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ORIGINAL ARTICLE

Exploring the EVolution in PrognOstic CapabiLity of MUltisequence Cardiac MagneTIc ResOnance in PatieNts Affected by Takotsubo Cardiomyopathy Based on Machine Learning Analysis

Design and Rationale of the EVOLUTION Study

AQ2 *Riccardo Cau,* Giuseppe Muscogiuri,†‡ Francesco Pisu,* Marco Gatti,§ Birgitta Velthuis,‖ Christian Loewe,¶ Filippo Cademartiri,# Gianluca Pontone,** Roberta Montisci,†† Marco Guglielmo,‡‡ Sandro Sironi,†§§ Antonio Esposito,‖‖¶¶ Marco Francone,## Nicholas Dacher,*** Charles Peebles,††† Gorka Bastarrika,‡‡‡ Rodrigo Salgado,§§§ and Luca Saba, MD**

Purpose: Takotsubo cardiomyopathy (TTC) is a transient but severe acute myocardial dysfunction with a wide range of outcomes from favorable to life-threatening. The current risk stratification scores of TTC patients do not include cardiac magnetic resonance (CMR) parameters. To date, it is still unknown whether and how clinical, trans-thoracic echocardiography (TTE), and CMR data can be integrated to improve risk stratification.

Methods: EVOLUTION (Exploring the eVolution in prognOstic capabiLity of mUlti-sequence cardiac magneTIc resOnance in patieNts affected by Takotsubo cardiomyopathy) is a multicenter, international registry of TTC patients who will undergo a clinical, TTE, and CMR evaluation. Clinical data including demographics, risk factors, comorbidities, laboratory values, ECG, and results from TTE and CMR analysis will be collected, and each patient will be followed-up for in-hospital and long-term outcomes. Clinical outcome measures during hospitalization will include cardiovascular death, pulmonary edema, arrhythmias, stroke, or transient ischemic attack. Clinical long-term outcome measures will include cardiovascular death, pulmonary edema, heart failure, arrhythmias, sudden cardiac death, and major adverse cardiac and cerebrovascular events defined as a composite endpoint of death from any cause, myocardial infarction, recurrence of TTC, transient ischemic attack, and stroke. We will develop a comprehensive clinical and imaging score that predicts TTC outcomes and test the value of machine learning models, incorporating clinical and imaging parameters to predict prognosis.

Conclusions: The main goal of the study is to develop a comprehensive clinical and imaging score, that includes TTE and CMR data, in a large cohort of TTC patients for risk stratification and outcome prediction as a basis for possible changes in patient management.

Key Words: Takotsubo, cardiac magnetic resonance, machine learning, prognosis, risk stratification

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HIGHLIGHTS

- EVOLUTION (Exploring the eVolution in prognOstic capabiLity of mUlti-sequence cardiac magneTIc resOnance in patieNts affected by Takotsubo cardiomyopathy) is a retrospective, international registry of Takotsubo cardiomyopathy (TTC) patients.
- This study aims to improve risk stratification in TTC patients.
- Cardiac magnetic resonance (CMR)-derived morphologic and tissue characterization parameters may improve risk stratification and outcome prediction.
- Machine learning (ML) derived parameters may be useful in risk stratification and patient management.

BACKGROUND AND RATIONALE

TTC is an acute myocardial dysfunction with a wide range of outcomes from favorable to life-threatening.[1,2] Historically, TTC has been considered a benign condition with a prompt restoration of myocardial function and excellent outcome. However, a growing body of evidence demonstrates an occurrence of complications in about 52% of patients.[3]

Recent studies suggest that TTC may result in subclinical myocardial dysfunction with a persistent heart failure phenotype[4–6] and a similar in-hospital[7] and long-term adverse

