Importance of systematic right ventricular assessment in cardiac resynchronization therapy candidates: a machine-learning approach

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Short title: machine learning and right ventricular function in CRT

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Declaration of interest: Nothing to disclose

HIGHLIGHTS

- The prediction of the impact of CRT on LV function and outcomes is often difficult
- CRT candidates are a highly heterogeneous population
- Machine learning allows the analysis of a huge amount of clinical and imaging data
- Machine learning can identify clusters of patients with different characteristics and prognosis
- RV-derived features are important for the characterization of CRT-candidates

ABSTRACT

Background

Despite all having systolic heart failure and broad QRS, patients screened for cardiac resynchronization therapy (CRT) are highly heterogeneous, and it remains extremely challenging to predict the impact of the device on left ventricular (LV) function and outcomes.

Objectives

We sought to evaluate the relative impact of clinical, electrocardiographic, and echocardiographic data on the left ventricular (LV) remodeling and prognosis of CRT-candidates by the application of machine learning (ML) approaches.

Methods

193 patients with systolic heart failure undergoing CRT according to current recommendations were prospectively included in this multicentre study. We used a combination of the Boruta algorithm and random forest methods to identify features predicting both CRT volumetric response and prognosis. The model performance was tested by the area under the receiver operating curve (AUC). We also applied the K-medoid method to identify clusters of phenotypically similar patients.

Results

From 28 clinical, electrocardiographic, and echocardiographic-derived variables, 16 features were predictive of CRT response, and 11 features were predictive of prognosis.

Among the predictors of CRT-response, 8 variables (50%) pertained to right ventricular (RV) size or function. Tricuspid annular plane systolic excursion was the main feature associated with prognosis. The selected features were associated with a particularly good prediction of both CRT response (AUC 0.81, 95% CI: 0.74-0.87) and outcomes (AUC 0.84, 95% CI: 0.75-0.93). An unsupervised ML approach allowed the identifications of two phenogroups of patients who differed significantly in clinical variables and parameters of biventricular size, and RV function. The two phenogroups had significant different prognosis (HR 4.70, 95% CI: 2.1-10.0, $p<0.0001$; log-rank $p<0.0001$).

Conclusions

Machine learning can reliably identify clinical and echocardiographic features associated with CRT-response and prognosis. The evaluation of both RV-size and function parameters has pivotal importance for the risk stratification of CRT-candidates and should be systematically assessed in patients undergoing CRT.

Keywords: cardiac resynchronization therapy, heart failure, machine learning, right ventricle

Abbreviations

ApR, apical rocking

AUC, area under the curve

BNP, brain-type natriuretic peptide

CRT, cardiac resynchronization therapy

EDV, end-diastolic volume

ESV, end-systolic volume

FAC, fractional area change

GFR, glomerular filtration rate

GLS, global longitudinal strain

HFrEF, heart failure with reduced ejection fraction

IHD, ischemic heart disease

LAVi, indexed left atrial volume

LBBB, left bundle branch block

LV, left ventricle

LVEF, left ventricular ejection fraction

NYHA, New York Heart Association functional class.

PAPs, estimated systolic pulmonary artery pressure

RAP, right atrial pressure

RAV, right atrial volume

RV, right ventricle

RVDA, right ventricular diastolic area

RVSA, right ventricular systolic area

RVLS, right ventricular free wall longitudinal strain

SF, septal flash

TAPSE, tricuspid annular plane systolic excursion

TRVmax, maximal tricuspid regurgitation velocity

INTRODUCTION

Cardiac resynchronization therapy (CRT) is an established treatment for patients with heart failure and reduced ejection fraction (HFrEF) who have wide QRS and remain symptomatic despite optimized medical therapy[1]. Nevertheless, nearly 30% of patients undergoing CRT according to recommendations are not-responders to this treatment[2], and some patients die from heart failure despite the initial improvement in left ventricular ejection fraction (LVEF) and cardiac remodeling[34]. CRT-response and the outcome rely upon several factors which include clinical characteristics, typical ventricular conduction disturbances[5], and the evaluation of the specific electromechanical substrate responsible for LV discoordination[67].

The comprehensive integration and interpretation of this huge mass of heterogeneous data is difficult for the human brain and makes CRT an interesting field of application for personalized medicine[8]. Previous studies have shown that the application of machine learning (ML) algorithms to CRT can predict CRT response[910] and prognosis[11]. Some of these studies were focused on the analysis of specific electrocardiographic data such as QRS morphology and duration[11], on the computational analysis of strain derived-curves[10], or on the unsupervised examination of strain curve dynamics, clinical and standard echocardiographic data[9]. Our study aimed to apply supervised and non-supervised machine learning approaches to a comprehensive amount of commonly available clinical, electrocardiographic, and echocardiographic data to 1) evaluate the relative importance of each feature in the prediction of CRT-response and prognosis by a supervised machine learning approach and 2) to identify specific phenogroups of patients which are at increased risk of poor outcomes.

MATERIALS AND METHODS

Population

209 patients with systolic heart failure undergoing CRT implantation according to current guidelines[1] at Oslo University Hospital (Norway), Leuven University Hospital (Belgium), Rennes

University Hospital (France), Aalst OLV Hospital (Belgium), and Karolinska University Hospital (Sweden) between August 2015 and November 2017 were prospectively included in this observational, multicentre study. Sixteen patients were excluded from the final analysis because of study withdrawal (n=4), lead extraction due to infective endocarditis (n=1), and lack of fundamental echocardiographic data (n=11). As a result, 193 patients were included in the study. At the time of CRT implantation, all patients were receiving optimized medical therapy. Clinical data including age, sex, and treatments were collected for each patient. The functional status was assessed by the estimation of the New York Heart Association (NYHA) functional class. Ischemic heart disease (IHD) was defined as a history of myocardial infarction and coronary revascularization or angiographic evidence of multiple vessel disease or single-vessel disease with ≥75% stenosis of the left main or proximal left anterior descending artery[12].

All patients gave their written informed consent for study participation.

The study was conducted following the "Good Clinical Practice" guidelines of the Declaration of Helsinki and was approved by the Regional Ethical Committees of every participating centre. The study was registered at clinicaltrials.gov (identifier NCT02525185).

