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Machine learning for prediction of sudden cardiac death in heart failure patients with low left ventricular ejection fraction: study protocol for a retro-prospective multicentre registry in China

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Keywords:	Heart failure < CARDIOLOGY, sudden cardiac death, machine learning, risk model

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4 **Machine learning for prediction of sudden cardiac death in heart**
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6 **failure patients with low left ventricular ejection fraction: study**
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8 **protocol for a retro-prospective multicentre registry in China**
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ABSTRACT

Introduction

Left ventricular ejection fraction (LVEF) $\leq 35\%$, as current major implantable cardioverter-defibrillator (ICD) indication for primary prevention of sudden cardiac death (SCD) in heart failure (HF) patients has been widely recognized to be inefficient. More precisely selecting patients with low LVEF ($\leq 35\%$) is needed to optimize deployment of ICD. Most of the existing prediction models are not appropriate to identify ICD candidates at high risk of SCD in HF patients with low LVEF. Compared to traditional statistical analysis, machine learning (ML) can employ computer algorithms to identify patterns in large datasets, analyze rules automatically and build both linear and non-linear models in order to make data-driven predictions. This study is aimed to develop and validate new models using ML to improve the prediction of SCD in HF patients with low LVEF.

Methods and analysis

We will conduct a retro-prospective, multicentre, observational registry of Chinese HF patients with low LVEF. The HF patients with LVEF $\leq 35\%$ after optimized medication at least 3 months will be enrolled in this trial. The primary end points are all-cause death and SCD. The secondary end points are malignant arrhythmia, sudden cardiac arrest, cardiopulmonary resuscitation and rehospitalization due to HF. The baseline demographic, clinical, biological, electrophysiological, social and psychological variables will be collected. ML techniques will be used to develop a SCD prediction model. As compared to traditional multivariable COX regression model derived from the same database, the performance of ML model will be evaluated.

Ethics and dissemination

The study protocol has been approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (2017-SR-06). All results will be published in international peer-reviewed journals and presented at relevant conferences.

Clinical trial registration ChiCTR-POC-17011842.

INTRODUCTION

Heart failure (HF), with increased prevalence in Asia as well as western countries, has become a major public health problem. The prevalence of HF in Asia is 1.2%-6.7% depending on the population studied.^[1] In China, there are 4.2 million HF patients, and 500,000 new cases are being diagnosed each year.^[1] Although the survival rate after HF diagnosis has been increased due to obvious improvement in medical therapy, the mortality of HF remains high and around 50% of people diagnosed with HF will die within 5 years.^[2] Sudden cardiac death (SCD), as a result of cardiac arrest, mainly due to lethal arrhythmias like ventricular tachycardia or ventricular fibrillation, is responsible for over 50% of all HF deaths.^[3]

The most effective strategy for prevention of SCD in patients with HF, is the implantable cardioverter-defibrillator (ICD), associated with 50% relative risk reduction in arrhythmia-related death in secondary prevention,^[4] and 54% relative risk reduction in primary prevention.^[5] At present, left ventricular ejection fraction (LVEF) $\leq 35\%$ is the major ICD indication for primary prevention of SCD.^[6] However, real-world data show that only 3% to 5% of ICD patients for primary prevention with LVEF $< 30\%$ to 35% receive life-saving therapies on an annual basis,^[7] whereas majority of SCD victims have LVEF $> 35\%$.^[8, 9] Furthermore, obvious decline in rate of SCD for HF patients with reduced LVEF, which was consistent with the cumulative benefit of optimizing medication including angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), beta-blocker, and mineralocorticoid receptor antagonist (MRAs), has been observed.^[10] Therefore, the utility of this criterion has dwindled. New strategies of identifying high risk HF patients most likely to benefit from primary prevention ICD is urgently needed. Because of higher risk SCD in patients with LVEF $\leq 35\%$ than with LVEF $> 35\%$,^[11] identifying patients with low EF at high risk of SCD will be more efficient and economically important.

Over the last decade, lots of multivariate prognostic models derived for chronic HF patients have been proposed (Table 1).^[12-22] However, these models are not appropriate to identify ICD candidates at high risk of SCD in HF patients with low LVEF. Firstly, chronic heart failure both with reduced LVEF (HFREF) and with

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3 preserved LVEF (HFpEF) were represented in all models except I-PRESERVE score,
4 which included only HFpEF. To the best of our knowledge, there is no specific trial
5 for the prognosis of low LVEF population, which is extremely important. Additionally,
6 although all the scores are “not parsimonious”, some critical factors have not been
7 incorporated into all prognostic models, for example, medications are contained in
8 only 3 out of 11 scores,^[15, 19, 21] and optimized medication was not required as
9 inclusion criteria in all 11 studies. Furthermore, the major limitation of most
10 prognostic models is inability to predict SCD risk. Electrical risk factors are not
11 involved in all these models. Although currently some non-invasive factors, including
12 mechanical dyssynchrony measured by echocardiography, myocardial fibrosis
13 detected with cardiovascular magnetic resonance, and cardiac autonomic dysfunction
14 assessed by 123-metaiodobenzylguanidine scintigraphy, have been evaluated to
15 predict SCD in HF patients,^[23] it is difficult to widely use them to predict SCD in
16 large HF population. Resting 12-lead ECG and Holter, as the longest surviving,
17 broadly available, easily deployed and inexpensive tests, can provide a measure of
18 cumulative electrical risk, combination of which may significantly improve the SCD
19 risk prediction beyond EF.^[24]

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Table 1. Risk model for HF in the literature

Author	Database	Year	Variables (n)	Patients (n)	End points
Agostoni	MECKI	2012	6	2716	Cardiovascular death; urgent cardiac transplant
Barlera	GISSI-HF	2013	14	6975	all-cause mortality
Collier	EMPHASIS-HF	2013	10	2737	all-cause mortality
Komajda	I-PRESERVE	2011	12	4128	all-cause mortality
Levy	SHFM	2006	14	1125	Survival
O'Connor	HF-ACTION	2012	4	2331	all-cause mortality
Pocock	CHARM	2006	21	7599	all-cause mortality
Pocock	MAGGIC	2012	13	39372	all-cause mortality
Senni	CVM-HF	2006	13	292	all-cause mortality
Senni	3C-HF	2013	11	2016	all-cause mortality; urgent heart transplant (1 year)
Vazquez	MUSIC	2009	10	992	all-cause mortality; cardiac mortality; pump failure death, sudden death

Based on above reasons, the novel risk assessment tools should meet the following

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3 requirements: (1) the risk model should be developed from special low LVEF
4 population ($\leq 35\%$) to accelerate its clinical application and promote the innovation of
5 ICD indications for primary prevention. (2) The narrow focus on the LVEF as main
6 predictor of SCD risk should be broadened, and more cardiac and non-cardiac factors
7 should be included. (3) Electrical risk factors, which are broadly available, easily
8 deployed and inexpensive, should be considered as candidate predictors to evaluate
9 the risk of sudden arrhythmic death. (4) Although sometimes it is not easy to
10 determine the cause of death, SCD as the primary end point should be defined
11 whenever possible.
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20 Data processing is the next key step to develop prognostic models. This study
21 involves non-linear prediction models, a large number of patients and numerous
22 predictors among which there may be complicated correlations. Traditional
23 hypothesis-driven statistical analysis is difficult to overcome these challenges. The
24 machine learning (ML) approaches have great potential to improve the solution. They
25 employ computer algorithms to identify patterns in large datasets with a large number
26 of variables, analyze rules automatically and build both linear and non-linear models
27 in order to make data-driven predictions or decisions. Weng et al. [25] found that ML
28 significantly improved accuracy of cardiovascular risk prediction, increased the
29 number of patients who could benefit from preventive treatment and avoided
30 unnecessary treatment. However, ML has not been reported to be applied to SCD risk
31 prediction based on large HF population. Therefore, application of ML for prediction
32 of SCD in HF patients with low LVEF will be innovative and clinically significant.
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45 AIMS

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47 The purpose of our study is to develop and validate new models to improve the
48 prediction of SCD in HF patients with low LVEF. The new strategies of identifying
49 HF patients most likely to benefit from primary prevention ICD, will impulse the
50 revolution of ICD indications. The specific research objectives are:
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- 54 1. To develop prediction models to evaluate prognosis and SCD risk respectively
55 by ML methods and traditional COX regression in HF patients with low LVEF
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(≤35%).

2. To validate these prediction models in a prospective cohort and evaluate the performance of ML models, as compared to multivariable COX regression model derived from the same database.

METHODS AND ANALYSIS

Study design

This study is a retro-prospective, multicentre, non-interventional, observational clinical registry trial. The primary sponsor is The First Affiliated Hospital of Nanjing Medical University. This trial has been registered in the Chinese Clinical Trial Registry (ChiCTR-POC-17011842). The trial will be conducted across 14 cardiovascular departments in Tertiary A hospitals throughout the People's Republic of China:

The First Affiliated Hospital of Nanjing Medical University, Nanjing

Xiamen Cardiovascular Hospital, Xiamen University, Xiamen

Wuhan Asia Heart Hospital, Wuhan

Jiangning Hospital Affiliated to Nanjing Medical University, Nanjing

The Second People's Hospital of Lianyungang, Lianyungang

The Affiliated Hospital of Jiangsu University, Zhenjiang

Taixing People's Hospital, Taixing

The First People's Hospital of Huaian, Huaian

The First People's Hospital of Yancheng, Yancheng

Rugao People's Hospital, Rugao

The First People's Hospital of Zhangjiagang, Zhangjiagang

The Third People's Hospital of Suzhou, Suzhou

The Third People's Hospital of Wuxi, Wuxi

The Second Affiliated Hospital of Nanjing Medical University, Nanjing,

The data of the First Affiliated Hospital of Nanjing Medical University and Xiamen Cardiovascular Hospital Xiamen University will be retrospectively collected from

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3 January 2016 to December 2017. About 500 retrospective cases meet the inclusion
4 criteria according to preliminary estimation. The prospective recruitment has started
5 in the above 14 hospitals since January 2018. The retrospective cases and the first
6 1000 prospective cases will be used to develop the prediction models. And the next
7 1000 prospective cases will be used for model validation. The flow diagram of the
8 progress is illustrated in Figure 1.
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14 Figure 1 Flow diagram of progress
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18 **Inclusion criteria**

19 To participate in this trial, patients must comply with all of the following
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- 21 1. Diagnosis of HF_rEF according to the 2016 ESC HF Guideline^[6]
- 22 2. LVEF \leq 35% (measured by Simpson's methods) after optimized medication
23 including ACEI or ARB, beta-blocker and MRA if available and not contraindicated
24 at least 3 months.
- 25 3. Signed informed consent.
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32 **Exclusion criteria**

- 33 1. Hypertrophic cardiomyopathy
- 34 2. Rheumatic heart disease
- 35 3. Congenital heart disease
- 36 4. Pulmonary heart disease
- 37 5. Pericardial diseases and myocarditis
- 38 6. Acute myocardial infarction in recent 3 months, including STEMI and NSTEMI
- 39 7. Aortic dissection
- 40 8. Severe hematologic disease including leukemia, lymphoma, aplastic anemia, etc.
- 41 9. Autoimmune disease
- 42 10. Malignant tumor
- 43 11. Hormone replacement
- 44 12. Application of other interventional clinical trial
- 45 13. Non-drug therapies for improving heart function: CRT-P/D, ICD, heart
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3 transplantation, surgical resection of ventricular aneurysm, interventional left
4 ventricular restoration with Revivent^(TM) / Parachute^(TM) system), MitraClip therapy
5 for recurrent mitral regurgitation
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11 **Endpoints**

12 ***Primary end point***

13 All-cause death and SCD, including cardiac death and death from other causes

14 ***Secondary end point***

15 Lethal arrhythmia, sudden cardiac arrest, cardiopulmonary resuscitation,
16 rehospitalization due to HF
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24 **Recruitment and consent**

25 Participants will be identified and recruited at each of the participating centers. The
26 clinical status of potential participants will be assessed, and their medical records will
27 also be reviewed to confirm the eligibility according to inclusion and exclusion
28 criteria.
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33 The study details will be explained to all potentially eligible and interested subjects.
34 The patients who agree to attend this study will sign the informed consent form (ICF)
35 indicating that they fully understand the study and their rights of confidentiality and
36 withdrawal from the study without giving a reason.
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43 **Baseline evaluation**

44 Prognostic models of HF in the last 10 years have been reviewed and the involved
45 risk factors have been ranked according to their corresponding hazard ratio in
46 respective risk model (Table 1, Figure 2). Age, sex, New York Heart Association
47 (NYHA) class, LVEF, prior HF hospitalization, course of HF, severe valvular heart
48 disease, atrial fibrillation, prior myocardial infarction / coronary artery bypass grafting
49 (CABG), renal dysfunction, chronic obstructive pulmonary disease (COPD), diabetes
50 mellitus, ischemic etiology, decreased systolic pressure, low body mass index (BMI),
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3 anemia, hyponatremia, high N-terminal pro brain natriuretic peptide (NT-proBNP),
4 uricemia, current smoker were included. Variables which were not listed in previous
5 models but appear relevant to higher risk of SCD in HF patients, and would therefore
6 merit consideration, include syncope or pre-syncope, frequent premature ventricular
7 beat, non-sustained ventricular tachycardia, complete left bundle branch block
8 (CLBBB), long QT interval, increased QT dispersion. In addition, self-care ability,
9 social support and psychological state including depression and anxiety, are also
10 predictors for subsequent poor prognosis in HF patients. The above risk factors have
11 been assessed and confirmed by an expert panel of cardiologists and statistician, and
12 will be collected in this study particularly.

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21 Figure 2 Hazard ratio of variables in different risk models

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23 The baseline data of all eligible subjects will be collected as following.