From the Departments of *Radiology; ††Cardiology, Azienda Ospedaliero Universitaria, Monserrato (Cagliari); †School of Medicine and Surgery, University of Milano-Bicocca; ‡Department of Radiology, IRCCS Istituto Auxologico Italiano, San Luca Hospital; **IRCCS Centro Cardiologico Monzino; ‖‖Experimental Imaging Center, IRCCS San Raffaele Scientific Institute; ¶¶School of Medicine, Vita Salute San Raffaele University, Milan; §Department of Radiology, Università degli studi di Torino, Turin; #IRCCS SDN, Naples; §§Department of Radiology, ASST Papa Giovanni XXIII Hospital, Bergamo; ##Humanitas University, Pieve Emanuele, Italy; ‖University Medical Center Utrecht; ‡‡Department of Cardiology, Universitair Medisch Centrum, Utrecht, The Netherlands; ¶Medizinische Universität Wien, Vienna, Austria; ***Cardiac MR/CT Unit, Department of Radiology, Rouen University Hospital, Rouen, France; †††University Hospital Southampton NHS Foundation Trust, Southampton, UK; ‡‡‡Department of Radiology, Clinica Universidad de Navarra, Pamplona, Spain; and §§§ Universitair Ziekenhuis Antwerpen, Edegem, Belgium.

The authors declare no conflicts of interest.

Correspondence to: Luca Saba, MD, Department of Radiology, Azienda Ospedaliero Universitaria (A.O.U.), di Cagliari—Polo di Monserrato s.s. 554, Monserrato (Cagliari) 09045, Italy (e-mail: lucasaba@tiscali.it).

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outcomes[6] to myocardial infarction. Some papers have suggested different clinical and trans-thoracic echocardiography (TTE) variables associated with in-hospital complications.[3,8–11]

The recently published GEIST (German and Italian Stress Cardiomyopathy) multicenter prognostic study investigated a population of 1007 patients with TTC and developed a clinical prognostic score incorporating clinical and echocardiographic variables to stratify the risk of in-hospital complications.[8] The authors reported that left ventricle ejection fraction (LVEF) (odds ratio [OR], 0.93; 95% Cl, 0.92-0.95; $P < 0.001$), right ventricle (RV) involvement (OR, 2.66; 95% Cl, 1.70-4.18; $P < 0.001$), history of neurological disorders (OR, 2.44; 95% Cl, 1.61-3.68; $P < 0.001$), and male sex (OR, 2.46; 95% Cl, 1.61 -3.75; $P < 0.001$) were independent predictors of in-hospital complications.[8]

On the other hand, reports about the long-term prognosis of TTC are controversial.[12] The findings of a systematic review and meta-regression of 54 studies that included 4679 patients published by Francesco et al[12] identified 3 clinical and imaging factors, namely older age, physical stress, and atypical ballooning pattern, to be significantly associated with worse long-term outcomes.

Some diagnostic[13] and risk stratification scores[8,14] have been proposed in TTC patients that focused on solely clinical data or clinical and TTE parameters without considering CMR data.

To our knowledge, there is no prognostic score that incorporates CMR-based morphologic and tissue characterization parameters with clinical and TTE data.

As also stipulated in the ESC guidelines,[15] CMR is progressively gaining more and more importance in TTC patients[2,16–19] due to its unique ability to noninvasive evaluate myocardial tissue characteristics.[20–22]

In addition, CMR is an excellent alternative for functional analysis in patients with suboptimal echocardiography image quality.[23] In TTC, the presence, localization, and extension of late gadolinium enhancement (LGE) are associated with the severity of clinical findings and prolonged recovery in TTC.[24] Thomas et al[25] investigated the clinical and prognostic relevance of arrhythmias in 178 patients with TTC, reporting life-threatening arrhythmias in 13.5% of patients (24/178) with a higher prevalence of LGE on CMR (33.3% vs. 7.2%; $P = 0.04$) in patients who developed life-threatening arrhythmias, suggesting that diffuse fibrosis in patients with arrhythmias may reflect a substrate for malignant arrhythmias.

Similarly, various studies suggested a significant prognostic value of parametric edema quantification (assessed by T1 and T2 mapping) and diffuse interstitial fibrosis (assessed by T1 mapping).[5,26–28] Feature tracking CMR of all 4 cardiac chambers has also been shown to provide important information regarding risk stratification.[29–32] In a multicenter study of 152 patients with TTC, left atrial strain impairment was associated with overall mortality, even after statistical correction for traditional cardiovascular risk factors and LVEF.[29]

Therefore, we will develop a score that integrates CMR parameters to clinical and TTE data to potentially improve risk stratification and outcome prediction in TTC patients. In this regard, the EVOLUTION registry has been developed to determine and validate a comprehensive score based on clinical and imaging biomarkers that predict TTC outcomes.