Echocardiography

All patients underwent standard transthoracic echocardiography using a Vivid E9 and E95 ultrasound system (GE Healthcare, Horten, Norway) equipped with an M5S 3.5-MHz transducer at baseline and 6-month follow-up. Two-dimensional, colour Doppler, pulsed-wave and continuous-wave Doppler data were stored on a dedicated workstation for the offline analysis (EchoPAC, GE EchoPAC, GE Healthcare, Horten, Norway). Left atrial, left ventricular (LV) volumes, and left ventricular ejection fraction (LVEF) were measured by the biplane method, as recommended[13]. Right ventricular size and function were measured in the modified four-chamber view as recommended[13]. Tricuspid annular plane systolic excursion (TAPSE) was measured in the apical 4-chamber view using M-mode echocardiography. Right atrial volume (RAV) was measured using the disk summation techniques in a dedicated apical four-chamber view[14]. RV fractional area

change (FAC) was measured as the percentage difference between RV diastolic and systolic area, divided by RV diastolic area. RV lateral strain was assessed by tracking the RV endocardium as indicated in recommendations[14]. Peak velocity of early (E) and late (A) diastolic filling were derived from transmitral Doppler recordings, and the E/A ratio was calculated. Pulsed-wave TDI-derived early diastolic velocity were obtained at the septal and lateral mitral annulus and the mean value (e') was used to estimate the E/e' ratio. In the presence of tricuspid regurgitation, continuous Doppler was used to estimate the maximal tricuspid velocity (TRV_{max}). Inferior vena cava diameter and respiratory changes were used to estimate right atrial pressure (RAP)[15]. Systolic pulmonary artery pressure (PAPs) was calculated as [$4*(TRV_{max})^2$+RAP] as recommended[15]. Right ventriculoarterial coupling was assessed by the ratio between tricuspid annular plane systolic excursion and PAPs (TAPSE/PAPs)[16].

Assessment of LV dyssynchrony

Septal flash (SF) and apical rocking (ApR) were visually assessed in Leuven by two experienced readers. In case of disagreement, a third reading was performed in Leuven by an independent expert to reach a consensus. Septal flash was defined as pre-ejection septal shortening or rapid leftward septal motion immediately after onset QRS and was assessed visually in apical 2D images or, when in doubt, with longitudinal strain or M-mode in parasternal views[17]. Apical rocking was defined as a transverse rightward motion of the apex immediately after onset QRS, followed by a leftward motion of the apex during ejection[18]. LV mechanical dyssynchrony was defined by the presence of SF and/or ApR.

Cardiac resynchronization therapy

CRT delivery followed a standard protocol. The right atrial and ventricular leads were positioned conventionally. The LV lead was inserted in a lateral or postero-lateral vein if possible and coronary venography was used to optimize lead placement. The device was programmed in conventional biventricular pacing and retested before hospital discharge.

Positive response to CRT was defined as a decrease in LV end-systolic volume of ≥15%[2]. To optimize precision, all volumes were measured independently in three different centres (Rennes, Leuven and Oslo) and a majority decision was used in cases of disagreement on CRT-response.

Outcome

The outcome was a composite of heart transplantation, LV assisted device implantation or all-cause death during follow-up.

Baseline characteristics and machine learning approaches

Twenty-two baseline echocardiographic variables, with <10% missing data were identified. After filtering correlated variables using a cut-off Pearsons' coefficient>0.8, 18 variables, which included right and left ventricular function parameters, were selected. In addition to these echocardiographic data, the following variables were included in the machine learning (ML) algorithm: 1) clinical parameters: age, sex, NYHA class, IHD, ln NT-proBNP and glomerular filtration rate (GFR); 2) ECG-derived parameters, such as QRS duration and presence of typical left bundle branch block[19]; 3) dyssynchrony parameters and 4) CRT-volumetric response.
Implementations of data analysis and machine learning methods were performed in R-studio (version 1.2.1335).
Missing data were imputed using the MICE algorithm as described by Van Buuren et Groothuis-Oudshoorn ~~et~~ al.[20] ("mice" package) which allows imputing mixed datasets with continuous and categorical variables using Fully Conditional Specification (FCS) (Table 1S).

Unsupervised machine-learning approach

To identify clusters of phenotypically-similar patients, subjects were clustered using the partitioning around medoids (PAM or k-medoid) algorithm with Gower distance, which allows the analysis of datasets made of mixed-type data with numeric and categorical features ("cluster" package). Figure 1 shows an overview of the input data and the proposed data analysis. The final number of clusters was determined to maximize the silhouette index[21].

Supervised machine-learning approach

A feature selection phase was firstly applied by using the Boruta algorithm[22] ("Boruta" package) to select the best predictors of CRT-response and outcome. According to this method, each original feature is compared to the randomly generated features created by the algorithm. A feature that contributes positively to the predictive model has a performance which is superior to the best random feature, indicated as "shadowMax".

The random forest (RF) method [23] ("randomForest" package) is a popular and versatile supervised ensemble learner method that is based on the training of a set of uncorrelated trees to estimate a target variable for classification or regression purposes. This method was then applied to a reduced feature set to build ensemble classifiers to predict CRT-response and outcome. Receiver Operating Characteristic (ROC) curves and the corresponding area under the curve (AUC) were estimated to evaluate the classification performance of the RF method proposed method.

Statistical analysis

The normality of data distribution was assessed using the Shapiro-Wilk test. When the hypothesis of normality was rejected, a Box-Cox transformation was performed. Results were rounded and expressed as mean ± SD. The differences between the phenotype groups were tested using a one-way ANOVA analysis. Categorical variables were expressed as percentages. Comparison between groups was performed using the χ^2 test or Fisher's exact test when appropriate. Statistical significance was considered as a two-sided p-value <0.05. We used Cox regression models to calculate between-group differences in outcomes and the Kaplan–Meier method to calculate survival curves.

We used R statistical software (version 3.3.3) and SPSS (SPSS Version 20.0, IBM, Chicago, IL, USA) for statistical analysis.

RESULTS

The baseline characteristics of the population are depicted in Table 1.

The population had a mean age of 67 years. The majority of patients were males (70%), with a high prevalence (67%) of non-ischemic dilated cardiomyopathy. 168 (87%) patients had typical LBBB.