- 24 ● Demographic characteristics: date of birth, gender, height and weight
- 25 ● Life style behavior: smoking and drinking status
- 26 ● Vital signs: blood pressure and heart rate
- 27 ● NYHA class
- 28 ● Etiology of heart failure: The ischemic etiology will be confirmed if any following
29 point is met: a. prior myocardial infarction or revascularization history (coronary
30 artery bypass grafting, CABG / percutaneous coronary intervention, PCI); b. left
31 main or proximal segment of left anterior descending artery stenosis $\geq 75\%$
32 showed by coronary angiogram (CAG); c. at least two main coronary artery
33 branches stenosis $\geq 75\%$ showed by CAG. Otherwise non-ischemic HF should be
34 identified.
- 35 ● Prior HF hospitalization history: first HF hospitalization or not, times of prior HF
36 hospitalization, course of HF (since the HF symptoms appear, if unavailable, since
37 the decreased EF was found).
- 38 ● Coronary heart disease history: myocardial infarction or angina history, CAG
39 result, revascularization history, recent angina.
- 40 ● Arrhythmia history: atrial fibrillation, atrial flutter, premature atrial contraction
41 (PAC), premature ventricular contraction (PVC), non-sustained VT (NSVT),
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sustained VT (SVT), ventricular fibrillation, and some bradyarrhythmias.

- Syncope or pre-syncope history
- Cardiac arrest/ cardiopulmonary resuscitation history
- Other history: hypertension, diabetes mellitus, COPD, etc.
- Echocardiography: LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV) and LVEF measured by Simpson's method; Left atrial diameter, LV end-diastolic diameter (LVEDD) and LV end-systolic diameter (LVESD), pulmonary artery systolic pressure. The status of valve regurgitation will be evaluated (0-none; 1-mild; 2-mild to moderate; 3-moderate; 4- severe)
- ECG: Left / right bundle branch block will be recorded. QRS duration and QT interval will be tested and QT dispersion will be calculated.
- Holter: total heart beat of the whole day, minimum/ maximum/ average HR, onset of PVC, PAC, NSVT, VT, atrial fibrillation/ flutter.
- Laboratory tests results: serum creatinine, blood urea nitrogen (BUN), serum sodium, hemoglobin, Thyroid Stimulating Hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), NT-proBNP.
- medication: ACEI/ARB, beta-blocker, aldosterone antagonist, diuretic, digoxin, antiplatelet agent, anticoagulant, statin, calcium channel blocker, antiarrhythmics, Ivabradine and angiotensin receptor blocker-neprilysin inhibitor (ARNI).
- Evaluation of self-care behavior and social support: 9-item European Heart Failure Self-care Behavior Scale (9-EHFScBS) ^[26] will be used to determine the self-care levels in HF patients. Social Support Rating Scale (SSRS)^[27] will be used to evaluate the social support condition in HF patients.
- Assessment of psychological status: Hamilton Depression Scale (HAMD) and Hamilton Anxiety Scale (HAMA).

Patient visits

After enrolled in this research, all the subjects, will be followed-up periodically in outpatient department or by telephone interview every 3 months. As primary end point, all-cause death and SCD will be focused. Cause of death will be analyzed in

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3 detail. SCD is defined by the World Health Organization as unexpected death that
4 occurs within 1 hour from the onset of new or worsening symptoms (witnessed arrest)
5 or, if unwitnessed, within 24h from when the individual was last observed alive and
6 asymptomatic^[28]. The lethal arrhythmia including VT/VF, sudden cardiac arrest,
7 cardiopulmonary resuscitation, and rehospitalization due to HF will be recorded
8 carefully.
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14 During follow-up, lethal arrhythmia will be recognized more precisely for patients
15 who receive ICD or CRT/D implantation, and will be recorded as adverse event. The
16 patients, who receive CRT-P/D, heart transplantation, surgical resection of ventricular
17 aneurysm, interventional left ventricular restoration with Revivent^(TM) / Parachute^(TM)
18 system), MitraClip therapy for recurrent mitral regurgitation, or some other non-drug
19 therapy to improve heart function, will be followed up as usual.
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25 **Data collection**

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27 In prospective part, clinical data of subjects will be collected and filled in the
28 electrical data capture (EDC) system at baseline and particular follow-up visit. In
29 retrospective part, the same baseline information, except for 9-EHFScBS, SSRS,
30 HAMD, HAMA questionnaires, will also be captured and input into the EDC system.
31 The following prospective visits (every three months) will conducted regularly and
32 will be recorded in the EDC system. Investigator will record all the information of
33 adverse event (AE), study bias, withdraw from the study or death in EDC system. In
34 this study, the participants will be identified by study codes, and their names will not
35 appear in EDC system. All the personal information including contact information,
36 medical record and outcome, will not be revealed to any person who has not been
37 authorized by principle investigator. Professional staffs are responsible for database
38 management, data maintenance and regular data backup. Data quality will be
39 monitored regularly. The data collection checklist is showed in Table 2.
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50 Table 2 The checklist for data collection

Data collection	Baseline		regular visit	withdraw /death
	Retrospective cases	Prospective cases		
Informed consent	√	√		
Quantification verification	√	√		

(inclusion and exclusion)				
Baseline evaluation	✓	✓		
Medication	✓	✓		
Questionnaires 9-EHFScBS SSRS HAMD HAMA		✓		
Regular follow-up visit (every 3 months)			✓	
Survival state	✓		✓	✓
Adverse event	Once happen ✓			
Study bias	Once happen ✓			
Withdraw from the study	Once happen ✓			
Death	Once happen ✓			

Statistical analysis

Data classification and pre-processing

All above collected variables, which might be predictor of all adverse prognosis of HF described in end point events, will be classified as uncontrollable variables (e.g. age, gender, history), controllable variables associated with heart (e.g. NYHA class, LVEF, increased heart rate) and controllable variables beyond heart (e.g. smoking, anemia, diabetes mellitus). Appropriate dummy variables will be used for binary variables and categorical variables, and quantitative variables will be fitted as a single continuous measurement (e.g. age, heart rate, NT-proBNP), unless there is clear evidence of nonlinearity. In order to create possible simple risk score, some continuous variables will also be categorized into several groups according to both usual clinical cutpoints and expert advice.

Machine learning

Variable selection is the process of selecting a subset of relevant variables for use in model construction, which can substantially reduce the abundant information and decrease the number of variables that are input to the prediction model. In this study, the technique named as “information gain ranking” will be used to select appropriate variables. Information gain represents the effectiveness of a variable based on entropy,

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3 which characterizes the unpredictability of a system. The information gain of a
4 variable is evaluated as the entropy difference of the system when including and
5 excluding this variable. Then the variables whose information gain scores are less
6 than a threshold are considered to be insignificant and will be excluded in the
7 prediction.
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12 Predictive classifiers for SCD prediction in HF patients will be developed by the
13 following classification algorithms respectively: decision tree, logistic regression,
14 support vector machine, artificial neural network. [29] The performance and general
15 error estimation of these ML models will be assessed by 10-fold cross-validation. The
16 dataset will be randomly divided into 10 equal folds. 9 folds will be used as training
17 set with the remaining one fold as validation set. The validation results from 10
18 repeats will be combined to provide a measure of the overall performance. The
19 prediction models derived from the four classification algorithms above will be
20 evaluated based on the accuracy and interpretability. Finally, clinical experts and
21 computer specialists will discuss and choose the best model to predict the prognosis
22 and SCD in HF patients and then perform the further validation with the prospective
23 dataset.
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34 ***COX proportional-hazards regression***

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36 Univariable COX proportional-hazards modeling will be used to identify strong
37 independent baseline candidate predictors for the primary outcome and secondary
38 outcome. We will use both forward and backward stepwise procedure to derive the
39 multivariable COX proportional-hazards model with $p < 0.05$ as the inclusion criterion.
40 Every variable in the model will be multiplied by its β -coefficient and the products
41 will be summed to calculate the risk score. Risk function will be used to estimate the
42 level of risk. The calculating formula is as follows.
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$$49 \quad P = h(t_j; X_k) = h_0(t_j) \exp(SCORE)$$

$$50 \quad SCORE = X_k \beta_k = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_p x_p$$

51 ***External validation***

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54 The dynamic prospective cases will be used for external validation of the optimal ML
55 and COX models. The validation will be performed using the models to calculate the
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3 probability of the outcome of interest occurring for each individual included in the
4 validation sample, when compared with the events actually observed to occur in this
5 sample. The discrimination of each model will be estimated by receiver-operating
6 characteristic (ROC) curve. The calibration of the models will be assessed by
7 Hosmer-Lemeshow goodness-of-fit test. The ML prediction model will be compared
8 with the COX regression model .
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16 **Patient and public involvement statement**

17 During the design of this study, a survey of patient requirements, including
18 communication needs, follow-up frequency, visit cost etc., was conducted in
19 population of potential HF participants, which provided important evidence for
20 drawing up this study protocol to meet most of the patients' needs, build close contact
21 with patients, enhance the overall adherence and improve the accuracy of endpoint
22 event. This study is not the patient-led research, patients are not involved in the
23 recruitment to and conduct of the study. The participants will be informed of the study
24 results by phone at the end of this study. The alive patients will be evaluated with the
25 new prediction model, and the ICD intervention will be recommended to the high
26 SCD risk patients.
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38 **Study time frame**

39 The retrospective data collection in the two sub-centers started in March 2017, and
40 prospective enrollment in all 14 sub-centers has started in January 2018. The
41 follow-up period is scheduled to end in December 2019. The major part of data
42 analysis will be performed from January to March 2020. The study framework and
43 process is summarized in Figure 3.
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49 Figure 3 Study framework and process
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52 **ETHICS AND DISSEMINATION**

53 The study protocol has been approved by the Ethics Committee of The First Affiliated
54 Hospital of Nanjing Medical University (2017-SR-06). All necessary information
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3 about this study will be disclosed to the patients. Every subject will be asked to sign
4 the ICF, indicating that they fully understand the study and voluntarily participate in
5 this study. All results of this study will be published in international peer-reviewed
6 journals and presented at relevant conferences.
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10 11 12 **STRENGTHS AND LIMITATIONS**

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14 This is the first retro-prospective, multicentre registry study in China, aimed to
15 investigate the feasibility and accuracy of applying ML to predict SCD in HF patients
16 with low LVEF. Except for SCD, a broad range of outcomes, including all-cause death,
17 lethal arrhythmia, sudden cardiac arrest, cardiopulmonary resuscitation and
18 rehospitalization due to HF, will be evaluated in this study, and the corresponding
19 prediction models will also be developed, if available. The traditional multivariable
20 COX regression model will be derived from the same database and will be compared
21 to machine learning. This project has great promise to improve ICD patient selection.
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29 The limitations of this study are as follows: 1. The SCD prediction of HF patients
30 with LVEF>35% will not be evaluated based on the design of this study. 2.
31 Sometimes, It might be difficult to determine the end point of this study for some
32 patients, when dealing with SCD, lethal arrhythmia and sudden cardiac arrest,
33 especially outside the hospital.
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40 **CONCLUSION**

41 This study is aimed to investigate the feasibility and accuracy of machine learning to
42 predict SCD in HF patients with low LVEF. By the completion of this study, it is
43 expected to derive and validate the new prediction models. Our study has promise to
44 improve selection of ICD candidates for primary prevention in HF patients.
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51 **FOOTNOTES**

52
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54 Southern Mississippi for providing machine learning techniques; Rongbin Yu,
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8 Hospital of Jiangsu University (Zhenjiang, China), Taixing People's Hospital (Taixing,
9 China), The First People's Hospital of Huaian (Huaian, China), The First People's
10 Hospital of Yancheng (Yancheng, China), Rugao People's Hospital (Rugao, China),
11 The First People's Hospital of Zhangjiagang (Zhangjiagang, China), The Third
12 People's Hospital of Suzhou (Suzhou, China), The Third People's Hospital of Wuxi
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15 The authors also thank the HF patients who participated in the survey of patient
16 requirements during the design of this study.

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29 **Contributors** JGZ and FQM conceived and designed the study. ZHZ, XFH, ZYQ,
30 YW, YHC, YLW, YZ, ZC, XWZ, JY, JLZ, JHG, KBL, LC, RJZ, HJ participated in
31 different phases of the protocol design. WHZ provide expertise on data processing
32 and machine learning. SWT and YYW provided their expertise for traditional
33 statistical analysis. JGZ obtained funding. FQM drafted the final manuscript. All
34 authors have read the manuscript and provided feedback. JGZ approved the final
35 version of the manuscript prior to submission. FQM took responsibility for the
36 submission process.