Furthermore, this registry should test the value of ML models for the incorporation of clinical and imaging parameters to the determine outcome prognosis. This report describes the rationale, design, and methodology of the EVOLUTION registry.

METHODS

Study Design

EVOLUTION is a multicenter, international registry of TTC patients who will perform a clinical, TTE, and CMR evaluation. The registry will include data from sites in Europe, the United States, and Asia. According to the study design we aim to collect ~350 patients.

TTC Population

The target population of patients who will be eligible for enrolment in the EVOLUTION registry is composed of patients with a diagnosis of TTC fulfilling the criteria reported in the Position Statement of the European Society of Cardiology Heart Failure Association.[3] The above diagnostic criteria include regional wall motion abnormalities not limited to a single epicardial vascular distribution territory. The disease onset is usually preceded by a stressful trigger, culprit atherosclerotic coronary disease as assessed at invasive catheterization is usually absent, new ECG abnormalities are present, elevated serum natriuretic peptide, and a small increase in cardiac troponin are often detected. Left ventricle (LV) dysfunction full recovery is typically noted at follow-up.[3]

Patient Enrollment and Specific Diagnostic Procedure

Each site will screen consecutive TTC patients who underwent a clinically indicated TTE and CMR at baseline within 10 days of symptoms onset. The following clinical information will be collected: (1) demographics, (2) cardiovascular risk factors, (3) medical history, (4) triggers, (5) clinical presentation, (6) laboratory parameters, (7) ECG data, and (8) pharmacological therapy.

TTE will be performed with patients in left lateral decubitus in the parasternal (long-axis and short-axis) and apical (4, 2, and 3-chamber) views. For each patient the following measurements will be acquired and collected: LV end-diastolic and end-systolic volumes, LVEF calculated from the Simpson method, LV diastolic function in terms of traditional and Tissue Doppler-derived parameters.

The CMR data set will include functional sequences, such as cine bright blood steady-state free precession on the short axis and long axes (2, 3, and 4 chambers); and morphological and tissue characterization sequences, such as T2 short tau inversion recovery on both short and long axes and LGE acquisitions. Acquisition of precontrast and postcontrast T1 map, and T2 mapping is preferable but not mandatory. LGE imaging will be acquired 10 to 12 minutes after contrast media injection using magnitude-inversion recovery sequences acquired in both the short and long axis. The correct inversion time will be adjusted using the Look-Locker technique. See Table 1 for the CMR protocol.

CMR data are transferred to commercially available software for cardiac magnetic resonance imaging data analysis. The calculation of LV and RV volumetric parameters will be performed on cine images by a core lab following the recommendations of the Society of

TABLE 1. CMR Protocol

Sequence	Views	
Balanced steady-state free precession	Short axis and long axis (2-chamber view, 3-chamber view, and 4-chamber view)	Mandatory
T2 black blood	Short axis	Mandatory
Native T1 mapping	Short axis and at least 1 long-axis	Optional
T2 mapping	Short axis and at least 1 long-axis	Optional
Saturation recovery sequence (first pass-perfusion)	Short axis	Optional
Magnitude inversion recovery LGE	Short axis and long axis (2-chamber view, 3-chamber view, and 4-chamber view)	Mandatory
Postcontrast T1 mapping	Short axis and at least 1 long-axis	Optional

Cardiovascular Magnetic Resonance and European Association of Cardiovascular Imaging.[33,34]

Offline feature tracking CMR analyses will be conducted for evaluation of peak global longitudinal strain, global radial strain, and global circumferential strain in a 16-segment software-generated 2D model. Concerning global longitudinal strain, data on myocardial strain will be derived from 2, 3, and 4 chambers long-axis views. Regarding global radial strain and global circumferential strain, data on myocardial strain will be derived from apical, mid-ventricular, and basal short-axis views in all the patients. On all images, the epicardial and endocardial borders will be traced in end-diastole. After that, an automatic computation will be triggered, by which the applied software algorithm will be automatically outlined the border throughout the cardiac cycle. The quality of the tracking and contouring will be visually validated and manually corrected when needed.