CRT response

At 6-month follow-up, successful response to CRT was observed in 132 (68%) patients. After the application of the Boruta algorithm, 16 features were significantly associated with CRT-response (Figure 2A). Among all variables, 8 (50%) were obtained through the assessment of RV size or function. SF and ApR were the most important features, followed by IHD, E/e' ratio, RAV, RV diameters and RV systolic area, LV end-diastolic diameter, RV free wall strain, TAPSE/PAPs ratio, QRS width, LV-end diastolic volume, LV end-systolic diameter, TRV_{max} and FAC. The model obtained by the application of the RF method to this ensemble of features showed an AUC 0.81 (95% CI: 0.75-0.87) for the prediction of CRT-response (Figure 3A).

Predictors of prognosis

During a median follow-up of 37 months, the primary endpoint occurred in 29 (15%) patients. There were 11 non-cardiac deaths, 16 cardiac-related deaths, one heart transplantation and one LV assist device implantation.

The main features associated with the outcome are displayed in Figure 2B. The most important feature was TAPSE, followed by LV end-diastolic volume, LV end-systolic diameter, lnNT-proBNP, GFR, NYHA class, RV systolic area, LV-end-diastolic diameter, FAC, and LVEF, and RVLS.

These variables showed high accuracy in the prediction of the primary endpoint, with an overall AUC of 0.84 (95% CI: 0.75-0.93) (Figure 3B)

Clustering

Clustering with the K-medoid method allowed the identification of two phenotypically different groups of CRT candidates. Phenogroup 1 included 122 patients, with a mean age of 67 years, and a higher prevalence of women.

The baseline clinical and echocardiographic characteristics were imbalanced between the 2 groups.

Patients in phenogroup 1 had better kidney function, less dilated LV and a less restrictive filling pattern. LVEF was not different between phenogroups, but LV longitudinal function was better in Phenogroup 1. Also, patients in phenogroup 1 had less dilated RV and a significantly better RV function, with less impaired ventriculoarterial coupling. The prevalence of LV dyssynchrony was higher in phenogroup 1. Typical LBBB was more prevalent in phenogroup 1, but there was no significant difference in QRS width between the 2 groups. CRT volumetric response was highly prevalent in phenogroup 1 (Table 1).

Regarding the primary endpoint, phenogroup 2 had a significantly worse prognosis compared to phenogroup 1 (HR 4.70, 95% CI: 2.1-10.0, $p<0.0001$; log-rank $p<0.0001$) (Figure 4).

DISCUSSION

In this prospective, multicentric study, we have shown the feasibility and validity of the application of both supervised and unsupervised ML approaches to a comprehensive pattern of pre-implantation clinical, biochemical, electrocardiographic and echocardiographic data obtained in everyday clinical practice in CRT-candidates. Our analysis allowed: 1) the identification of groups of features which are significantly associated with CRT response and prognosis; 2) the identification of two phenogroups of patients with specific characteristics and differential outcomes. We also demonstrated that 3) RV size and function parameters have pivotal importance in the prediction of CRT response and prognosis.

Prediction of CRT-response

Current recommendations for CRT implantation rely upon the assessment of the symptomatic status of patients, LVEF and QRS width[1]. Nevertheless, 30-to-40% of patients who receive CRT according to guidelines are not-responders to treatment[2]. Kalsheur et al. have shown that the application of ML to CRT can provide a better classification of patients than the simple assessment of LBBB morphology and QRS duration[11]. Similarly, we were able to demonstrate that the application of the RF method to ECG data and the dynamic analysis of LV strain curves

significantly improves the prediction of CRT-response[10]. The relevance of imaging derived parameters in the selection of CRT candidates remains underestimated. In the current study, the application of supervised ML approaches was able to identify groups of features which are good predictors of CRT-response.

In our study, SF, ApR and IHD, were the most important variables associated with CRT response. These results are in line with an increasing amount of data underscoring the relevance of the visual assessment of LV mechanical discoordination and ischemic cardiomyopathy in determining in CRT response[24,25].

Noteworthy, QRS width was not the most important feature associated with CRT volumetric response, and its predictive role was improved by several RV-derived parameters such as RV basal and median diameter, right ventricular systolic area, RVLS and RV arterial coupling estimated by the TAPSE/PAPs ratio. These results are particularly relevant because the role of the right heart in CRT response is still debated[26,27,28,29, 30].

Physiologically, the RV and LV are interdependent, because of the sharing of the interventricular septum, the pericardial space, and myocardial fibres. Several experimental studies have shown that 20-40% of RV systolic pressure and flow results from LV contraction and 4-10% of left ventricular systolic pressure and stroke volume are due to right ventricular contraction. This systolic interaction is decreased by a stiff septum and increased by stiff ventricular free walls[31]. This relationship between the left and the right heart explains why RV dysfunction occurs in nearly 50% of patients with HF and reduced LVEF. On the other hand, RV failure might induce changes in LV geometry which cause an impairment in LV filling and decrease in cardiac output[32]. In the field of CRT, Storsen et al. have shown that LBBB causes an abnormal RV free wall motion which is reversed by CRT only in cases of preserved RV function. This pattern of activation might explain why RV failure is associated with a poor response to CRT[33].

Some small retrospective studies[27,29] and a post-hoc analysis of the prospective Cardiac Resynchronization Therapy Modular Registry (CRT-MORE)[30] have shown that TAPSE is a

predictor of CRT response. Compared with these previous studies, we performed a comprehensive analysis of RV function and we found that the ability of TAPSE to predict CRT-response was improved by the combination of both LV and RV-derived features. Our comprehensive model was able to predict CRT-response with an AUC of 0.81, which is superior to the value of 0.63 found for TAPSE alone in the CRT-MORE trial[30]. Despite this evidence, a large meta-analysis of different studies was not able to show a significant impact of RV performance on LV remodelling after CRT[26]. These discrepancies might be attributable to the fact that most of the published data have used only one or two parameters to assess RV function. Our study has the advantage of providing a multi-parametric assessment of the RV performance, including RV size, FAC, RV lateral strain and the TAPSE/PAPs ratio, which allow a comprehensive description of RV morphology and performance. The incorporation of these parameters into a model which includes the estimation of LV dyssynchrony, QRS width and LV size, improves the results compared to that achieved by analysis of single parameters and results in the identification of the model that best fits the primary clinical question.

Prediction of prognosis

To identify prognostic predictors in patients undergoing CRT, we combined supervised ML, which allowed the identification of variables specifically associated with outcome, and unsupervised ML analysis, which allowed the stratification of our population in two distinct groups of subjects with different characteristics and outcomes.