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Competing interests We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

Ethics approval This study has been approved by the Ethics Committee of The First Affiliated Hospital of Nanjing Medical University (2017-SR-06).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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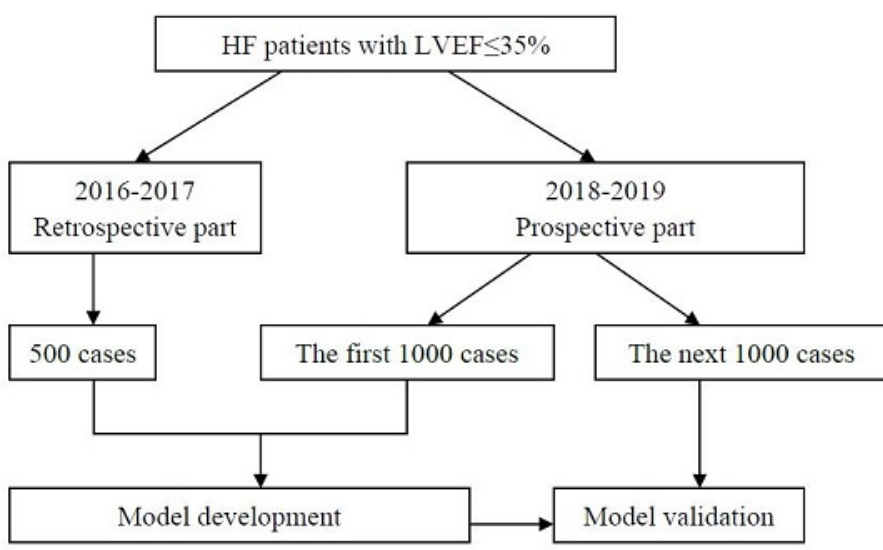
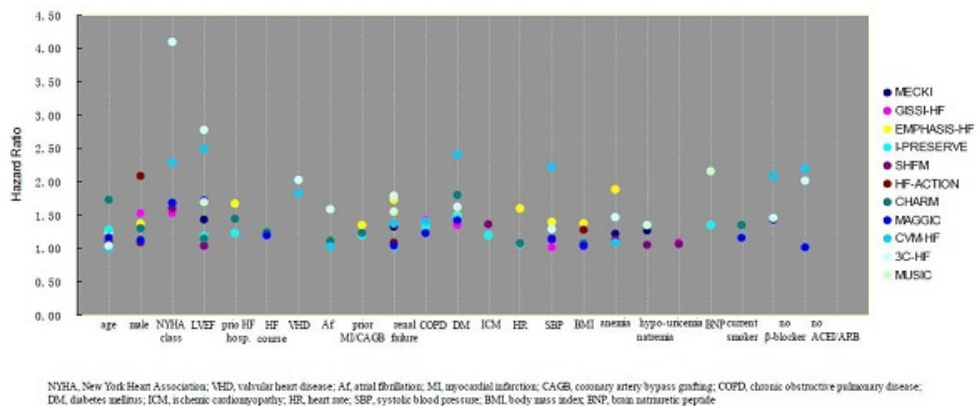


Figure 1 Flow diagram of progress

158x97mm (96 x 96 DPI)



NYHA, New York Heart Association; VHD, valvular heart disease; Af, atrial fibrillation; MI, myocardial infarction; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ICM, ischemic cardiomyopathy; HR, heart rate; SBP, systolic blood pressure; BMI, body mass index; BNP, brain natriuretic peptide

Figure 2 Hazard ratio of variables in different risk models

158x78mm (96 x 96 DPI)

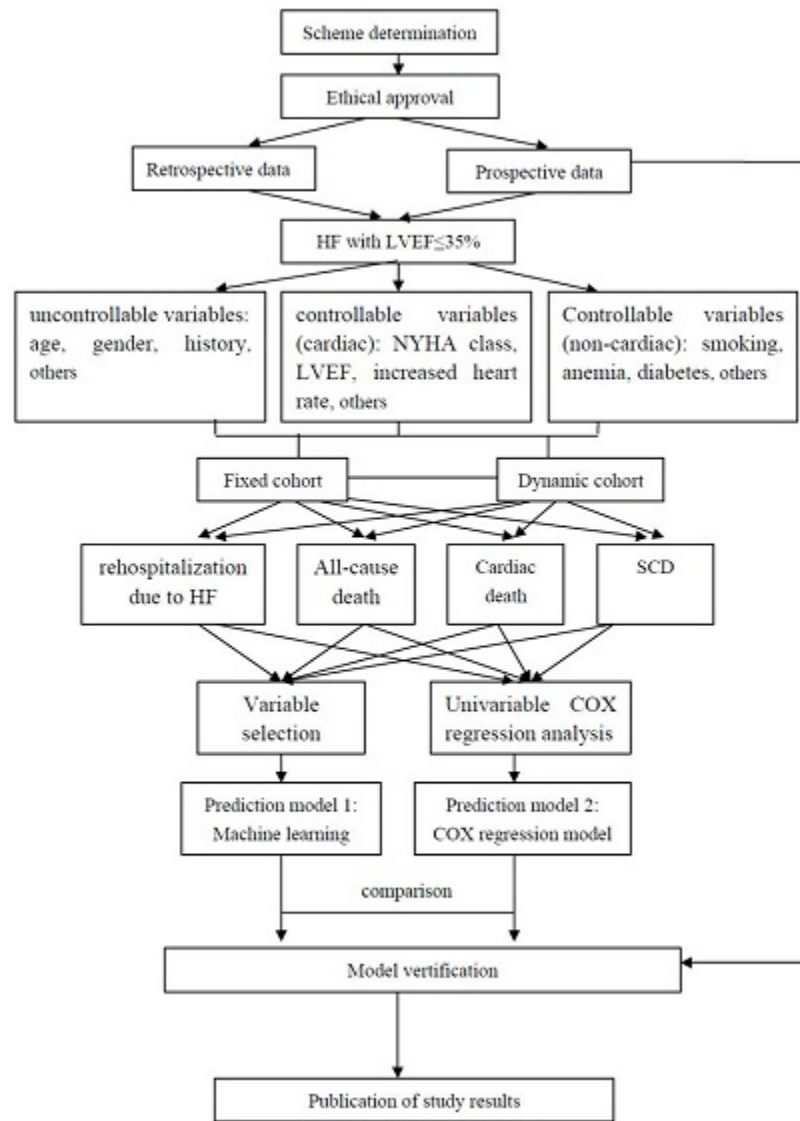


Figure 3 Study framework and process

76x101mm (150 x 150 DPI)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (P1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (P6)
	2b	All items from the World Health Organization Trial Registration Data Set (P6)
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support (P16)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (P1, P15-16)
	5b	Name and contact information for the trial sponsor (P1, P6)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities (P6, P15)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) (P6-7, P11)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (P3-P5)
	6b	Explanation for choice of comparators (P5)
Objectives	7	Specific objectives or hypotheses (P5-6)

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Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) (P6-7)
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Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained (P6)
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Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) (P7-P8)
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Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (Not applicable)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) (Not applicable)

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (Not applicable)
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	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial (Not applicable)
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Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended (P8)
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Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure1)
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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations (P6-7)
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Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size (P8)
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Methods: Assignment of interventions (for controlled trials)

Allocation:

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2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions (Not applicable)
8			
9	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
10	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
11	mechanism		describing any steps to conceal the sequence until interventions are
12			assigned (Not applicable)
13			
14	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
15			and who will assign participants to interventions (Not applicable)
16			
17	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
18	(masking)		participants, care providers, outcome assessors, data analysts), and
19			how (Not applicable)
20			
21		17b	If blinded, circumstances under which unblinding is permissible, and
22			procedure for revealing a participant's allocated intervention during
23			the trial (Not applicable)
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26 **Methods: Data collection, management, and analysis**

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28	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
29	methods		trial data, including any related processes to promote data quality (eg,
30			duplicate measurements, training of assessors) and a description of
31			study instruments (eg, questionnaires, laboratory tests) along with
32			their reliability and validity, if known. Reference to where data
33			collection forms can be found, if not in the protocol (P8-11)
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35		18b	Plans to promote participant retention and complete follow-up,
36			including list of any outcome data to be collected for participants who
37			discontinue or deviate from intervention protocols (P11-12)
38			
39	Data	19	Plans for data entry, coding, security, and storage, including any
40	management		related processes to promote data quality (eg, double data entry;
41			range checks for data values). Reference to where details of data
42			management procedures can be found, if not in the protocol (P11)
43			
44			
45	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
46	methods		Reference to where other details of the statistical analysis plan can be
47			found, if not in the protocol (P12-P14)
48			
49		20b	Methods for any additional analyses (eg, subgroup and adjusted
50			analyses) (Not applicable)
51			
52		20c	Definition of analysis population relating to protocol non-adherence
53			(eg, as randomised analysis), and any statistical methods to handle
54			missing data (eg, multiple imputation) (Not applicable)
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Methods: Monitoring

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| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct (P11) |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor |

Ethics and dissemination

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| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (P14) |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) (Not applicable) |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (P8) |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable (Not applicable) |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial (P11) |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site (P16) |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators (P11) |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation (Not applicable) |

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| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions (P14) |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers (Not applicable) |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code (Not applicable) |

16 Appendices

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| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates (see ICF) |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable (Not applicable) |

23 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013
24 Explanation & Elaboration for important clarification on the items. Amendments to the
25 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT
26 Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)"
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BMJ Open

Machine learning for prediction of sudden cardiac death in heart failure patients with low left ventricular ejection fraction: study protocol for a retro-prospective multicenter registry in China

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Manuscripts

Machine learning for prediction of sudden cardiac death in heart failure patients with low left ventricular ejection fraction: study protocol for a retro-prospective multicenter registry in China

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Keywords: heart failure, sudden cardiac death, machine learning, risk model

ABSTRACT

Introduction

Left ventricular ejection fraction (LVEF) $\leq 35\%$, as current significant implantable cardioverter-defibrillator (ICD) indication for primary prevention of sudden cardiac death (SCD) in heart failure (HF) patients, has been widely recognized to be inefficient. Improvement of patient selection for low LVEF ($\leq 35\%$) is needed to optimize deployment of ICD. Most of the existing prediction models are not appropriate to identify ICD candidates at high risk of SCD in HF patients with low LVEF. Compared to traditional statistical analysis, machine learning (ML) can employ computer algorithms to identify patterns in large datasets, analyze rules automatically and build both linear and non-linear models in order to make data-driven predictions. This study is aimed to develop and validate new models using ML to improve the prediction of SCD in HF patients with low LVEF.

Methods and analysis

We will conduct a retro-prospective, multi-center, observational registry of Chinese HF patients with low LVEF. The HF patients with LVEF $\leq 35\%$ after optimized medication at least 3 months will be enrolled in this study. The primary endpoints are all-cause death and SCD. The secondary endpoints are malignant arrhythmia, sudden cardiac arrest, cardiopulmonary resuscitation and rehospitalization due to HF. The baseline demographic, clinical, biological, electrophysiological, social and psychological variables will be collected. Both ML and traditional multivariable COX proportional hazards regression models will be developed and compared in the prediction of SCD. Moreover, the ML model will be validated in a prospective study.

Ethics and dissemination

The study protocol has been approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (2017-SR-06). All results of this study will be

published in international peer-reviewed journals and presented at relevant conferences.

Clinical trial registration ChiCTR-POC-17011842.

Strengths and limitations of this study

- This study is the first multicenter registry study in China, aimed to investigate the feasibility and accuracy of applying ML to predict SCD in HF patients with low LVEF.
- A broad range of outcomes, including SCD, all-cause death, lethal arrhythmia, sudden cardiac arrest, cardiopulmonary resuscitation and rehospitalization due to HF, will be evaluated in this study, and the corresponding prognostic models will be developed.
- Machine learning and the traditional multivariable COX proportional hazards regression model will be derived from the same database and be compared.
- HF patients with LVEF>35% will not be included based on the design of this study, which will restrict the application of the results of this study to the HF with low LVEF,
- It might be difficult to determine the endpoint of this study sometimes for some patients, when dealing with SCD, lethal arrhythmia and sudden cardiac arrest, especially when outside the hospital.

INTRODUCTION

Heart failure (HF), has become a major public health problem with increased prevalence in both Asia and Western countries. The prevalence of HF in Asia is 1.2%-6.7% depending on the population studied.^[1] In China, there are 4.2 million HF patients, and 500,000 new cases are being diagnosed each year.^[1] Although the survival rate after HF diagnosis has been increased due to improvement in medical therapy, the mortality of HF remains high. Around 50% of people diagnosed with HF will die within 5 years.^[2] The two most common causes of death in patients with HF are sudden cardiac death (SCD) and progressive pump failure. SCD in HF patients is usually caused by lethal arrhythmias such as ventricular tachycardia or ventricular fibrillation, and is reported to be responsible for nearly 50% of all cardiovascular death in HF patients.^[3, 4]

The most effective strategy for prevention of SCD in patients with HF is the implantable cardioverter-defibrillator (ICD), associated with 54% relative risk reduction in primary prevention^[5], and 50% relative risk reduction in arrhythmia-related death in secondary prevention.^[6] There is a higher risk of SCD in patients with LVEF \leq 35% than with LVEF $>$ 35%.^[7] At present, left ventricular ejection fraction (LVEF) \leq 35% is the major ICD indication for primary prevention of SCD.^[8] However, real-world data show that only 3% to 5% of ICD patients for primary prevention with LVEF \leq 35% receive shock therapies on an annual basis,^[9] whereas some SCD victims have LVEF $>$ 35%.^[10, 11] Identifying the patients who will be most likely to benefit from primary prevention ICD, is urgently needed. Based on the latest literature, LVEF \leq 35% is still an independent predictor of all-cause and cardiovascular mortality in chronic systolic HF, and displays a

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4 better combination of sensitivity and specificity than 40% cut-off.^[12] Finding ways to
5 evaluate the SCD risk in patients with lower EF will be more efficient and economically
6 significant. Furthermore, a noticeable decline in the rate of SCD for HF patients with
7 reduced LVEF has been observed, which was consistent with the cumulative benefit of
8 optimizing medication including angiotensin converting enzyme inhibitor (ACEI) or
9 angiotensin receptor blocker (ARB), beta-blocker, and mineralocorticoid receptor
10 antagonist (MRAs).^[13] Therefore, it is imperative to update the criterion for ICD
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19 Over the last decade, lots of multivariate prognostic models derived for chronic HF
20 patients have been proposed (Table 1).^[14-25] However, these models are not appropriate to
21 identify ICD candidates at high risk of SCD in HF patients with low LVEF. Most above
22 prognostic scores were developed from trial databases, and the subjects included various
23 types of heart failure. There is no specific study for the prognosis of low LVEF
24 population. Additionally, although all the scores are “not parsimonious”, some critical
25 factors are not incorporated into the prognostic models, for example, medications are
26 contained in I-PRESERVE^[17], MAGGIC^[21] and 3C-HF^[23]. Optimized medication was
27 not required as inclusion criteria in all 12 studies. Furthermore, the most above
28 prognostic models are not able to predict SCD risk. In recent years, the advances in strain
29 echocardiography^[26, 27], cardiac magnetic resonance^[26, 27] and cardiac radionuclide
30 imaging^[28, 29] have provided essential insights into the mechanisms of ventricular
31 arrhythmias, and have been recommended to predict the SCD in patients with HF.
32 Although these new methods are effective and noninvasive, the widespread use in large
33 HF population to predict SCD is difficult, due to high equipment and technical
34 requirements. Resting 12-lead ECG and Holter, as the longest surviving, broadly
35 available, quickly deployed and inexpensive tests, can provide a measure of cumulative
36 electrical risk, which may be combined with other factors to improve the SCD risk
37 prediction.^[30]
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4 Based on above reasons, the novel risk assessment tools should meet the following
5 requirements: (1) the risk model should be developed from the population with low
6 LVEF ($\leq 35\%$) to accelerate its clinical application and promote the accuracy of ICD
7 indications for primary prevention. (2) More cardiac and non-cardiac factors beyond
8 LVEF should be included. (3) Electrical risk factors should be included as candidate
9 predictors to evaluate the risk of sudden arrhythmic death. (4) Although sometimes it is
10 not easy to determine the cause of death, SCD as the primary endpoint should be defined
11 whenever possible.
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19 Data processing is the crucial step to develop the prognostic models. This study
20 involves non-linear prediction models, a large number of patients and numerous
21 predictors with complicated correlations. Traditional hypothesis-driven statistical analysis
22 is difficult to overcome these challenges. The machine learning (ML) approaches have
23 great potential to improve the solution. They employ computer algorithms to identify
24 patterns in large datasets with a large number of variables, analyze rules automatically
25 and build both linear and non-linear models in order to make data-driven predictions or
26 decisions.^[31] Weng et al. ^[32] found that ML significantly improved the accuracy of
27 cardiovascular risk prediction, increased the number of patients who could benefit from
28 preventive treatment and avoided unnecessary treatment. Recent studies have shown that
29 the application of machine learning techniques may have the potential to improve heart
30 failure outcomes and management, including cost savings by improving existing
31 diagnostic and treatment support systems.^[33] However, ML has not been reported to be
32 applied to SCD risk prediction based on large HF population. Therefore, the application
33 of ML for the prediction of SCD in HF patients with low LVEF is technically innovative
34 and clinically significant.
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52 AIMS

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54 The purpose of our study is to develop and validate new models to improve the prediction
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of SCD in HF patients with low LVEF. The new strategies of identifying HF patients most likely to benefit from primary prevention ICD will improve the revolution of ICD indications. The specific research objective is to develop prediction models to evaluate prognosis and SCD risk respectively by ML methods and traditional COX proportional hazard regression in HF patients with low LVEF ($\leq 35\%$).