Similarly, the left atrium (LA) and right atrium (RA) endocardial borders will be manually traced on a long axis view of the cine images when the atrium is at its minimum volume. In particular, the 4, 3, and 2-chamber views will be used to derive LA longitudinal strain. LA appendage and pulmonary veins will have to be excluded from segmentation. RA longitudinal strain will be based on the 4-chamber view only. After manual segmentation, the software automatically will track the myocardial borders throughout the entire cardiac cycle. The quality of the tracking and contouring will be visually validated and manually corrected by a radiologist with 3 years of experience in cardiac imaging. There are 3 peaks in the strain curve, including reservoir, conduit, and booster strain. Accordingly, their corresponding strain rate parameters will be included.

Inclusion and Exclusion Criteria

Inclusion criteria will be TTC (according to the Position Statement of the European Society of Cardiology Heart Failure Association[3]) in adult patients (age 18 y and older) and availability at baseline of clinical variables, standard TTE, and CMR acquisition.

Table 2 summarizes the inclusion and exclusion criteria of the study.

Study Objectives and Endpoints

The primary aim of the study is to identify, quantify, and integrate CMR data with demographic, clinical, and TTE parameters for the refinement of risk stratification in TTC patients. In particular, we will investigate CMR data and their correlation to in-hospital and long-term outcomes.

Table 3 and Table 4 summarizes the objectives and endpoints of the study.

Follow-up

In-hospital Outcomes

Local site personnel will screen consecutive TTC patients and collect the following in-hospital complications: death, pulmonary edema, cardiogenic shock, arrhythmias, stroke, and transient ischemic attack.

Long-term Outcomes

Similarly, dedicated personnel of each local institution will screen consecutive TTC patients and collect the following long-term complications in patients with a minimum follow-up period of 24 months: cardiovascular death, pulmonary edema, arrhythmias, heart failure, sudden cardiac death, and major adverse cardiac and cerebrovascular events (MACCE) defined as a composite endpoint of death from any cause, myocardial infarction, recurrence of TTC, transient ischemic attack, and stroke.

ML

All available CMR, TTE, and clinical variables will be used for the ML analysis. For this analysis, we will consider the composite endpoint MACCE to ensure that enough events will be available for model development, as ML-based analyses typically require more events as compared with classical statistical analyses.[35] Briefly, we will develop a risk model that will output patient-level future risk of MACCE (ie, probabilities from 0 to 1). Our pipeline will comprise missing data imputation based on a sparsity-aware k-nearest neighbors strategy, feature selection for selecting the subset of features with the highest prognostic value based on information gain criteria, model building using an ensemble of survival gradient-boosted trees and 10 repetitions of the 5-fold stratified cross-validation (CV) and repeated external site testing.

TABLE 2. Inclusion and Exclusion Criteria

Inclusion criteria	TTC (according to Position Statement of the European Society of Cardiology Heart Failure Association[3]) in adult patients (age $\geq$ 18 y)
	Availability at baseline of clinical variables, standard TTE, and CMR acquisition
Exclusion criteria	$<$ 18 y old
	Lack of TTE and CMR examinations
	Preexisting cardiomyopathies
	Previous myocardial infarction
	Suspected or known prior irreversible myocardial damage
	Valvular heart disease.

TABLE 3. Study Objectives

Primary objective	The primary aim of the study is to develop a comprehensive clinical and imaging score (incorporating TTE and CMR data) that improves risk stratification of TTC patients
Secondary objective	To investigate the diagnostic value of CMR parameters to predict in-hospital and long-term outcomes in TTC patients To compare the proposed risk stratification score of TTC patients with previous existing scores To investigate the contribution of machine learning model to predict in-hospital and long-term outcomes as compared with standard clinical score

Missing Data Imputation

Missing data (if any) will be imputed following a sparsity-aware k-nearest neighbors strategy. Briefly, missing values for a subject's feature will be replaced with the mean value from k-nearest subjects according to a similarity metric that supports missing values.

