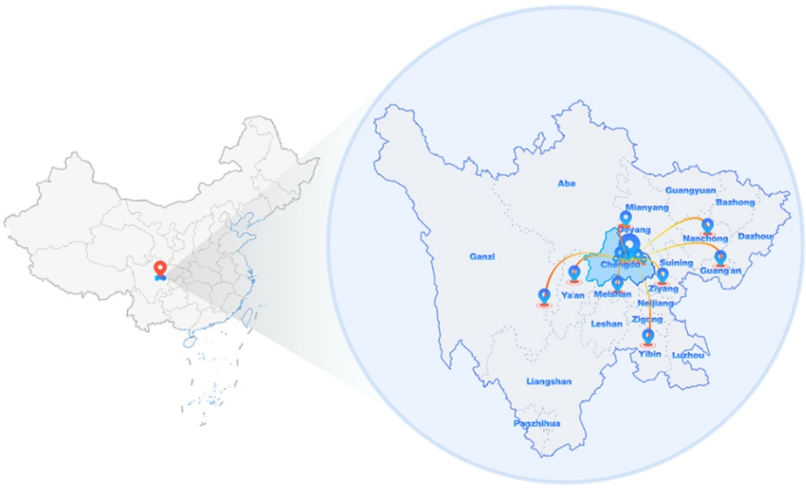


Figure 1

101x57mm (300 x 300 DPI)

BMJ Open: first published as 10.1136/bmjopen-2024-090075 on 3 December 2024. Downloaded from http://bmjopen.bmj.com/ on June 12, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

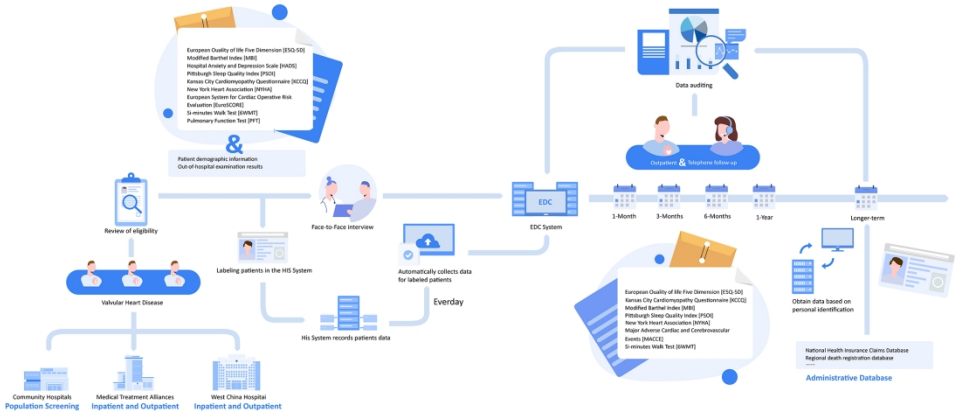


Figure 2

203x108mm (300 x 300 DPI)

BMJ Open: first published as 10.1136/bmjopen-2024-090075 on 3 December 2024. Downloaded from http://bmjopen.bmj.com/ on June 12, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Domain	Type of assessment	The Whole-Life Cycle Comprehensive Management Time Schedule – Inpatients; Outpatients; Community Population															
		Enroll	6m	12m	2y	3y	...	Ny	In-hospital	1m	3m	6m	12m	2y	3y	4y	...	Ny
Biological Sample	Blood	●		●	●	●	●	●	●			○	●	●	●	●	●	●
	Urine	●		●	●	●	●	●	●			○	●	●	●	●	●	●
	Stool	●		●	●	●	●	●	●			○	●	●	●	●	●	●
	Myocardial tissue								●									
	Valves leaflets																	
Medical Examination	12-ECG	●	●	●	●	●	●	●	●	●	○	●	●	●	●	●	●	●
	Echocardiography	●	●	●	●	●	●	●	●	●	○	●	●	●	●	●	●	●
	Cardiac 4D-CT								●			●	○	○	○	○	○	○
Electronic Health Record	Demographic	●							●									
	Perioperative data								●									
	Adverse outcomes	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Functional Capacity	6MWT	●	○	●	●	●	●	●	●	●	○	○	●	●	●	●	●	●
	PFT	●	○	●	●	●	●	●	●	●	○	○	●	●	●	●	●	●
Patient Reported Outcome	KCCQ-12	●	○	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
	EQ-5D and EQ-VAS	●	○	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
	Lower limb edema	●	○	●	●	●	●	●	●	●	○	●	●	●	●	●	●	●
	PSQI	●	○	●	●	●	●	●	●	●	○	●	●	●	●	●	●	●
	HADS	●	○	●	●	●	●	●	●	●	○	●	●	●	●	●	●	●
Wearable Device	Continuous physiological data	○	○	○	○	○	○	○	●	●	○	○	○	○	○	○	○	○

ECG: Electrocardiogram; 4D-CT: 4-Dimensional Computed Tomography; 6MWT: 6-minute Walking Test; PFT: Pulmonary Function Test; KCCQ: The Kansas City Cardiomyopathy Questionnaire; EQ-5D: EuroQol Five Dimension Scale; EQ-VAS: EuroQol Visual Analogue Scale; PSQI: Pittsburgh Sleep Quality Index; HADS: Hospital Anxiety and Depression Scale. ●Mandatory; ○Available.

Figure 3

203x105mm (300 x 300 DPI)

BMJ Open: first published as 10.1136/bmjopen-2024-090075 on 3 December 2024. Downloaded from http://bmjopen.bmj.com/ on June 12, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

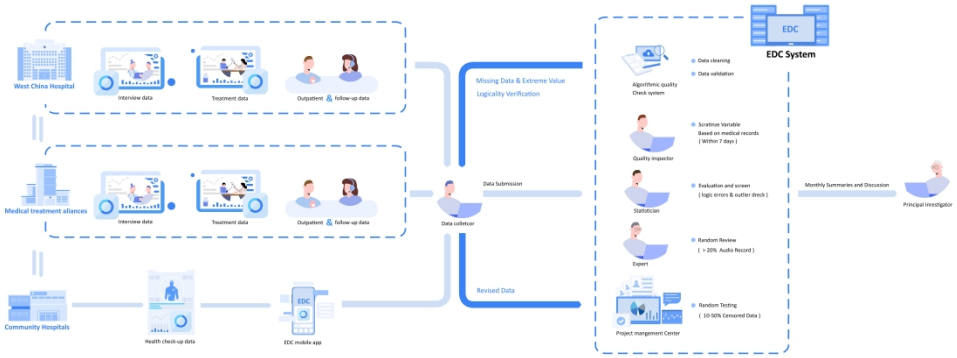


Figure4

680x297mm (300 x 300 DPI)

BMJ Open: first published as 10.1136/bmjopen-2024-090075 on 3 December 2024. Downloaded from http://bmjopen.bmj.com/ on June 12, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.