METHODS AND ANALYSIS

Study design

This study is a retro-prospective, multi-center, non-interventional, observational clinical registry. The primary sponsor is The First Affiliated Hospital of Nanjing Medical University. This study has been registered in the Chinese Clinical Trial Registry (ChiCTR-POC-17011842). The study will be conducted across 14 cardiovascular departments in Tertiary A hospitals throughout the People's Republic of China. (see Supplement)

The cases from January 2016 to December 2017 in the First Affiliated Hospital of Nanjing Medical University and Xiamen Cardiovascular Hospital Xiamen University will be collected retrospectively and followed-up prospectively. About 500 retrospective cases meet the inclusion criteria according to preliminary estimation. The prospective recruitment has started in the above 14 hospitals since January 2018. The retrospective cases and the first 1000 prospective cases will be used to develop the prediction models. And the next 1000 prospective cases will be used for model validation. The flow diagram of the progress is illustrated in Figure 1.

Inclusion criteria

To participate in this study, patients must comply with all of the following

1. Diagnosis of HF_rEF according to the 2016 ESC HF Guideline^[8]
2. LVEF $\leq 35\%$ (measured by Simpson's methods) after optimized medication including

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4 ACEI or ARB, beta-blocker and MRA if available and not contraindicated at least 3
5 months.

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7 3. Signed informed consent.
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10 11 **Exclusion criteria**

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13 The patient with any of the following will be excluded:
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- 15 1. Hypertrophic cardiomyopathy
- 16 2. Rheumatic heart disease
- 17 3. Congenital heart disease
- 18 4. Pulmonary heart disease
- 19 5. Pericardial diseases and myocarditis
- 20 6. Acute myocardial infarction in recent 3 months, including STEMI and NSTEMI
- 21 7. Aortic dissection
- 22 8. Severe hematologic disease including leukemia, lymphoma, aplastic anemia, etc.
- 23 9. Autoimmune disease
- 24 10. Malignant tumor
- 25 11. Hormone replacement
- 26 12. Application of other interventional clinical trials
- 27 13. Non-drug therapies for improving heart function: CRT-P/D, ICD, heart
28 transplantation, surgical resection of ventricular aneurysm, interventional left ventricular
29 restoration with Revivent^(TM) / Parachute^(TM) system), MitraClip therapy for recurrent
30 mitral regurgitation

31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 **Endpoints**

50 51 ***Primary endpoint***

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53 All-cause death and SCD, including cardiac death and death from other causes

54 55 ***Secondary endpoint***

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4 Lethal arrhythmia, sudden cardiac arrest, cardiopulmonary resuscitation, rehospitalization
5 due to HF
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9 **Recruitment and consent**

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11 Participants will be identified and recruited at each of the participating centers. The
12 clinical status of potential participants will be assessed, and their medical records will
13 also be reviewed to confirm the eligibility according to the inclusion and exclusion
14 criteria.
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19 The study details will be explained to all potentially eligible and interesting subjects.
20 The patients who agree to attend this study will sign the informed consent form (ICF)
21 indicating that they fully understand the study and their rights of confidentiality and
22 withdrawal from the study without giving a reason.
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29 **Baseline evaluation**

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31 Prognostic models of HF in the last 10 years have been reviewed, and the associated risk
32 factors have been ranked according to their corresponding hazard ratio in respective risk
33 models (Table 1, Figure 2). Age, sex, New York Heart Association (NYHA) class, LVEF,
34 prior HF hospitalization, course of HF, severe valvular heart disease, atrial fibrillation,
35 prior myocardial infarction / coronary artery bypass grafting (CABG), renal dysfunction,
36 chronic obstructive pulmonary disease (COPD), diabetes mellitus, ischemic etiology,
37 decreased systolic pressure, low body mass index (BMI), anemia, hyponatremia, high
38 N-terminal pro-brain natriuretic peptide (NT-proBNP), uricemia, current smoker were
39 included. Variables which were not listed in previous models but appear relevant to
40 higher risk of SCD in HF patients, and would therefore, merit consideration, including
41 syncope or pre-syncope, frequent premature ventricular beat, non-sustained ventricular
42 tachycardia, complete left bundle branch block (CLBBB), long QT interval, increased QT
43 dispersion. In addition, self-care ability, social support and psychological state including
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4 depression and anxiety, are also predictors for subsequent poor prognosis in HF patients.
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6 The above risk factors have been assessed and confirmed by an expert panel of
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8 cardiologists and statisticians and will be collected in this study particularly.

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10 The baseline data that will be collected in all eligible subjects are as follows.

- 11 ● Demographic characteristics: date of birth, gender, height and weight
- 12 ● Lifestyle behavior: smoking and drinking status
- 13 ● Vital signs: blood pressure and heart rate
- 14 ● NYHA class
- 15 ● Etiology of heart failure: The ischemic etiology will be confirmed if any following
16 point is met: a. prior myocardial infarction or revascularization history (coronary
17 artery bypass grafting, CABG / percutaneous coronary intervention, PCI); b. left main
18 or proximal segment of the left anterior descending artery stenosis $\geq 75\%$ showed by
19 coronary angiogram (CAG); c. at least two main coronary artery branches stenosis
20 $\geq 75\%$ showed by CAG. Otherwise, non-ischemic HF should be identified.
- 21 ● Prior HF hospitalization history: first HF hospitalization or not, times of prior HF
22 hospitalization, the course of HF (since the HF symptoms appear; if unavailable,
23 since the decreased EF was found).
- 24 ● Coronary heart disease history: myocardial infarction or angina history, CAG result,
25 revascularization history, recent angina.
- 26 ● Arrhythmia history: atrial fibrillation, atrial flutter, premature atrial contraction
27 (PAC), premature ventricular contraction (PVC), non-sustained VT (NSVT),
28 sustained VT (SVT), ventricular fibrillation, and some bradyarrhythmias.
- 29 ● Syncope or pre-syncope history
- 30 ● Cardiac arrest/ cardiopulmonary resuscitation history
- 31 ● Other histories: hypertension, diabetes mellitus, COPD, etc.
- 32 ● Echocardiography: LV end-diastolic volume (LVEDV), LV end-systolic volume
33 (LVESV) and LVEF measured by Simpson's method; Left atrial diameter, LV
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4 end-diastolic diameter (LVEDD) and LV end-systolic diameter (LVESD), pulmonary
5 artery systolic pressure. The status of valve regurgitation will be evaluated (0-none;
6 1-mild; 2-mild to moderate; 3-moderate; 4- severe)
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- 9 ● ECG: Left / right bundle branch block will be recorded. QRS duration and QT
10 interval will be tested, and QT dispersion will be calculated.
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- 12 ● Holter: total heartbeat of the whole day, minimum/ maximum/ average HR, onset of
13 PVC, PAC, NSVT, VT, atrial fibrillation/ flutter.
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- 15 ● Laboratory tests results: serum creatinine, blood urea nitrogen (BUN), serum sodium,
16 hemoglobin, Thyroid Stimulating Hormone (TSH), free triiodothyronine (FT3), free
17 thyroxine (FT4), NT-proBNP.
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- 19 ● Medication: ACEI/ARB 、 beta-blocker, aldosterone antagonist, diuretic, digoxin,
20 antiplatelet agent, anticoagulant, statin, calcium channel blocker, antiarrhythmics,
21 Ivabradine and angiotensin receptor blocker-neprilysin inhibitor (ARNI).
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- 23 ● Evaluation of self-care behavior and social support: 9-item European Heart Failure
24 Self-care Behavior Scale (9-EHFScBS)^[34] will be used to determine the self-care
25 levels in HF patients. Social Support Rating Scale (SSRS)^[35] will be used to evaluate
26 the social support condition in HF patients.
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- 28 ● Assessment of psychological status: Hamilton Depression Scale (HAMD) and
29 Hamilton Anxiety Scale (HAMA).
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- 31 ● Socioeconomic and educational status: marital status, educational status, monthly
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46 **Patient visits**

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48 After being enrolled in this research, all the subjects will be followed-up periodically in
49 the outpatient department or by telephone interview every 3 months. The compliance
50 with medications will be evaluated. As the primary endpoint, all-cause death and SCD
51 will be focused. Cause of death will be analyzed in detail. SCD is defined by the World
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4 Health Organization as unexpected death that occurs within 1 hour from the onset of new
5 or worsening symptoms (witnessed arrest) or, if unwitnessed, within 24h from when the
6 individual was last observed alive and asymptomatic^[36]. The lethal arrhythmia including
7 VT/VF, sudden cardiac arrest, cardiopulmonary resuscitation, and rehospitalization due
8 to HF will be recorded carefully.
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13 During follow-up, lethal arrhythmia will be recognized more precisely for patients who
14 receive ICD or CRT/D implantation, and will be recorded as an adverse event. The
15 patients, who receive CRT-P/D, heart transplantation, surgical resection of a ventricular
16 aneurysm, interventional left ventricular restoration with Revivent^(TM) / Parachute^(TM)
17 system), MitraClip therapy for recurrent mitral regurgitation, or some other non-drug
18 therapy to improve heart function, will be followed up as usual.
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27 **Data collection**

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29 In the prospective part, clinical data of subjects will be collected and filled in the
30 electrical data capture (EDC) system at baseline and particular follow-up visit. In the
31 retrospective part, the same baseline information, except for 9-EHFScBS, SSRS, HAMD,
32 HAMA questionnaires, will also be captured and input into the EDC system. The
33 following prospective visits (every three months) will be conducted regularly and will be
34 recorded in the EDC system. Investigators will record all the information of adverse
35 events (AE), study bias, withdrawal from the study or death in EDC system. In this study,
36 the participants will be identified by study codes, and their names will not appear in the
37 EDC system. All the personal information including contact information, medical record
38 and outcome, will not be revealed to any person who has not been authorized by a
39 principal investigator. Professional staffs are responsible for database management, data
40 maintenance and regular data backup. Data quality will be monitored regularly. The data
41 collection checklist is showed in Table 2.
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Data pre-processing

All above-collected variables, which might be predictors of all adverse prognosis of HF described in endpoint events, will be classified as uncontrollable variables (e.g. age, gender, history), controllable variables associated with heart (e.g. NYHA class, LVEF, increased heart rate) and controllable variables beyond heart (e.g. smoking, anemia, diabetes mellitus). Appropriate dummy variables will be used for binary variables and categorical variables, and quantitative variables will be fitted as a single continuous measurement (e.g. age, heart rate, NT-proBNP), unless there is clear evidence of nonlinearity. In order to create a practice simple risk score, some continuous variables will also be categorized into several groups according to both common clinical cut points and expert advice.

Machine learning

Variable selection is the process of selecting a subset of relevant variables for use in model construction, which can substantially reduce the abundant information and decrease the number of variables that are input to the prediction model. In this study, the technique named as “information gain ranking” will be used to select appropriate variables. Information gain represents the effectiveness of a variable based on entropy, which characterizes the unpredictability of a system. The information gain of a variable is evaluated as the entropy difference of the system when including and excluding this variable. Then the variables whose information gain scores are less than a threshold are considered to be insignificant and will be excluded from the prediction.

Prediction models for SCD in HF patients will be developed by the following classification algorithms respectively: decision trees, logistic regression, support vector machine, random forest, and artificial neural network. [29] The performance and general error estimation of these ML models will be assessed by 10-fold cross-validation. The dataset will be randomly divided into 10 equal folds. 9 folds will be used as the training

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4 set with the remaining one fold as the validation set. The validation results from 10
5 repeats will be combined to provide a measure of the overall performance. The prediction
6 models derived from the above classification algorithms above will be evaluated based on
7 the accuracy and interpretability. Finally, clinical experts and computer specialists will
8 discuss and choose the best model to predict the prognosis of SCD in HF patients and
9 then perform further validation with the prospective dataset.
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16 17 **COX proportional hazards regression**

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19 Univariable COX proportional hazards modeling will be used to identify strong
20 independent baseline candidate predictors for the primary and secondary outcomes. We
21 will use both forward and backward stepwise procedure to derive the multivariable COX
22 proportional hazards model with $p < 0.05$ as the inclusion criterion. Every variable in the
23 model will be multiplied by its β -coefficient, and the products will be summed to
24 calculate the risk score. Risk function will be used to estimate the level of risk. The
25 calculating formula is as follows.^[37]
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$$32 \quad P = h(t_j; X_k) = h_0(t_j) \exp(SCORE)$$

$$33 \quad SCORE = X_k \beta_k = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_p x_p$$

34 35 36 37 38 **Model validation**

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40 The dynamic prospective cases will be used for external validation of the optimal ML and
41 COX proportional hazards models. The validation will be performed using the models to
42 calculate the probability of the outcome of interest occurring for each individual included
43 in the validation sample when compared with the events actually observed to occur in this
44 sample. The discrimination of each model will be estimated by receiver-operating
45 characteristic (ROC) curve. The calibration of the models will be assessed by the
46 Hosmer-Lemeshow goodness-of-fit test. The ML prediction model will be compared with
47 the COX proportional hazards regression model.
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Patient and public involvement statement

During the design of this study, a survey of patient requirements, including communication needs, follow-up frequency, visit cost etc., was conducted in population of potential HF participants, which provided important evidence for drawing up this study protocol to meet most of the patients' needs, build close contact with patients, enhance the overall adherence and improve the accuracy of endpoint event. This study is not a patient-led research, and patients are not involved in the recruitment of the study. The study results will be informed to the participants by phone at the end of this study. The alive patients will be evaluated with the new prediction model, and the ICD intervention will be recommended to the high SCD risk patients.