We found that TAPSE is the most important feature associated with outcome, followed by LV size, NYHA functional class, kidney function, FAC, LVEF and RVLS. The combination of these variables through the application of the RF method enhanced the appraisal of the likelihood of favourable clinical evolution after CRT.

These results are strengthened by the clustering analysis. This agnostic approach allowed the classification of our population in two distinct groups of patients who represent different archetypes

of CRT-candidates. On one side, we have subjects with more advanced heart failure, as witnessed by a pronounced biventricular dilatation, a higher prevalence of RV dysfunction and kidney failure. On the other side, we have patients with less severe disease, higher prevalence of SF and ApR and a better prognosis.

Our findings have several implications: 1) the presence of advanced heart failure features before CRT-implantation can significantly impact prognosis, independently from the result of CRT; 2) the assessment of RV function has pivotal importance in the risk stratification of patients.

Previous studies have shown that RV dysfunction assessed by TAPSE is a prognostic determinant in HF patients, regardless of the degree of RV dysfunction[16]. In a post-hoc analysis of the CARE-HF trial, Damy et al. have also demonstrated that baseline TAPSE is a predictor of outcome in patients undergoing CRT, together with baseline NYHA and NTproBNP[28]. Our results reinforce these data and put into perspective the importance of a comprehensive evaluation of HF patients receiving CRT, which should systematically include the evaluation of RV size and function. We need to underscore that the aim of the application of machine learning methods in the clinical field is not to identify the importance of a single parameter -such as TAPSE –, but to handle large datasets with complex interactions between variables to find the algorithm that best suits the clinical problem[34]. Another important finding of our study is that despite the prevalence of CRT-response being higher among patients with a better outcome, volumetric response to CRT was not the main feature associated with prognosis.

This means that some patients who are considered CRT-responders can still experience a poor outcome, probably because of the presence of concomitant factors such as advanced HF, cardiorenal syndrome and RV dysfunction[28]. Whether the severity of HF and/or concomitant RV dysfunction before device implantation should influence the selection of CRT-candidates requires further study and underscores the subtle relationship between outcome and response to treatment[35]. On one hand, it is evident that the dichotomization of CRT-candidates in responders and non-responders according to volumetric remodelling is simplistic because there is a wide spectrum of

response to CRT, which goes from mild LV remodelling to complete functional recovery, and this progressive remodelling can take more than 6 months to settle. On the other hand, some patients might have such an advanced cardiopathy (eg severely dilated heart, biventricular dysfunction and/or cardiorenal syndrome), that the success of CRT might not be sufficient to change the natural history of heart failure disease progression and the outcome[36]. These observations suggest that finding the good therapeutic window for CRT implantation has pivotal importance. By incorporating a large amount of data, ML might be useful for the characterization and identification of patients with different "risk profiles", favouring the generation of pathophysiological hypothesis, and facilitating the tailored management of patients, which represent a significant step forwards personalized medicine.

Limitations

This study has several limitations. First, data are obtained from a medium-size population of patients undergoing CRT according to current recommendations. The availability of more data, including electrophysiological data obtained at the moment of CRT implantation and the analysis of a wider population might have strengthened and improved our results. Second, compared to previous studies[2,5,11,28,30], our population displayed a lower prevalence of ischemic heart disease and a higher prevalence of typical LBBB. This means that our results should be applied with caution to patients with ischemic cardiomyopathy and or non-LBBB QRS morphology, who are known to present a lower rate of CRT-response. Third, we did not perform an external validation of our results, which limit their applicability and should represent an object of further research. Fourth, patients were followed-up for 37 months and a longer follow-up might have been useful to strengthen the value of our model for the prediction of events. Moreover, data on heart failure hospitalizations during follow-up are not available. This is an important adverse event that requires assessment in CRT recipients.

Conclusions

The application of machine learning methods to a set of common clinical, electrocardiographic and echocardiographic data emphasize the importance of a multiparametric approach for both the identification of CRT-response and the prediction of prognosis after CRT. Our results underscore the importance of RV function on both CRT response and outcome and the pivotal role of the global assessment of heart function in patients undergoing CRT. Despite these interesting results, additional studies on a broader population will be necessary to fully validate and understand the clinical application of machine learning to CRT. Although there remains much to understand, as demonstrated in our study, it is likely that application of ML-derived algorithms will allow the stratification of CRT-candidates to guide patients towards specific therapeutic approaches and additional focused clinical trials.

Acknowledgement

JM Aalen was supported by a grant from the Norwegian Health Association.

CK Larsen was recipient of a clinical research fellowship from the South-Eastern Norway Regional Health Authority.

J Duchenne was supported by a research grant of the University Leuven (OT12/084).

JU Voigt holds a research mandate of the Research Foundation Flanders (FKM1832917N).

VLR was supported by the French National Research Agency (ANR) (ANR-16-CE19-0008-01) (project MAESTRo).

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Table 1. Clinical and echocardiographic characteristics of the overall population and according to phenogroups.

	Overall (n= 193)	**Phenogroup 1** (n= 122)	**Phenogroup 2** (n= 71)	**p-value**
Age, years	67±11	67 ±11	67±11	0.97
Female sex, n(%)	57(29)	46(37)	11(15)	0.0019
Ischemic heart disease, n(%)	64(33)	23(19)	41(58)	< 0.0001
NYHA class, n(%) **I** **II** **III** **IV**	 14(7) 107(56) 70(36) 2(1)	 7(6) 80(66) 35(28) 0	 7(10) 27(38) 35(49) 2(2)	
lnNT-proBNP, pg/ml	6.13±1.61	6.07±1.62	6.23±1.62	0.51
eGFR, ml/min	63±23	66±23	57±23	0.01
QRS width, msec	167±21	166±19	169±25	0.80
LBBB, n(%)	169(88)	113(93)	56(79)	0.01
LV-EDD, mm	63±12	62±10	66±13	0.007
LV-ESD, mm	52±13	51±13	55±13	0.024
LV-EDV, mm	211± 86	202± 84	226± 88	0.04
LV-ESV, mm	153±73	146±68	165±79	0.084
LVEF, %	29±8	29±7	29±9	0.67
LV-GLS, %	-8.47±3.84	-9.12± 3.70	-7.36±3.84	0.002
LAVI, ml/m^2	47±17	45±16	50±17	0.03
E/Ea	16± 9	15±7	19± 12	0.02
RVBD, mm	41±8	38±7	45±8	< 0.0001
RVMD, mm	31±8	29±7	35±7	< 0.0001
RV lenght, mm	81±12	78±12	86±12	< 0.0001
Tricuspid annulus, mm	36±7	34±7	39±7	< 0.0001
RAV, ml	63± 34	52± 29	80±36	< 0.0001
RVDA, cm^2	22±7	20±5	26±7	< 0.0001
RVSA, cm^2	13± 6	10±4	16±7	< 0.0001
FAC, %	44±12	48±9	38±13	< 0.0001
TAPSE, mm	19±5	10±5	18±6	< 0.0001
RVLS, %	-20.04±6.12	-20.85± 5.03	-18.66± 7.47	0.030
TRVmax, m/sec	2.41± 0.63	2.30± 0.63	2.58±0.60	< 0.0001
RAP, mmHg	6.83±3.71	5.86± 3.24	8.49±3.91	< 0.0001
PAPs, mmHg	31.60±12.88	29.00± 11.38	36.07±14.10	0.0002
TAPSE/PAPs, mm/mmHg	0.80±0.86	0.92±1.02	0.60± 0.39	0.0002
Septal Flash, n(%)	130(67)	117 (96)	13 (18)	< 0.0001
Apical Rocking, n(%)	123 (64)	112 (92)	11 (15)	< 0.0001
CRT responder, n(%)	132 (68)	108 (89)	24 (34)	< 0.0001