Feature Selection

We will use the information gain ratio to identify the subset of features with the highest prognostic value.[36,37] The information gain is a measure of a feature's impact on the model's predictions, with a value of zero indicating no impact. In greater detail, for each CV split, a second CV scheme will divide the outer training subset into inner training and validation subsets, fit a boosted ensemble on the training subset, and store feature rankings based on information gain. Finally, the union of the CV-derived feature subsets having an information gain ratio greater than zero will be used for model building.

Model Development

An ensemble of survival gradient-boosted trees for predicting individualized risk of MACCE at 2 years will be developed using the extreme gradient boosting (XGBoost) with survival embeddings framework.[38,39] Within this framework, the XGBoost algorithm will be used to build a binary classifier that identifies subjects (possibly right-censored) that experienced MACCE during follow-up by outputting a continuous score (from 0 to 1) which is interpreted as a risk score. During training the negative log-likelihood for the accelerated failure time model is minimized by sequentially fitting decision trees with different weights distributions over the data set subjects according to the performance of the previous estimators. Class imbalance due to a small event rate will be handled by assigning greater weights to subjects with the event. Finally, to obtain patient-level unbiased and calibrated survival curves, the risk score will be used to fit a parametric Weibull accelerated failure time regression. A 2-graph receiver-operating characteristic analysis will be performed to determine the optimal cut-off values to stratify patients into low, intermediate, and high-risk categories.[40]

We will refrain from performing hyperparameter tuning given the relatively small sample size and instead opt for parameter values determined in previous studies.

CV

The entire ML process (missing data imputation, feature selection, and model development) will be executed within repeated external site testing.[43] In this scheme, each of the sites is sequentially held out and used as an external testing cohort for the model developed on the remaining sites. This approach reduces the variance due to inter-site differences and may reflect more accurately the performance of ML when applying the model to new cohorts in real-world clinical practice. Predictions on each independent site will be accumulated and used to evaluate the ML model.

This CV protocol allows for robust performance estimations in relatively small samples,[42] as compared with the biased hold-out method.[44]

Model Evaluation

Models will be evaluated according to discrimination ability using the concordance-index measure and calibration

TABLE 4. Study Endpoints

Primary endpoint	All-cause mortality
Secondary endpoint	Cardiovascular death defined as death due to acute coronary syndrome, heart failure/cardiogenic shock, cerebrovascular accident (stroke), peripheral vascular disease, systemic embolus, pulmonary embolus, cardiac or vascular procedural complications
	Pulmonary edema defined as respiratory distress and pulmonary rales due to pulmonary congestion, as confirmed by chest radiography, a respiratory rate of more than 20 breaths per minute, and an arterial hydrogen ion concentration greater than 45 nmol/L
	Cardiogenic shock defined as systolic blood pressure lower than 90 mm Hg for more than 30 min and clinical signs of pulmonary congestion and impaired organ perfusion
	Heart failure was defined as a progression to New York Heart association (NYHA) class III or IV, LVEF < 50% or hospitalization due to HF complications
	Arrhythmias defined as presence of atrial or ventricular arrhythmias
	Stroke defined as focal neurological impairment of sudden onset, and lasting ≥ 24 h (or leading to death), and of presumed vascular origin
	TIA defined as transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischemia, without acute infarction
	Recurrence defined as new wall motion abnormalities in the absence of obstructive coronary disease after recovery of the index TTS events
	MACE defined as a composite endpoint of death from any cause, myocardial infarction, recurrence of TTC, TIA, and stroke

TIA indicates transient ischemic attack.