Study timeframe

The retrospective data collection in the two sub-centers started in March 2017, and prospective enrollment in all 14 sub-centers has started in January 2018. The follow-up period is scheduled to end in December 2019. The major part of data analysis will be performed from January to March 2020. The study framework and process is summarized in Figure 3.

ETHICS AND DISSEMINATION

The study protocol has been approved by the Ethics Committee of The First Affiliated Hospital of Nanjing Medical University (2017-SR-06). All necessary information about this study will be disclosed to the patients. Every subject will be asked to sign the ICF, indicating that they fully understand the study and voluntarily participate in this study. All results of this study will be published in international peer-reviewed journals and presented at relevant conferences.

DISCUSSION

The evaluation of SCD risk in HF patients is a problem that urgently needed to be solved. The existing prediction strategies for the SCD risk in HF patients lack clinical practice value for various reasons. ICD indication for primary prevention of SCD could be optimized by identifying the high SCD risk patients in HF with low LVEF ($\leq 35\%$). It is of great practical value and economic significance.

We reviewed some predictive studies of HF in the past years and ranked the risk factors according to their corresponding hazard ratio, which have been included in our study as candidate risk factors. Otherwise, some other variables which appear relevant to risk of SCD in HF patients are also collected. Therefore, the efficiency and practicality of predictive model development has been highly improved.

This study is the first multicenter registry study in China, aimed to investigate the feasibility and accuracy of applying ML to predict SCD in HF patients with low LVEF. A broad range of outcomes, including SCD, all-cause death, lethal arrhythmia, sudden cardiac arrest, cardiopulmonary resuscitation and rehospitalization due to HF, will be evaluated in this study, and the corresponding prognostic models will be developed. Machine learning and the traditional multivariable COX proportional hazards regression model will be derived from the same database and will be compared.

The limitations of this study are as follows: 1. HF patients with LVEF $>35\%$ will not be included based on the design of this study, which will restrict the application of the results of this study to the HF with low LVEF. 2. It might be difficult to determine the endpoint of this study sometimes for some patients, when dealing with SCD, lethal arrhythmia and sudden cardiac arrest, especially when outside the hospital.

Table 1. The risk model for HF in the literature

Author	Database	Year	Variables (n)	Patients (n)	Endpoints
Agostoni ^[14]	MECKI	2012	6	2716	Cardiovascular death; urgent cardiac transplant
Barlera ^[15]	GISSI-HF	2013	14	6975	all-cause mortality

Collier ^[16]	EMPHASIS-HF	2013	10	2737	all-cause mortality
Komajda ^[17]	I-PRESERVE	2011	12	4128	all-cause mortality
Levy ^[18]	SHFM	2006	14	1125	Survival
O'Connor ^[19]	HF-ACTION	2012	4	2331	all-cause mortality
Pocock ^[20]	CHARM	2006	21	7599	all-cause mortality
Pocock ^[21]	MAGIC	2012	13	39372	all-cause mortality
Senni ^[22]	CVM-HF	2006	13	292	all-cause mortality
Senni ^[23]	3C-HF	2013	11	2016	all-cause mortality; urgent heart transplant (1year)
Vazquez ^[24]	MUSIC	2009	10	992	all-cause mortality; cardiac mortality; pump failure death, sudden death
Nicole ^[25]	BARDICHE-index	2017	8	1811	all-cause mortality; all-cause hospitalization; CHF-related hospitalization

Table 2 The checklist for data collection

Data collection	Baseline		regular visit	withdraw /death
	Retrospective cases	Prospective cases		
Informed consent	✓	✓		
Quantification verification (inclusion and exclusion)	✓	✓		
Baseline evaluation	✓	✓		
Medication	✓	✓		
Questionnaires 9-EHFScBS SSRS HAMD HAMA socioeconomic and educational status		✓		
Regular follow-up visit (every 3 months)			✓	
Survival state	✓		✓	✓
Adverse event		Once happen	✓	
Study bias		Once happen	✓	
Withdraw from the study		Once happen	✓	
Death		Once happen	✓	

Figure 1 Flow diagram of progress

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Figure 2 Hazard ratio of variables in different risk models

NYHA, New York Heart Association; VHD, valvular heart disease; Af, atrial fibrillation; MI, myocardial infarction; CAGB, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ICM, ischemic cardiomyopathy; HR, heart rate; SBP, systolic blood pressure; BMI, body mass index; BNP, brain natriuretic peptide

Figure 3 Study framework and process

FOOTNOTES

Acknowledgements The authors thank Xiamen Cardiovascular Hospital, Xiamen University (Xiamen, China), Wuhan Asia Heart Hospital (Wuhan, China), Jiangning Hospital Affiliated to Nanjing Medical University, (Nanjing, China), The Second People's Hospital of Lianyungang (Lianyungang, China), The Affiliated Hospital of Jiangsu University (Zhenjiang, China), Taixing People's Hospital (Taixing, China), The First People's Hospital of Huaian (Huaian, China), The First People's Hospital of Yancheng (Yancheng, China), Rugao People's Hospital (Rugao, China), The First People's Hospital of Zhangjiagang (Zhangjiagang, China), The Third People's Hospital of Suzhou (Suzhou, China), The Third People's Hospital of Wuxi (Wuxi, China), The Second Affiliated Hospital of Nanjing Medical University (Nanjing, China) for collaboration including recruitment and follow-up of HF patients. The authors also thank the HF patients who participated in the survey of patient requirements during the design of this study.

Contributors JGZ and FQM conceived and designed the study. ZHZ, XFH, ZYQ, YW, YHC, YLW, YZ, ZC, XWZ, JY, JLZ, JHG, KBL, LC, RJZ, HJ participated in different phases of the protocol design. WHZ provide expertise in data processing and machine learning. SWT and YYW provided their expertise for traditional statistical analysis. JGZ obtained funding. FQM drafted the final manuscript. All authors have read the manuscript and provided feedback. JGZ approved the final version of the manuscript before submission. FQM took responsibility for the submission process.

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Competing interests We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

Ethics approval This study has been approved by the Ethics Committee of The First Affiliated Hospital of Nanjing Medical University (2017-SR-06).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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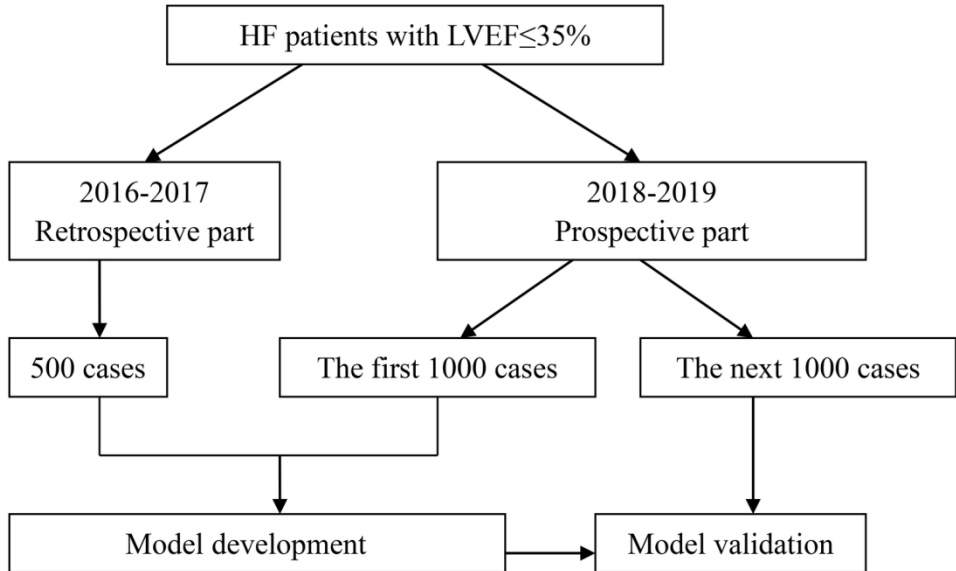


Figure 1 Flow diagram of progress

140x104mm (300 x 300 DPI)

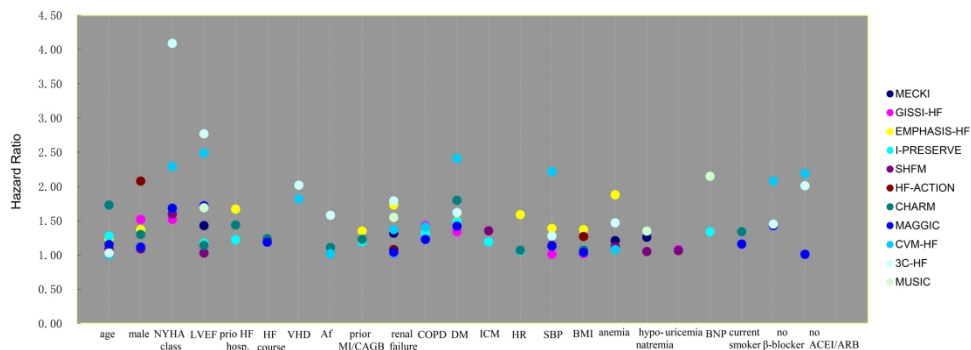


Figure 2 Hazard ratio of variables in different risk models
 NYHA, New York Heart Association; VHD, valvular heart disease; Af, atrial fibrillation; MI, myocardial infarction; CAGB, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ICM, ischemic cardiomyopathy; HR, heart rate; SBP, systolic blood pressure; BMI, body mass index; BNP, brain natriuretic peptide

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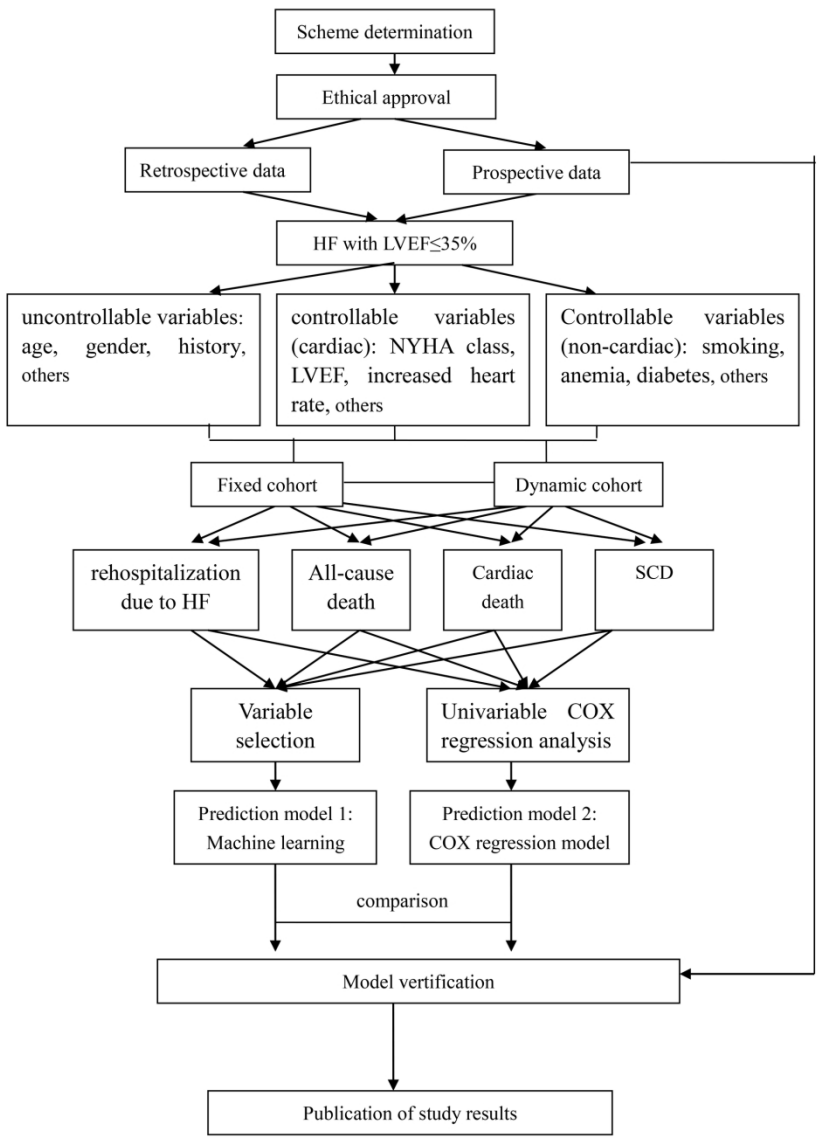


Figure 3 Study framework and process

158x226mm (300 x 300 DPI)

List of Hospitals

The First Affiliated Hospital of Nanjing Medical University, Nanjing

Xiamen Cardiovascular Hospital, Xiamen University, Xiamen

Wuhan Asia Heart Hospital, Wuhan

Jiangning Hospital Affiliated to Nanjing Medical University, Nanjing

The Second People's Hospital of Lianyungang, Lianyungang

The Affiliated Hospital of Jiangsu University, Zhenjiang

Taixing People's Hospital, Taixing

The First People's Hospital of Huaian, Huaian

The First People's Hospital of Yancheng, Yancheng

Rugao People's Hospital, Rugao

The First People's Hospital of Zhangjiagang, Zhangjiagang

The Third People's Hospital of Suzhou, Suzhou

The Third People's Hospital of Wuxi, Wuxi

The Second Affiliated Hospital of Nanjing Medical University, Nanjing



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (P1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (P7)
	2b	All items from the World Health Organization Trial Registration Data Set (P7)
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support (P17-18)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (P1, P17)
	5b	Name and contact information for the trial sponsor (P1, P7)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities (P7, P17)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) (P7, P11-12)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (P4-6)
	6b	Explanation for choice of comparators (P5-6)
Objectives	7	Specific objectives or hypotheses (P6)