BNP, brain natriuretic peptide; CRT, cardiac resynchronization therapy; EDD, end-diastolic diameter; EDV, end-diastolic volume; ESD, end-systolic diameter; ESV, end-systolic volume;

FAC, fractional area change; GFR, glomerular filtration rate; LBBB, left bundle branch block; LV left ventricle; LVEF, left ventricular ejection fraction; NYHA, New York heart association functional class; PAPs, estimated pulmonary artery systolic pressure; RAP, right atrial pressure; RAV, right atrial volume; RV, right ventricle; RVBD, right ventricular basal diameter; RVDA, right ventricular diastolic area; RVLS, RV longitudinal strain; RVMD, right ventricular median diameter; RVSA, right ventricular systolic area; TAPSE, tricuspid annular plane systolic excursion; TRVmax, maximal tricuspid regurgitation velocity

Table 1S. Missing data

Age, years	0%
Female sex	0%
IHD, n(%)	0%
NYHA class	0.51 %
lnNT-proBNP, pg/ml	13.98 %
eGFR, ml/min	1.55 %
QRSd, ms	0%
LBBB, n(%)	0.51%
LV-EDD, mm	2.07 %
LV-ESD, mm	2.07 %
LV-EDV, mm	0%
LV-ESV, mm	0%
LV-EF, %	0%
LV-GLS, %	1.03%
LAVI, ml/m^2	0%
E/Ea	6.21%
RVBD, mm	3.10 %
RVMD, mm	5.18 %
RV lenght, mm	4.66 %
Tricuspid annulus, mm	3.62 %
RAV, ml	2.59 %
RVDA, cm^2	4.66 %
RVSA, cm^2	5.18 %
FAC, %	5.18 %
TAPSE, mm	2.59 %
RVLS, %	16.06 %
TRVmax, m/sec	21.24 %
RAP, mmHg	22.27 %
PAPs, mmHg	18.65 %
TAPSE/PAPs, mm/mmHg	20.20 %
Septal Flash, n(%)	0 %
Apical Rocking, n(%)	0 %
CRT responder, n(%)	0 %

Figure 1. Framework illustrating the machine learning applied methods

Input data consists of clinical parameters, cardiac biomarkers, electrocardiographic data and echocardiographic variables (left panel).

Unsupervised machine learning (right, upper panel): the k-Medoid clustering method was applied to predefined features to select cluster of similar patients.

Supervised machine learning (right, lower panel): a feature selection phase was firstly applied by using the Boruta algorithm to select the best predictors of CRT-response or outcome. The random forest method is then applied to selected features to ensemble classifiers to predict CRT-response or outcome.

BNP, brain natriuretic peptide; ECG, electrocardiogram; GFR, glomerular filtration rate; IHD, ischemic heart disease; LBBB, left bundle branch block; LA, left atrium; LV, left ventricle; NYHA, New York Heart Association functional class; RV, right ventricle, TRV_{max}, maximal tricuspid regurgitation velocity.

Figure 2. Feature selection for the response to CRT (A) and outcome (B)

The Boruta algorithm was applied to select the best predictors of CRT-response and outcome.

Figure 3. Receiver Operating Characteristics curve analysis for the prediction of CRT response (A) and outcome (B)

The random forest method was on the most important feature to build ensemble classifiers to predict CRT-response and outcome. Receiver Operating Characteristic (ROC) curves and the corresponding area under the curve (AUC) were estimated to evaluate the classification performance of the RF method proposed method.

Figure 4. Kaplan-Meier survival curve showing survival stratified by phenogroups

The final number of cluster was determined to maximize the silhouette index. Two clusters were identified (left panel). The survival stratification of these two phenogroups is depicted in the right panel.

Central illustration.

Application of machine learning methods to CRT-candidates allows the identification of phenogroup of patients with significant differently prognosis (upper panel) and the identification of specific features which are predictors of CRT-response and prognosis (lower panel). Parameters derived from the assessment of right ventricular size and function have pivotal importance in the risk stratification of CRT-candidates and should be systematically assessed before CRT-implantation.