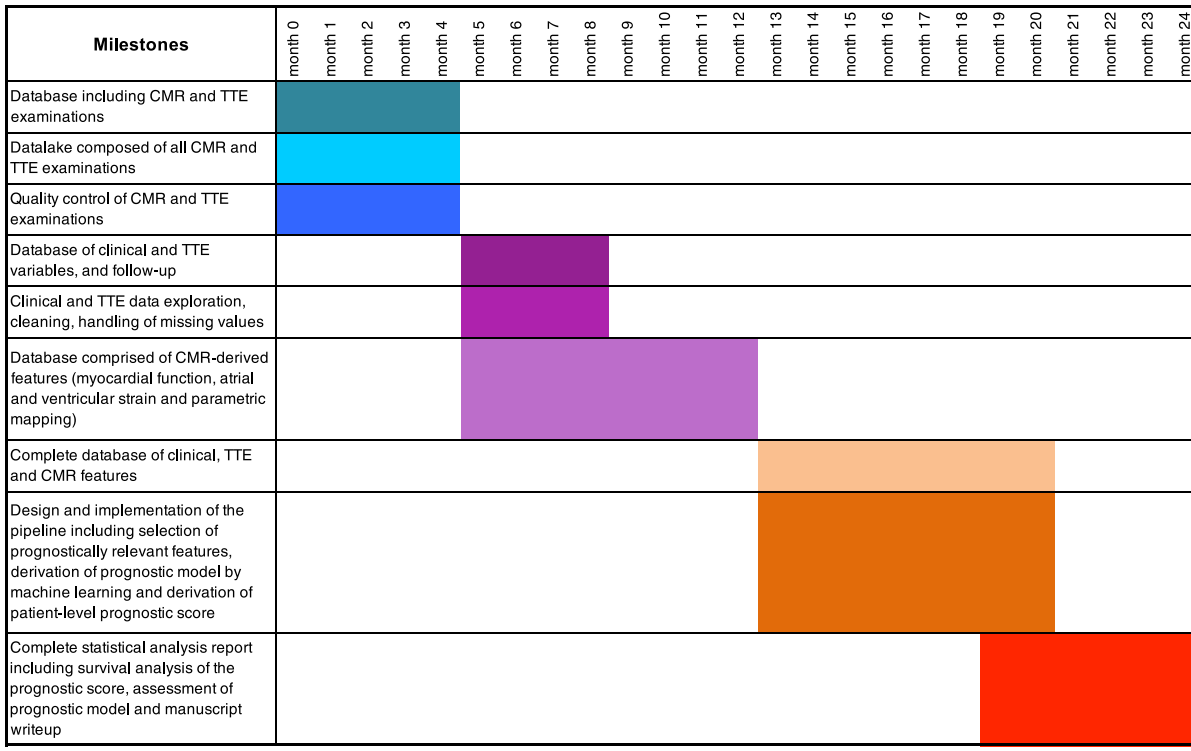

FIGURE 1. Gantt chart illustrating project schedule. full color online

using observed versus predicted plots and the Brier score. The Kaplan-Meier estimator will be used to qualitatively assess stratification by ML score in the 3 subgroups (low, medium, and high-risk). The log-rank test will be used to test for differences between survival curves and determine whether patients assigned to higher-risk categories will be more likely to experience the event than those assigned to lower-risk categories. The derived ML risk score will also be compared with clinically available diagnostic and prognostic scores such as the GRACE, GEIST, and InterTAK scores according to discrimination and calibration.

Predictions Analysis

We will use the Shapley Additive Explanations (SHAP) framework to analyze the contribution of each feature to the model's outputs. SHAP allows for both global and local explanations: calculating the average SHAP value of a feature across all subjects gives a global measure of importance, while the SHAP values for a single subject represent the individual contribution of each feature to the model-predicted risk score. Positive SHAP values indicate positive contributions toward the class of interest (ie, the subject experienced an event), whereas negative values have the opposite impact.

Timelines

The deadline for the collection of all data is August 1, 2023, and for data analysis is November 1, 2023. The manuscript draft is expected by March 31, 2024 (Fig. 1).

Sample Size Determination

The minimum sample size required for developing a multivariable time-to-event prognostic model was estimated following Riley and colleagues. The sample size must meet 3 criteria: (1) target a reasonably small rate of overfitting ($< 10\%$); (2) achieve an absolute difference in apparent and adjusted $R^2 \leq 5\%$; and (3) target an absolute margin of error for the population outcome risk $\leq 5\%$.[45] Note, however, that the method proposed by Riley et al was not conceived for ML applications originally, but rather for simpler multivariable prediction models. Furthermore, our pipeline encompasses an automated feature selection process that increases the complexity of the ML model. Hence, more samples than estimated may be required to meet these criteria.

Building on previous findings of Santoro et al[8] and Templin et al,[7] we considered a mortality rate of 5.6% per person-year and we assumed an adjusted Cox-Snell R^2 of 0.15 as a baseline. Furthermore, considering a mean follow-up of 24 months, a time point for prediction of 24 months and a maximum of 6 candidate predictors, the minimum sample size required is 330 patients, corresponding to an average of 6.16 events per predictor variable and a total of ~37 events.