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Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) (P6-7)
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Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained (P6-7)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) (P7-8)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (Not applicable)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) (Not applicable)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (Not applicable)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial (Not applicable)
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended (P8)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure1)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations (P7)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size (P8)

Methods: Assignment of interventions (for controlled trials)

Allocation:

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2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions (Not applicable)
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10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
12	mechanism		describing any steps to conceal the sequence until interventions are
13			assigned (Not applicable)
14			
15	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
16			and who will assign participants to interventions (Not applicable)
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19	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
20	(masking)		participants, care providers, outcome assessors, data analysts), and
21			how (Not applicable)
22			
23		17b	If blinded, circumstances under which unblinding is permissible, and
24			procedure for revealing a participant's allocated intervention during
25			the trial (Not applicable)
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Methods: Data collection, management, and analysis

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30	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
31	methods		trial data, including any related processes to promote data quality (eg,
32			duplicate measurements, training of assessors) and a description of
33			study instruments (eg, questionnaires, laboratory tests) along with
34			their reliability and validity, if known. Reference to where data
35			collection forms can be found, if not in the protocol (P8-12)
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38		18b	Plans to promote participant retention and complete follow-up,
39			including list of any outcome data to be collected for participants who
40			discontinue or deviate from intervention protocols (P11)
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42	Data	19	Plans for data entry, coding, security, and storage, including any
43	management		related processes to promote data quality (eg, double data entry;
44			range checks for data values). Reference to where details of data
45			management procedures can be found, if not in the protocol (P11-12)
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48	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
49	methods		Reference to where other details of the statistical analysis plan can be
50			found, if not in the protocol (P12-P14)
51			
52		20b	Methods for any additional analyses (eg, subgroup and adjusted
53			analyses) (Not applicable)
54			
55		20c	Definition of analysis population relating to protocol non-adherence
56			(eg, as randomised analysis), and any statistical methods to handle
57			missing data (eg, multiple imputation) (Not applicable)
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Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct (P11-12)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (P14)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) (Not applicable)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (P8)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable (Not applicable)
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial (P11-12)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site (P18)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators (P11-12)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation (Not applicable)

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| Dissemination
policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions (P14) |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers (Not applicable) |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code (Not applicable) |

16 Appendices

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|-------------------------------|----|--|
| Informed consent
materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates (see ICF) |
| Biological
specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable (Not applicable) |

25 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013
26 Explanation & Elaboration for important clarification on the items. Amendments to the
27 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT
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Machine learning for prediction of sudden cardiac death in heart failure patients with low left ventricular ejection fraction: study protocol for a retro-prospective multicenter registry in China

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4 **Machine learning for prediction of sudden cardiac death in heart**
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6 **failure patients with low left ventricular ejection fraction: study**
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9 **protocol for a retro-prospective multicenter registry in China**
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Keywords: heart failure, sudden cardiac death, machine learning, risk model

ABSTRACT

Introduction

Left ventricular ejection fraction (LVEF) $\leq 35\%$, as current significant implantable cardioverter-defibrillator (ICD) indication for primary prevention of sudden cardiac death (SCD) in heart failure (HF) patients, has been widely recognized to be inefficient. Improvement of patient selection for low LVEF ($\leq 35\%$) is needed to optimize deployment of ICD. Most of the existing prediction models are not appropriate to identify ICD candidates at high risk of SCD in HF patients with low LVEF. Compared to traditional statistical analysis, machine learning (ML) can employ computer algorithms to identify patterns in large datasets, analyze rules automatically and build both linear and non-linear models in order to make data-driven predictions. This study is aimed to develop and validate new models using ML to improve the prediction of SCD in HF patients with low LVEF.

Methods and analysis

We will conduct a retro-prospective, multi-center, observational registry of Chinese HF patients with low LVEF. The HF patients with LVEF $\leq 35\%$ after optimized medication at least 3 months will be enrolled in this study. The primary endpoints are all-cause death and SCD. The secondary endpoints are malignant arrhythmia, sudden cardiac arrest, cardiopulmonary resuscitation and rehospitalization due to HF. The baseline demographic, clinical, biological, electrophysiological, social and psychological variables will be collected. Both ML and traditional multivariable COX proportional hazards regression models will be developed and compared in the prediction of SCD. Moreover, the ML model will be validated in a prospective study.

Ethics and dissemination

The study protocol has been approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (2017-SR-06). All results of this study will be published in international peer-reviewed journals and presented at relevant conferences.

Clinical trial registration ChiCTR-POC-17011842.

Strengths and limitations of this study

- This study is the first multicenter registry study in China, aimed to investigate the feasibility and accuracy of applying ML to predict SCD in HF patients with low LVEF.
- A broad range of outcomes, including SCD, all-cause death, lethal arrhythmia, sudden cardiac arrest, cardiopulmonary resuscitation and rehospitalization due to HF, will be evaluated in this study, and the corresponding prognostic models will be developed.
- Machine learning and the traditional multivariable COX proportional hazards regression model will be derived from the same database and be compared.
- HF patients with LVEF>35% will not be included based on the design of this study, which will restrict the application of the results of this study to the HF with low LVEF,
- It might be difficult to determine the endpoint of this study sometimes for some patients, when dealing with SCD, lethal arrhythmia and sudden cardiac arrest, especially when outside the hospital.

INTRODUCTION

Heart failure (HF), has become a major public health problem with increased prevalence in both Asia and Western countries. The prevalence of HF in Asia is 1.2%-6.7% depending on the population studied.^[1] In China, there are 4.2 million HF patients, and 500,000 new cases are being diagnosed each year.^[1] Although the survival rate after HF diagnosis has been increased due to improvement in medical therapy, the mortality of HF remains high. Around 50% of people diagnosed with HF will die within 5 years.^[2] The two most common causes of death in patients with HF are sudden cardiac death (SCD) and progressive pump failure. SCD in HF patients is usually caused by lethal arrhythmias such as ventricular tachycardia or ventricular fibrillation, and is reported to be responsible for nearly 50% of all cardiovascular death in HF patients.^[3, 4]

The most effective strategy for prevention of SCD in patients with HF is the implantable cardioverter-defibrillator (ICD), associated with 54% relative risk reduction in primary prevention^[5], and 50% relative risk reduction in arrhythmia-related death in secondary prevention.^[6] There is a higher risk of SCD in patients with LVEF \leq 35% than with LVEF $>$ 35%.^[7] At present, left ventricular ejection fraction (LVEF) \leq 35% is the major ICD indication for primary prevention of SCD.^[8] However, real-world data show that only 3% to 5% of ICD patients for primary prevention with LVEF \leq 35% receive shock therapies on an annual basis,^[9] whereas some SCD victims have LVEF $>$ 35%.^[10, 11] Identifying the patients who will be most likely to benefit from primary prevention ICD, is urgently needed. Based on the latest literature, LVEF \leq 35% is still an independent predictor of all-cause and cardiovascular mortality in chronic systolic HF, and displays a better combination of sensitivity and specificity than 40% cut-off.^[12] Finding ways to evaluate the SCD risk in patients with lower EF will be more efficient and economically significant. Furthermore, a noticeable decline in the rate of SCD for HF patients with reduced LVEF has been observed, which was consistent with the cumulative benefit of optimizing medication including angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), beta-blocker, and mineralocorticoid receptor

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4 antagonist (MRAs).^[13] Therefore, it is imperative to update the criterion for ICD
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6 implantation

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8 Over the last decade, lots of multivariate prognostic models derived for chronic HF
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10 patients have been proposed (Table 1).^[14-25] However, these models are not
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12 appropriate to identify ICD candidates at high risk of SCD in HF patients with low
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14 LVEF. Most above prognostic scores were developed from trial databases, and the
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16 subjects included various types of heart failure. There is no specific study for the
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18 prognosis of low LVEF population. Additionally, although all the scores are “not
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20 parsimonious”, some critical factors are not incorporated into the prognostic models,
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22 for example, medications are contained in I-PRESERVE^[17], MAGGIC^[21] and
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24 3C-HF^[23]. Optimized medication was not required as inclusion criteria in all 12
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26 studies. Furthermore, the most above prognostic models are not able to predict SCD
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28 risk. In recent years, the advances in strain echocardiography^[26, 27], cardiac magnetic
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30 resonance^[26, 27] and cardiac radionuclide imaging^[28, 29] have provided essential
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32 insights into the mechanisms of ventricular arrhythmias, and have been recommended
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34 to predict the SCD in patients with HF. Although these new methods are effective and
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36 noninvasive, the widespread use in large HF population to predict SCD is difficult,
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38 due to high equipment and technical requirements. Resting 12-lead ECG and Holter,
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40 as the longest surviving, broadly available, quickly deployed and inexpensive tests,
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42 can provide a measure of cumulative electrical risk, which may be combined with
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44 other factors to improve the SCD risk prediction.^[30]

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46 Based on above reasons, the novel risk assessment tools should meet the following
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48 requirements: (1) the risk model should be developed from the population with low
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50 LVEF ($\leq 35\%$) to accelerate its clinical application and promote the accuracy of ICD
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52 indications for primary prevention. (2) More cardiac and non-cardiac factors beyond
53
54 LVEF should be included. (3) Electrical risk factors should be included as candidate
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56 predictors to evaluate the risk of sudden arrhythmic death. (4) Although sometimes it
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58 is not easy to determine the cause of death, SCD as the primary endpoint should be
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60 defined whenever possible.

Data processing is the crucial step to develop the prognostic models. This study

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3 involves non-linear prediction models, a large number of patients and numerous
4 predictors with complicated correlations. Traditional hypothesis-driven statistical
5 analysis is difficult to overcome these challenges. The machine learning (ML)
6 approaches have great potential to improve the solution. They employ computer
7 algorithms to identify patterns in large datasets with a large number of variables,
8 analyze rules automatically and build both linear and non-linear models in order to
9 make data-driven predictions or decisions.^[31] Weng et al. ^[32] found that ML
10 significantly improved the accuracy of cardiovascular risk prediction, increased the
11 number of patients who could benefit from preventive treatment and avoided
12 unnecessary treatment. Recent studies have shown that the application of ML
13 techniques may have the potential to improve heart failure outcomes and management,
14 including cost savings by improving existing diagnostic and treatment support
15 systems.^[33] ML algorithms also have been applied to predict SCD in some recent
16 studies and results indicate their significant advantages for predicting SCD.^[34, 35]
17 However, more studies based on large-scale cohort are needed to evaluate ML for
18 prediction of SCD in HF patients. Therefore, the application of ML for the prediction
19 of SCD in HF patients with low LVEF is technically innovative and clinically
20 significant.

41 AIMS

42 The purpose of our study is to develop and validate new models to improve the
43 prediction of SCD in HF patients with low LVEF. The new strategies of identifying
44 HF patients most likely to benefit from primary prevention ICD will improve the
45 revolution of ICD indications. The specific research objective is to develop prediction
46 models to evaluate prognosis and SCD risk respectively by ML methods and
47 traditional COX proportional hazard regression in HF patients with low LVEF
48 ($\leq 35\%$).

58 METHODS AND ANALYSIS

59 Study design

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4 This study is a retro-prospective, multi-center, non-interventional, observational
5 clinical registry. The primary sponsor is The First Affiliated Hospital of Nanjing
6 Medical University. This study has been registered in the Chinese Clinical Trial
7 Registry (ChiCTR-POC-17011842). The study will be conducted across 14
8 cardiovascular departments in Tertiary A hospitals throughout the People's Republic
9 of China. (see Supplement)
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15 The cases from January 2016 to December 2017 in the First Affiliated Hospital of
16 Nanjing Medical University and Xiamen Cardiovascular Hospital Xiamen University
17 will be collected retrospectively and followed-up prospectively. About 500
18 retrospective cases meet the inclusion criteria according to preliminary estimation.
19 The prospective recruitment has started in the above 14 hospitals since January 2018.
20 The retrospective cases and the first 1000 prospective cases will be used to develop
21 the prediction models. And the next 1000 prospective cases will be used for model
22 validation. The flow diagram of the progress is illustrated in Figure 1.
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33 **Inclusion criteria**

34 To participate in this study, patients must comply with all of the following

- 35 1. Diagnosis of HFrEF according to the 2016 ESC HF Guideline^[8]
- 36 2. LVEF \leq 35% (measured by Simpson's methods) after optimized medication
37 including ACEI or ARB, beta-blocker and MRA if available and not contraindicated
38 at least 3 months.
- 39 3. Signed informed consent.
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48 **Exclusion criteria**

49 The patient with any of the following will be excluded:

- 50 1. Hypertrophic cardiomyopathy
- 51 2. Rheumatic heart disease
- 52 3. Congenital heart disease
- 53 4. Pulmonary heart disease
- 54 5. Pericardial diseases and myocarditis
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- 4 6. Acute myocardial infarction in recent 3 months, including STEMI and NSTEMI
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- 6 7. Aortic dissection
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- 8 8. Severe hematologic disease including leukemia, lymphoma, aplastic anemia, etc.
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- 10 9. Autoimmune disease
- 11
- 12 10. Malignant tumor
- 13
- 14 11. Hormone replacement
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- 16 12. Application of other interventional clinical trials
- 17
- 18 13. Non-drug therapies for improving heart function: CRT-P/D, ICD, heart
- 19 transplantation, surgical resection of ventricular aneurysm, interventional left
- 20 ventricular restoration with Revivent^(TM) / Parachute^(TM) system), MitraClip therapy
- 21 for recurrent mitral regurgitation
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28 **Endpoints**

29 ***Primary endpoint***

30 All-cause death and SCD, including cardiac death and death from other causes

31 ***Secondary endpoint***

32 Lethal arrhythmia, sudden cardiac arrest, cardiopulmonary resuscitation,
33 rehospitalization due to HF
34

35 **Recruitment and consent**

36 Participants will be identified and recruited at each of the participating centers. The
37 clinical status of potential participants will be assessed, and their medical records will
38 also be reviewed to confirm the eligibility according to the inclusion and exclusion
39 criteria.
40

41 The study details will be explained to all potentially eligible and interesting
42 subjects. The patients who agree to attend this study will sign the informed consent
43 form (ICF) indicating that they fully understand the study and their rights of
44 confidentiality and withdrawal from the study without giving a reason.
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Baseline evaluation

Prognostic models of HF in the last 10 years have been reviewed, and the associated risk factors have been ranked according to their corresponding hazard ratio in respective risk models (Table 1, Figure 2). Age, sex, New York Heart Association (NYHA) class, LVEF, prior HF hospitalization, course of HF, severe valvular heart disease, atrial fibrillation, prior myocardial infarction / coronary artery bypass grafting (CABG), renal dysfunction, chronic obstructive pulmonary disease (COPD), diabetes mellitus, ischemic etiology, decreased systolic pressure, low body mass index (BMI), anemia, hyponatremia, high N-terminal pro-brain natriuretic peptide (NT-proBNP), uricemia, current smoker were included. Variables which were not listed in previous models but appear relevant to higher risk of SCD in HF patients, and would therefore, merit consideration, including syncope or pre-syncope, frequent premature ventricular beat, non-sustained ventricular tachycardia, complete left bundle branch block (CLBBB), long QT interval, increased QT dispersion. In addition, self-care ability, social support and psychological state including depression and anxiety, are also predictors for subsequent poor prognosis in HF patients. The above risk factors have been assessed and confirmed by an expert panel of cardiologists and statisticians and will be collected in this study particularly.