CRT, cardiac resynchronization therapy; RV, right ventricle

Fig 1

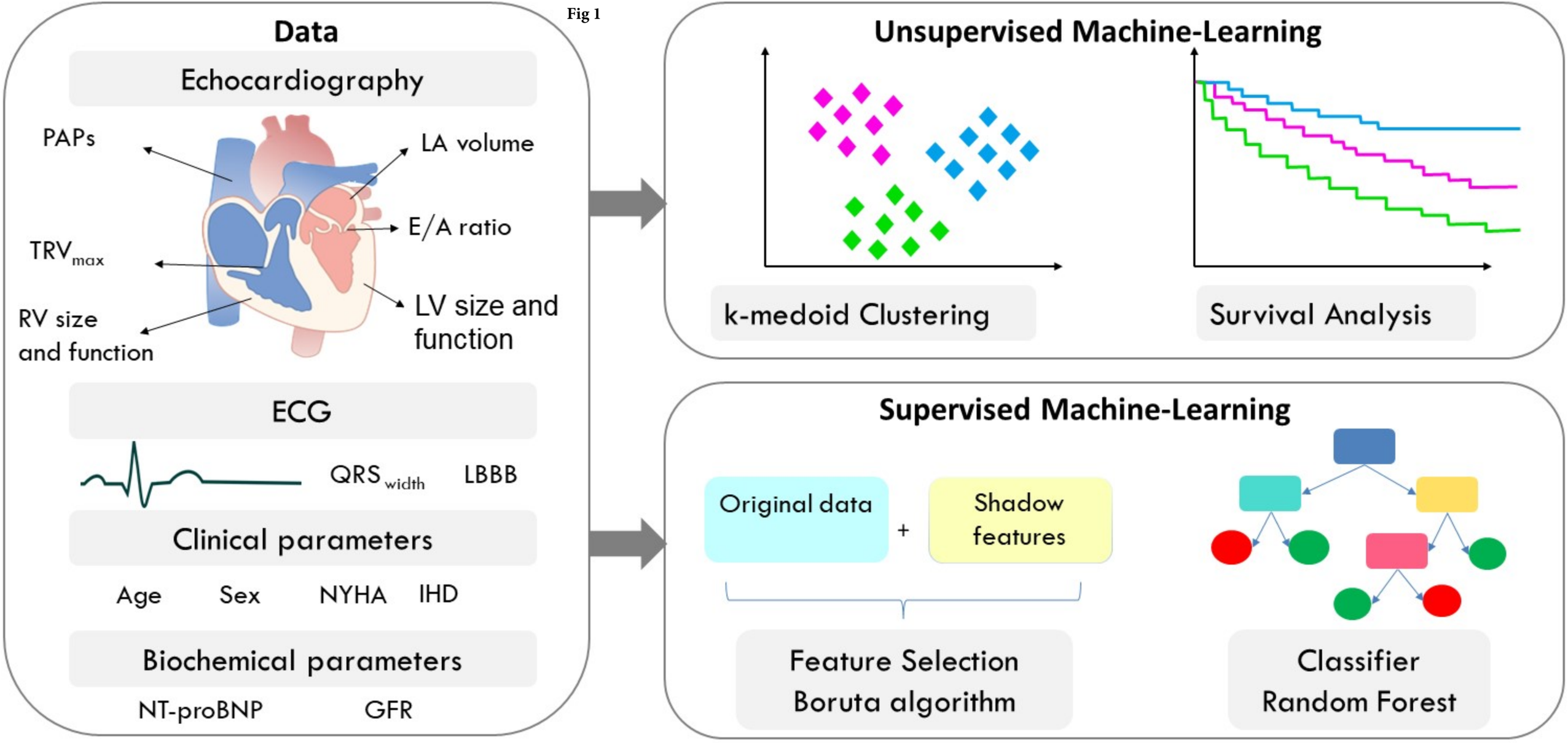

Data
Echocardiography
PAPs
LA volume
E/A ratio
TRV max
LV size and function
RV size and function
ECG
QRS width
LBBB
Clinical parameters
Age
Sex
NYHA
IHD
Biochemical parameters
NT-proBNP
GFR
Unsupervised Machine-Learning
k-medoid Clustering
Survival Analysis
Supervised Machine-Learning
Original data
+
Shadow features
Feature Selection
Boruta algorithm
Classifier
Random Forest