Within the 5-fold CV of the ML analysis, each training subset will comprise on average 264 subjects ([330/5] × 4) and 30 events, and 66 subjects with 7 events for each testing subset. Given that we can safely model—by guarding against overfitting—~6.16 events per candidate predictor, we will restrict the number of predictors to 5 (30 [events in the training fold] divided by 6.16 [events per predictor]) when training the model within the CV framework.

Statistics

Descriptive statistics will be used to describe the study population; the normality of residuals for continuous variables will be tested using the Shapiro-Wilks test of normality. Normally distributed variables will be reported as

the mean ± SD; non-normally distributed data will be reported as median and interquartile range. Categorical data will be summarized in tables and reported as numbers and proportions. A χ^2 or Fisher exact test will be used to test for relationships between 2 categorical variables, depending on the expected frequencies of each level. The 2-sample *t* test and Wilcoxon-Mann-Whitney will be used to determine differences between 2 independent subgroups of a continuous or ordinal variable, depending on the normality of residuals. One-way analysis of variance and Kruskal-Wallis will be used for variables with 3 or more independent subgroups. Survival function at follow-up related to endpoints of interest will be assessed via Kaplan-Meier survival analysis and the Log-Rank test will be used to compare estimated survival curves. Univariable Cox proportional hazard models will be used to identify candidate prognostic factors; variables with $P < 0.1$ will be entered in a multiple Cox regression, which allows modeling interactions between factors. Residual methods will be used to assess Cox proportional hazard assumptions. The discriminatory ability of the multivariable survival model will be assessed via the concordance index. Correlated concordance indexes will be tested for statistically significant differences using the compareC R package.

Variables that remain statistically significant in the multivariable model will be used to derive a composite score for predicting in-hospital and long-term complications. The ability of the score to adequately predict the events of interest will be evaluated in a dedicated validation cohort.

Two-tailed *P*-values <0.05 will be considered statistically significant. The analysis will be conducted using the R software (R Core Team, 2020).

DISCUSSION

Both in-hospital and long-term prognoses remain controversial in TTC patients,[12] emphasizing the need for a better risk stratification score to identify high-risk patients who may benefit from strict in-hospital management and long-term clinical follow-up. Different clinical characteristics and TTE-derived parameters have been shown to be associated with in-hospital and long-term outcomes.[3,8–11,46] So far, none of these prognostic scores proposed considered the role of CMR, with its unique capability to noninvasive evaluate tissue characterization. Indeed, CMR allows a comprehensive functional and structural changes evaluation in TTC patients, including a detailed estimation of RV function in case of suboptimal acoustic echocardiography windows.[16,47]

Myocardial tissue alterations are associated with worse prognosis in different cardiomyopathies and its evaluation allows to improve risk stratification in these patients.[48–53] In TTC, the diagnostic role of CMR has been widely explored,[2,3,16,47,54–56] whereas its role regarding disease prognosis remains controversial.[24,47,56] In recent years, thanks to the continuous improvement in technology, computed tomography has shown promising applications for myocardial characterization representing a potential alternative to CMR in the detection of scarred myocardium and quantification of myocardial extracellular volume fraction.[57–60]

To date, there are no registered clinical trials or published studies that investigate the prognostic role of CMR, and its potential added value in a prognostic score combined with clinical and TTE data. The EVOLUTION registry will focus on a large cohort of TTC patients with the final aim to develop a risk stratification score that includes CMR parameters in addition to the standard clinical and TTE work-up of patients with TTC. Concerning a large amount of available data, we will also evaluate the contribution of ML models to predict in-hospital and long-term outcomes as compared to standard clinical scores. Indeed, ML is able to mesh a large amount of quantitative imaging data to clinical parameters,[17,61] demonstrating a better outcome prediction in comparison with clinical or imaging data alone.[62–65]

In conclusion, the objective of the EVOLUTION registry is to develop a score that integrates clinical, TTE, and CMR to provide more reliable risk stratification and outcome prediction as a basis for optimized patient management in a large cohort of TTC patients.

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