The baseline data that will be collected in all eligible subjects are as follows.

- Demographic characteristics: date of birth, gender, height and weight
- Lifestyle behavior: smoking and drinking status
- Vital signs: blood pressure and heart rate
- NYHA class
- Etiology of heart failure: The ischemic etiology will be confirmed if any following point is met: a. prior myocardial infarction or revascularization history (coronary artery bypass grafting, CABG / percutaneous coronary intervention, PCI); b. left main or proximal segment of the left anterior descending artery stenosis $\geq 75\%$ showed by coronary angiogram (CAG); c. at least two main coronary artery branches stenosis $\geq 75\%$ showed by CAG. Otherwise, non-ischemic HF should be identified.

- Prior HF hospitalization history: first HF hospitalization or not, times of prior HF hospitalization, the course of HF (since the HF symptoms appear; if unavailable, since the decreased EF was found).
- Coronary heart disease history: myocardial infarction or angina history, CAG result, revascularization history, recent angina.
- Arrhythmia history: atrial fibrillation, atrial flutter, premature atrial contraction (PAC), premature ventricular contraction (PVC), non-sustained VT (NSVT), sustained VT (SVT), ventricular fibrillation, and some bradyarrhythmias.
- Syncope or pre-syncope history
- Cardiac arrest/ cardiopulmonary resuscitation history
- Other histories: hypertension, diabetes mellitus, COPD, etc.
- Echocardiography: LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV) and LVEF measured by Simpson's method; Left atrial diameter, LV end-diastolic diameter (LVEDD) and LV end-systolic diameter (LVESD), pulmonary artery systolic pressure. The status of valve regurgitation will be evaluated (0-none; 1-mild; 2-mild to moderate; 3-moderate; 4- severe)
- ECG: Left / right bundle branch block will be recorded. QRS duration and QT interval will be tested, and QT dispersion will be calculated.
- Holter: total heartbeat of the whole day, minimum/ maximum/ average HR, onset of PVC, PAC, NSVT, VT, atrial fibrillation/ flutter.
- Laboratory tests results: serum creatinine, blood urea nitrogen (BUN), serum sodium, hemoglobin, Thyroid Stimulating Hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), NT-proBNP.
- Medication: ACEI/ARB、 beta-blocker, aldosterone antagonist, diuretic, digoxin, antiplatelet agent, anticoagulant, statin, calcium channel blocker, antiarrhythmics, Ivabradine and angiotensin receptor blocker-neprilysin inhibitor (ARNI).
- Evaluation of self-care behavior and social support: 9-item European Heart Failure Self-care Behavior Scale (9-EHFScBS) ^[36] will be used to determine the self-care levels in HF patients. Social Support Rating Scale (SSRS)^[37] will be used to evaluate the social support condition in HF patients.

- Assessment of psychological status: Hamilton Depression Scale (HAMD) and Hamilton Anxiety Scale (HAMA).
- Socioeconomic and educational status: marital status, educational status, monthly income, sources of medical expenses, medical insurance

Patient visits

After being enrolled in this research, all the subjects will be followed-up periodically in the outpatient department or by telephone interview every 3 months. The compliance with medications will be evaluated. As the primary endpoint, all-cause death and SCD will be focused. Cause of death will be analyzed in detail. SCD is defined by the World Health Organization as unexpected death that occurs within 1 hour from the onset of new or worsening symptoms (witnessed arrest) or, if unwitnessed, within 24h from when the individual was last observed alive and asymptomatic^[38]. The lethal arrhythmia including VT/VF, sudden cardiac arrest, cardiopulmonary resuscitation, and rehospitalization due to HF will be recorded carefully.

During follow-up, lethal arrhythmia will be recognized more precisely for patients who receive ICD or CRT/D implantation, and will be recorded as an adverse event. The patients, who receive CRT-P/D, heart transplantation, surgical resection of a ventricular aneurysm, interventional left ventricular restoration with Revivent^(TM) / Parachute^(TM) system), MitraClip therapy for recurrent mitral regurgitation, or some other non-drug therapy to improve heart function, will be followed up as usual.

Data collection

In the prospective part, clinical data of subjects will be collected and filled in the electrical data capture (EDC) system at baseline and particular follow-up visit. In the retrospective part, the same baseline information, except for 9-EHFScBS, SSRS, HAMD, HAMA questionnaires, will also be captured and input into the EDC system. The following prospective visits (every three months) will be conducted regularly and will be recorded in the EDC system. Investigators will record all the information of

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4 adverse events (AE), study bias, withdrawal from the study or death in EDC system.
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6 In this study, the participants will be identified by study codes, and their names will
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8 not appear in the EDC system. All the personal information including contact
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10 information, medical record and outcome, will not be revealed to any person who has
11
12 not been authorized by a principal investigator. Professional staffs are responsible for
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14 database management, data maintenance and regular data backup. Data quality will be
15
16 monitored regularly. The data collection checklist is showed in Table 2.

17 18 19 **Data pre-processing**

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21 All above-collected variables, which might be predictors of all adverse prognosis of
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23 HF described in endpoint events, will be classified as uncontrollable variables (e.g.
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25 age, gender, history), controllable variables associated with heart (e.g. NYHA class,
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27 LVEF, increased heart rate) and controllable variables beyond heart (e.g. smoking,
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29 anemia, diabetes mellitus). Appropriate dummy variables will be used for binary
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31 variables and categorical variables, and quantitative variables will be fitted as a single
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33 continuous measurement (e.g. age, heart rate, NT-proBNP), unless there is clear
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35 evidence of nonlinearity. In order to create a practice simple risk score, some
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37 continuous variables will also be categorized into several groups according to both
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39 common clinical cut points and expert advice.

40 41 42 **Machine learning**

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44 Variable selection is the process of selecting a subset of relevant variables for use in
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46 model construction, which can substantially reduce the abundant information and
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48 decrease the number of variables that are input to the prediction model. In this study,
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50 the technique named as “information gain ranking” will be used to select appropriate
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52 variables. Information gain represents the effectiveness of a variable based on entropy,
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54 which characterizes the unpredictability of a system. The information gain of a
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56 variable is evaluated as the entropy difference of the system when including and
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58 excluding this variable. Then the variables whose information gain scores are less
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60 than a threshold are considered to be insignificant and will be excluded from the

prediction.

Prediction models for SCD in HF patients will be developed by the following classification algorithms respectively: decision trees, logistic regression, support vector machine, random forest, and artificial neural network. [29] The performance and general error estimation of these ML models will be assessed by 10-fold cross-validation. The dataset will be randomly divided into 10 equal folds. 9 folds will be used as the training set with the remaining one fold as the validation set. The validation results from 10 repeats will be combined to provide a measure of the overall performance. The prediction models derived from the above classification algorithms above will be evaluated based on the accuracy, sensitivities, specificities and the area under the Receiver operating characteristic curve. Finally, clinical experts and computer specialists will discuss and choose the best model to predict the prognosis of SCD in HF patients and then perform further validation with the prospective dataset.

COX proportional hazards regression

Univariable COX proportional hazards modeling will be used to identify strong independent baseline candidate predictors for the primary and secondary outcomes. We will use both forward and backward stepwise procedure to derive the multivariable COX proportional hazards model with $p < 0.05$ as the inclusion criterion. Every variable in the model will be multiplied by its β -coefficient, and the products will be summed to calculate the risk score. Risk function will be used to estimate the level of risk. The calculating formula is as follows.[39]

$$P = h(t_j; X_k) = h_0(t_j) \exp(SCORE)$$

$$SCORE = X_k \beta_k = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_p x_p$$

Model validation

The dynamic prospective cases will be used for external validation of the optimal ML and COX proportional hazards models. The validation will be performed using the models to calculate the probability of the outcome of interest occurring for each

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4 individual included in the validation sample when compared with the events actually
5 observed to occur in this sample. The discrimination of each model will be estimated
6 by receiver-operating characteristic (ROC) curve. The calibration of the models will
7 be assessed by the Hosmer-Lemeshow goodness-of-fit test. The ML prediction model
8 will be compared with the COX proportional hazards regression model.
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15 **Patient and public involvement statement**

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17 During the design of this study, a survey of patient requirements, including
18 communication needs, follow-up frequency, visit cost etc., was conducted in
19 population of potential HF participants, which provided important evidence for
20 drawing up this study protocol to meet most of the patients' needs, build close contact
21 with patients, enhance the overall adherence and improve the accuracy of endpoint
22 event. This study is not a patient-led research, and patients are not involved in the
23 recruitment of the study. The study results will be informed to the participants by
24 phone at the end of this study. The alive patients will be evaluated with the new
25 prediction model, and the ICD intervention will be recommended to the high SCD
26 risk patients.
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39 **Study timeframe**

40 The retrospective data collection in the two sub-centers started in March 2017, and
41 prospective enrollment in all 14 sub-centers has started in January 2018. The
42 follow-up period is scheduled to end in December 2019. The major part of data
43 analysis will be performed from January to June 2020. The study framework and
44 process is summarized in Figure 3.
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52 **ETHICS AND DISSEMINATION**

53 The study protocol has been approved by the Ethics Committee of The First Affiliated
54 Hospital of Nanjing Medical University (2017-SR-06). All necessary information
55 about this study will be disclosed to the patients. Every subject will be asked to sign
56 the ICF, indicating that they fully understand the study and voluntarily participate in
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4 this study. All results of this study will be published in international peer-reviewed
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6 journals and presented at relevant conferences.
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9 10 **DISCUSSION**

11 The evaluation of SCD risk in HF patients is a problem that urgently needed to be
12
13 solved. The existing prediction strategies for the SCD risk in HF patients lack clinical
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15 practice value for various reasons. ICD indication for primary prevention of SCD
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17 could be optimized by identifying the high SCD risk patients in HF with low LVEF
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19 ($\leq 35\%$). It is of great practical value and economic significance.
20

21 We reviewed some predictive studies of HF in the past years and ranked the risk
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23 factors according to their corresponding hazard ratio, which have been included in our
24
25 study as candidate risk factors. Otherwise, some other variables which appear relevant
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27 to risk of SCD in HF patients are also collected. Therefore, the efficiency and
28
29 practicality of predictive model development has been highly improved.
30

31 This study is the first multicenter registry study in China, aimed to investigate the
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33 feasibility and accuracy of applying ML to predict SCD in HF patients with low
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35 LVEF. A broad range of outcomes, including SCD, all-cause death, lethal arrhythmia,
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37 sudden cardiac arrest, cardiopulmonary resuscitation and rehospitalization due to HF,
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39 will be evaluated in this study, and the corresponding prognostic models will be
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41 developed. Machine learning and the traditional multivariable COX proportional
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43 hazards regression model will be derived from the same database and will be
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45 compared.
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47 The limitations of this study are as follows: 1. HF patients with LVEF $>35\%$ will
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49 not be included based on the design of this study, which will restrict the application of
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51 the results of this study to the HF with low LVEF. 2. It might be difficult to determine
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53 the endpoint of this study sometimes for some patients, when dealing with SCD,
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55 lethal arrhythmia and sudden cardiac arrest, especially when outside the hospital.
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Table 1. The risk model for HF in the literature

Author	Database	Year	Variables (n)	Patients (n)	Endpoints
Agostoni ^[14]	MECKI	2012	6	2716	Cardiovascular death; urgent cardiac transplant
Barlera ^[15]	GISSI-HF	2013	14	6975	all-cause mortality
Collier ^[16]	EMPHASIS-HF	2013	10	2737	all-cause mortality
Komajda ^[17]	I-PRESERVE	2011	12	4128	all-cause mortality
Levy ^[18]	SHFM	2006	14	1125	Survival
O'Connor ^[19]	HF-ACTION	2012	4	2331	all-cause mortality
Pocock ^[20]	CHARM	2006	21	7599	all-cause mortality
Pocock ^[21]	MAGGIC	2012	13	39372	all-cause mortality
Senni ^[22]	CVM-HF	2006	13	292	all-cause mortality
Senni ^[23]	3C-HF	2013	11	2016	all-cause mortality; urgent heart transplant (1year)
Vazquez ^[24]	MUSIC	2009	10	992	all-cause mortality; cardiac mortality; pump failure death, sudden death
Nicole ^[25]	BARDICHE-index	2017	8	1811	all-cause mortality; all-cause hospitalization; CHF-related hospitalization