Figure 2 A

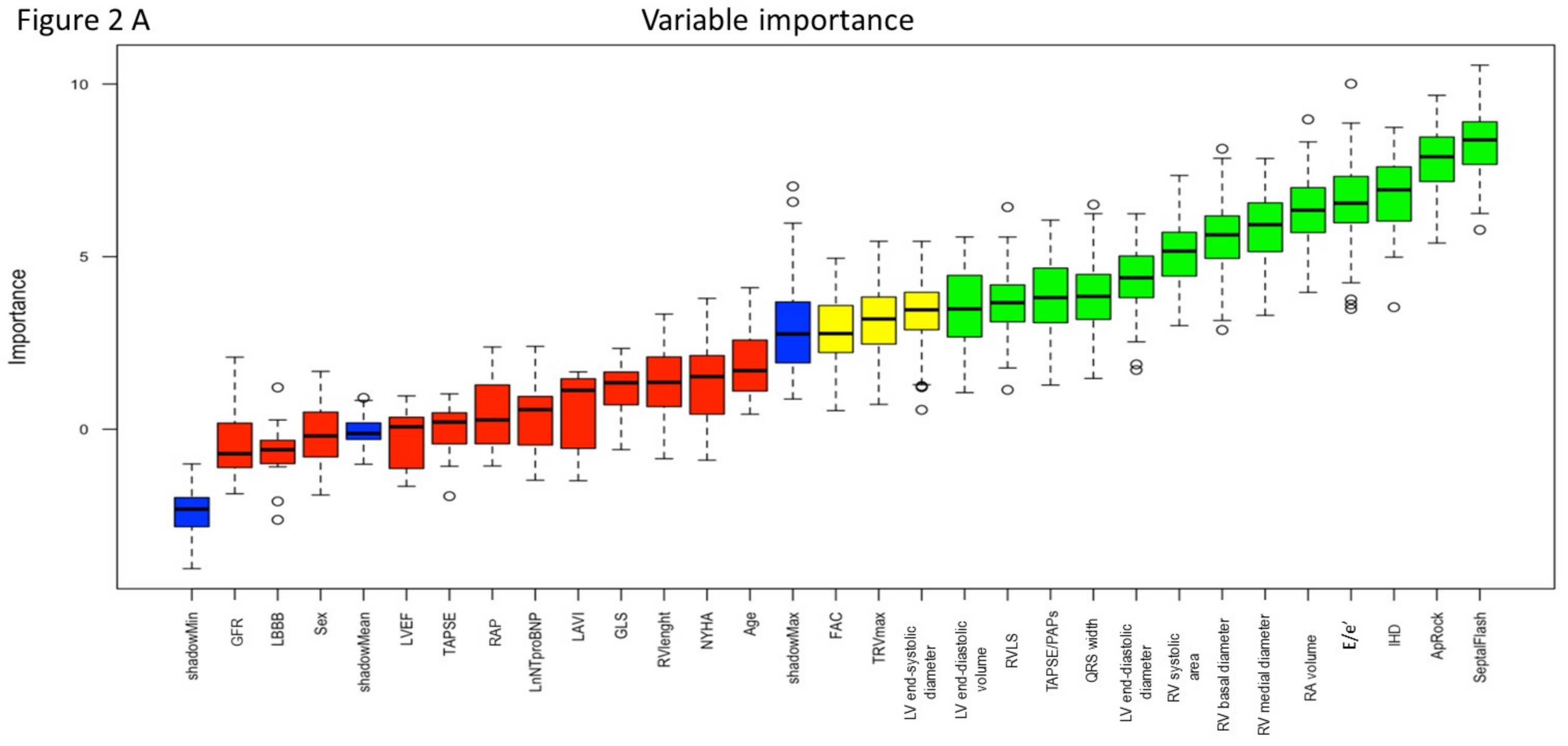

Variable importance
Importance
10
5
0
shadowMin
GFR
LBBB
Sex
shadowMean
LVEF
TAPSE
RAP
LnNTproBNP
LAVI
GLS
RVlenght
NYHA
Age
shadowMax
FAC
TRVmax
LV end-systolic diameter
LV end-diastolic volume
RVLS
TAPSE/PAPs
QRS width
LV end-diastolic diameter
RV systolic area
RV basal diameter
RV medial diameter
RA volume
E/e'
IHD
ApRock
SeptalFlash

Figure 2 B

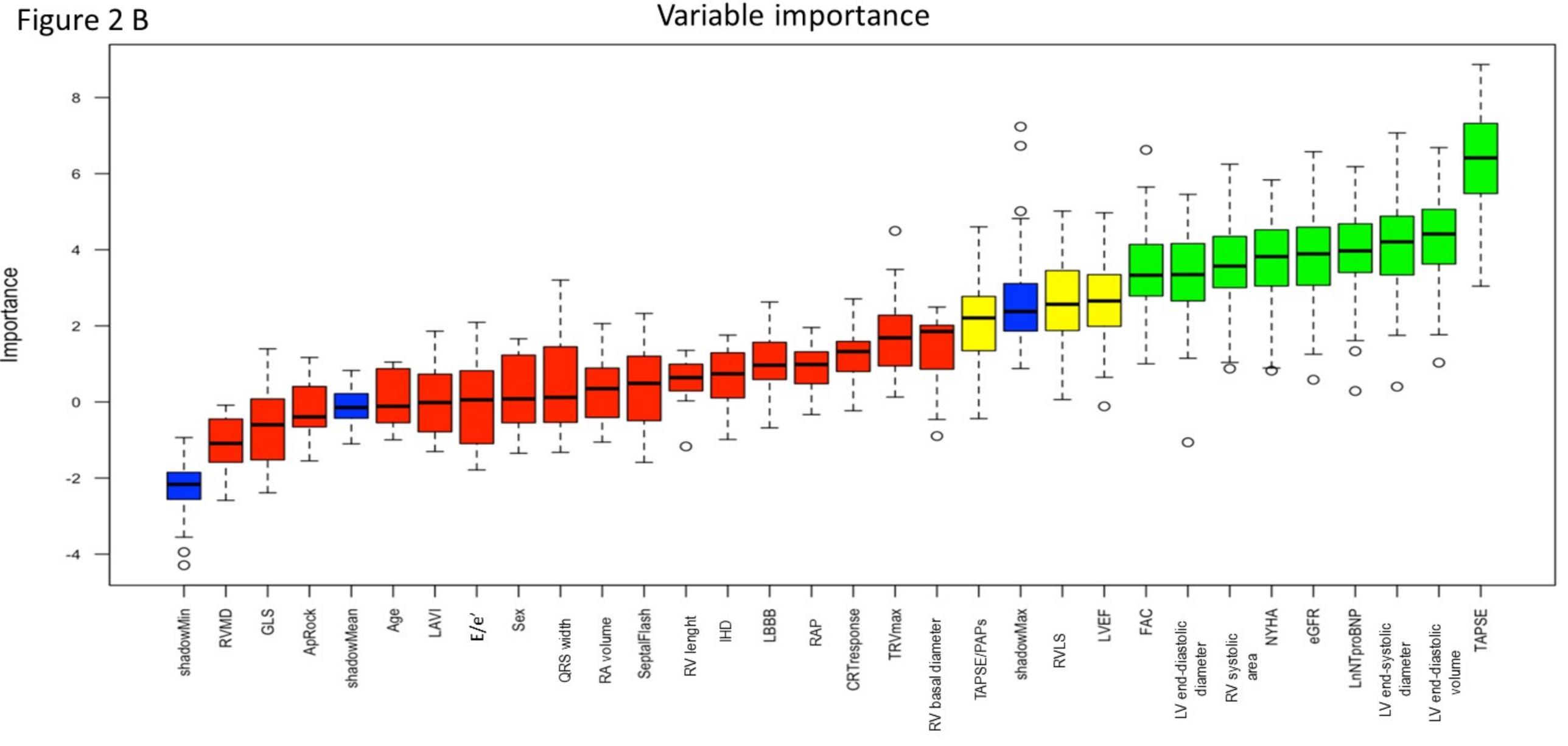

Variable importance
Importance
8
6
4
2
0
-2
-4
shadowMin
RVMD
GLS
ApRock
shadowMean
Age
LAVI
E/e'
Sex
QRS width
RA volume
SeptalFlash
RV lenght
IHD
LBBB
RAP
CRTresponse
TRVmax
RV basal diameter
TAPSE/PAPs
shadowMax
RVLS
LVEF
FAC
LV end-diastolic diameter
RV systolic area
NYHA
eGFR
LnNTproBNP
LV end-systolic diameter
LV end-diastolic volume
TAPSE