Table 2 The checklist for data collection

Data collection	Baseline		regular visit	withdraw /death
	Retrospective cases	Prospective cases		
Informed consent	✓	✓		
Quantification verification (inclusion and exclusion)	✓	✓		
Baseline evaluation	✓	✓		
Medication	✓	✓		
Questionnaires 9-EHFScBS SSRS HAMD HAMA socioeconomic and educational status		✓		
Regular follow-up visit (every 3 months)			✓	
Survival state	✓		✓	✓
Adverse event	Once happen ✓			
Study bias	Once happen ✓			
Withdraw from the study	Once happen ✓			
Death	Once happen ✓			

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3 Figure 1 Flow diagram of progress
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6 Figure 2 Hazard ratio of variables in different risk models

7 NYHA, New York Heart Association; VHD, valvular heart disease; Af, atrial fibrillation; MI, myocardial
8 infarction; CAGB, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease;

9 DM, diabetes mellitus; ICM, ischemic cardiomyopathy; HR, heart rate; SBP, systolic blood pressure; BMI, body
10 mass index; BNP, brain natriuretic peptide
11
12

13
14 Figure 3 Study framework and process
15

16 FOOTNOTES

17
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20 Hospital Affiliated to Nanjing Medical University, (Nanjing, China), The Second
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22 Jiangsu University (Zhenjiang, China), Taixing People's Hospital (Taixing, China),
23 The First People's Hospital of Huaian (Huaian, China), The First People's Hospital of
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30 requirements during the design of this study.
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33
34 **Contributors** JGZ and FQM conceived and designed the study. ZHZ, XFH, ZYQ,
35 YW, YHC, YLW, YZ, ZC, XWZ, JY, JLZ, JHG, KBL, LC, RJZ, HJ participated in
36 different phases of the protocol design. WHZ provide expertise in data processing and
37 machine learning. SWT and YYW provided their expertise for traditional statistical
38 analysis. JGZ obtained funding. FQM drafted the final manuscript. All authors have
39 read the manuscript and provided feedback. JGZ approved the final version of the
40 manuscript before submission. FQM took responsibility for the submission process.
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42

43
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15 **Competing interests** We have read and understood BMJ policy on declaration of
16 interests and declare that we have no competing interests.
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18

19 **Ethics approval** This study has been approved by the Ethics Committee of The First
20 Affiliated Hospital of Nanjing Medical University (2017-SR-06).
21
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23 **Provenance and peer review** Not commissioned; externally peer reviewed.
24

25 **Data sharing statement** No additional data are available.
26

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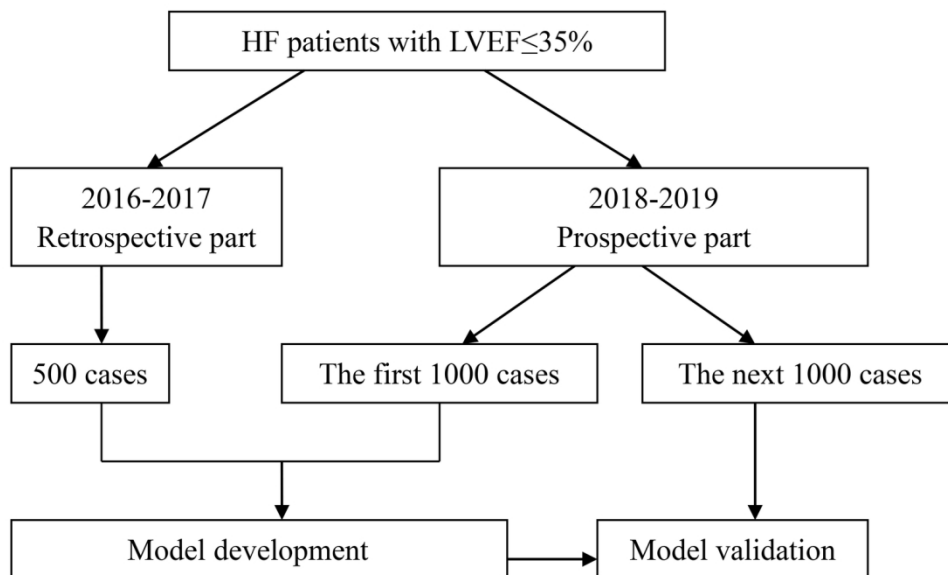


Figure 1 Flow diagram of progress

140x104mm (300 x 300 DPI)

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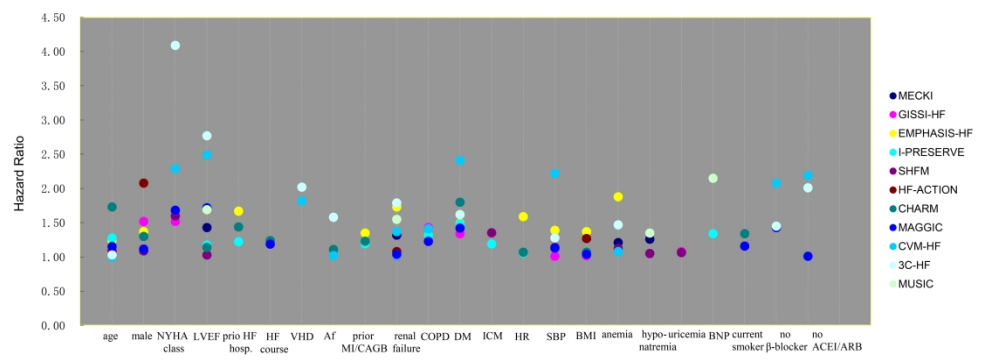


Figure 2 Hazard ratio of variables in different risk models
 NYHA, New York Heart Association; VHD, valvular heart disease; Af, atrial fibrillation; MI, myocardial infarction; CAGB, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ICM, ischemic cardiomyopathy; HR, heart rate; SBP, systolic blood pressure; BMI, body mass index; BNP, brain natriuretic peptide

325x126mm (300 x 300 DPI)

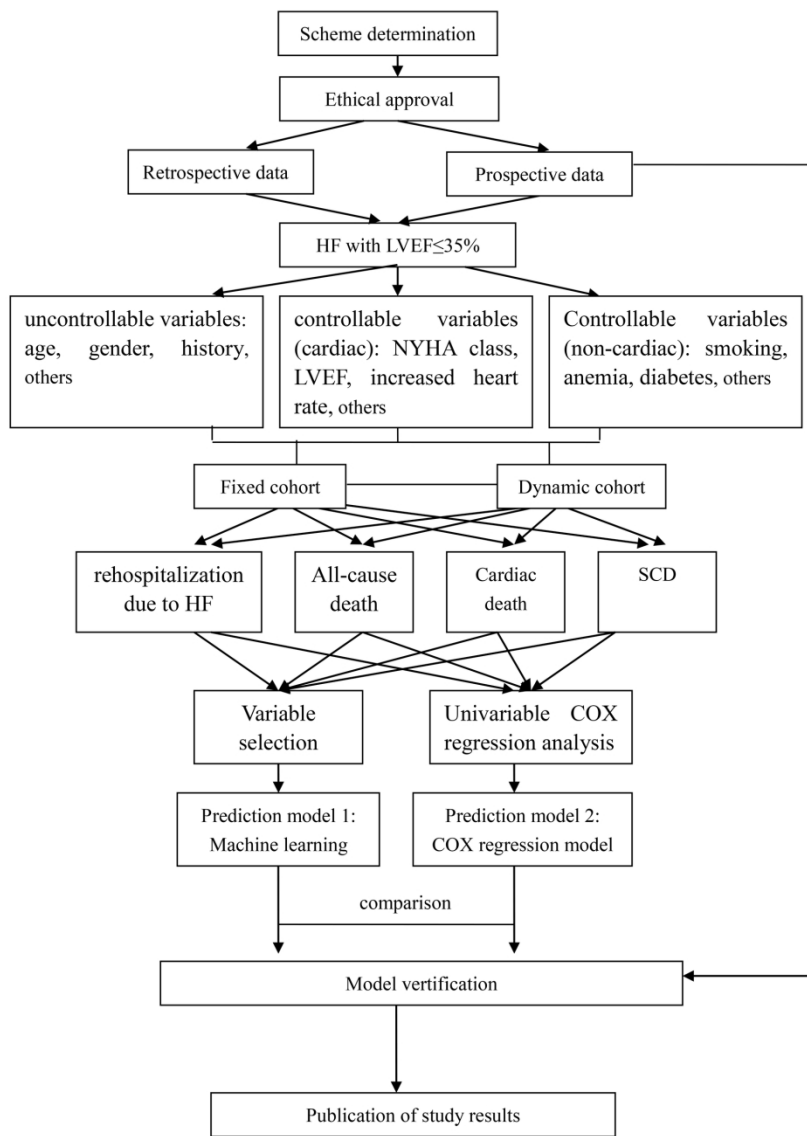


Figure 3 Study framework and process

158x226mm (300 x 300 DPI)

List of Hospitals

The First Affiliated Hospital of Nanjing Medical University, Nanjing

Xiamen Cardiovascular Hospital, Xiamen University, Xiamen

Wuhan Asia Heart Hospital, Wuhan

Jiangning Hospital Affiliated to Nanjing Medical University, Nanjing

The Second People's Hospital of Lianyungang, Lianyungang

The Affiliated Hospital of Jiangsu University, Zhenjiang

Taixing People's Hospital, Taixing

The First People's Hospital of Huaian, Huaian

The First People's Hospital of Yancheng, Yancheng

Rugao People's Hospital, Rugao

The First People's Hospital of Zhangjiagang, Zhangjiagang

The Third People's Hospital of Suzhou, Suzhou

The Third People's Hospital of Wuxi, Wuxi

The Second Affiliated Hospital of Nanjing Medical University, Nanjing



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (P1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (P7)
	2b	All items from the World Health Organization Trial Registration Data Set (P7)
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support (P17-18)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (P1, P17)
	5b	Name and contact information for the trial sponsor (P1, P7)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities (P7, P17)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) (P7, P11-12)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (P4-6)
	6b	Explanation for choice of comparators (P5-6)
Objectives	7	Specific objectives or hypotheses (P6)

1
2 Trial design 8 Description of trial design including type of trial (eg, parallel group,
3 crossover, factorial, single group), allocation ratio, and framework (eg,
4 superiority, equivalence, noninferiority, exploratory) **(P6-7)**
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8 **Methods: Participants, interventions, and outcomes**
9

10 Study setting 9 Description of study settings (eg, community clinic, academic hospital)
11 and list of countries where data will be collected. Reference to where
12 list of study sites can be obtained **(P6-7)**
13

14 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility
15 criteria for study centres and individuals who will perform the
16 interventions (eg, surgeons, psychotherapists) **(P7-8)**
17
18

19 Interventions 11a Interventions for each group with sufficient detail to allow replication,
20 including how and when they will be administered **(Not applicable)**
21
22 11b Criteria for discontinuing or modifying allocated interventions for a
23 given trial participant (eg, drug dose change in response to harms,
24 participant request, or improving/worsening disease) **(Not applicable)**
25

26 11c Strategies to improve adherence to intervention protocols, and any
27 procedures for monitoring adherence (eg, drug tablet return,
28 laboratory tests) **(Not applicable)**
29

30 11d Relevant concomitant care and interventions that are permitted or
31 prohibited during the trial **(Not applicable)**
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34 Outcomes 12 Primary, secondary, and other outcomes, including the specific
35 measurement variable (eg, systolic blood pressure), analysis metric
36 (eg, change from baseline, final value, time to event), method of
37 aggregation (eg, median, proportion), and time point for each
38 outcome. Explanation of the clinical relevance of chosen efficacy and
39 harm outcomes is strongly recommended **(P8)**
40
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42 Participant 13 Time schedule of enrolment, interventions (including any run-ins and
43 timeline washouts), assessments, and visits for participants. A schematic
44 diagram is highly recommended **(see Figure1)**
45

46 Sample size 14 Estimated number of participants needed to achieve study objectives
47 and how it was determined, including clinical and statistical
48 assumptions supporting any sample size calculations **(P7)**
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51 Recruitment 15 Strategies for achieving adequate participant enrolment to reach
52 target sample size **(P8)**
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54 **Methods: Assignment of interventions (for controlled trials)**
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56 Allocation:
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2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions (Not applicable)
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10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
12	mechanism		describing any steps to conceal the sequence until interventions are
13			assigned (Not applicable)
14			
15	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
16			and who will assign participants to interventions (Not applicable)
17			
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19	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
20	(masking)		participants, care providers, outcome assessors, data analysts), and
21			how (Not applicable)
22			
23		17b	If blinded, circumstances under which unblinding is permissible, and
24			procedure for revealing a participant's allocated intervention during
25			the trial (Not applicable)
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Methods: Data collection, management, and analysis

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30	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
31	methods		trial data, including any related processes to promote data quality (eg,
32			duplicate measurements, training of assessors) and a description of
33			study instruments (eg, questionnaires, laboratory tests) along with
34			their reliability and validity, if known. Reference to where data
35			collection forms can be found, if not in the protocol (P8-12)
36			
37			
38		18b	Plans to promote participant retention and complete follow-up,
39			including list of any outcome data to be collected for participants who
40			discontinue or deviate from intervention protocols (P11)
41			
42	Data	19	Plans for data entry, coding, security, and storage, including any
43	management		related processes to promote data quality (eg, double data entry;
44			range checks for data values). Reference to where details of data
45			management procedures can be found, if not in the protocol (P11-12)
46			
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48	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
49	methods		Reference to where other details of the statistical analysis plan can be
50			found, if not in the protocol (P12-P14)
51			
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53		20b	Methods for any additional analyses (eg, subgroup and adjusted
54			analyses) (Not applicable)
55			
56		20c	Definition of analysis population relating to protocol non-adherence
57			(eg, as randomised analysis), and any statistical methods to handle
58			missing data (eg, multiple imputation) (Not applicable)
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Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct (P11-12)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (P14)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) (Not applicable)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (P8)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable (Not applicable)
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial (P11-12)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site (P18)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators (P11-12)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation (Not applicable)

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| Dissemination
policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions (P14) |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers (Not applicable) |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code (Not applicable) |

16 Appendices

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| Informed consent
materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates (see ICF) |
| Biological
specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable (Not applicable) |

25 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013
26 Explanation & Elaboration for important clarification on the items. Amendments to the
27 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT
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