Fig 3

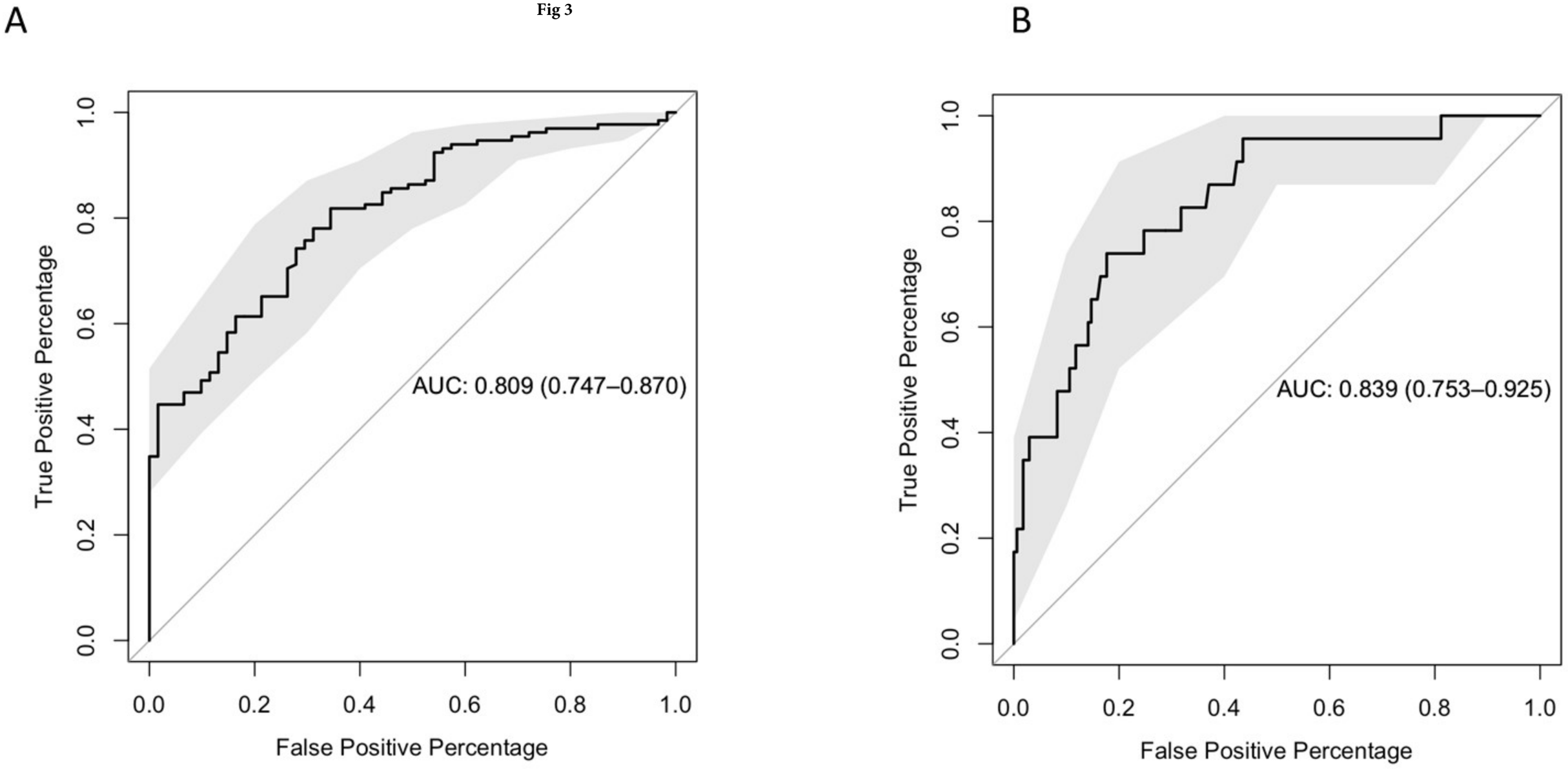
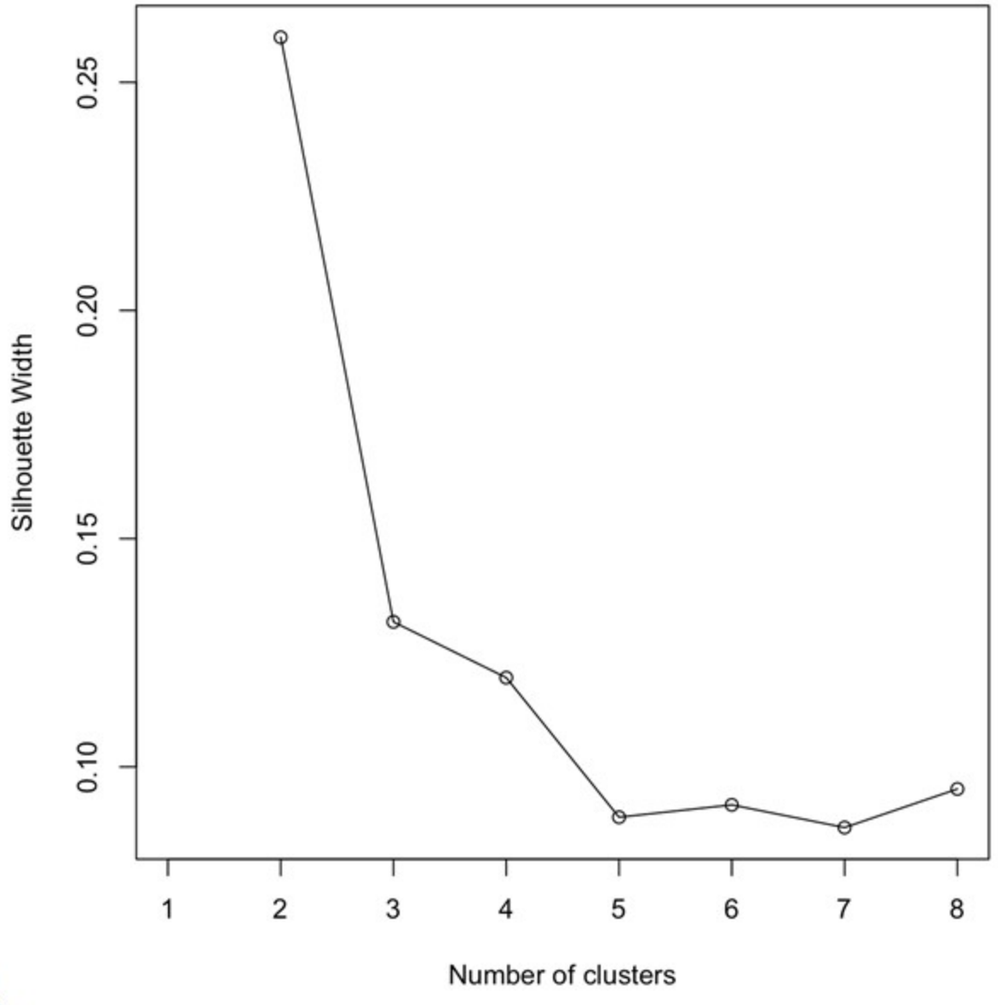
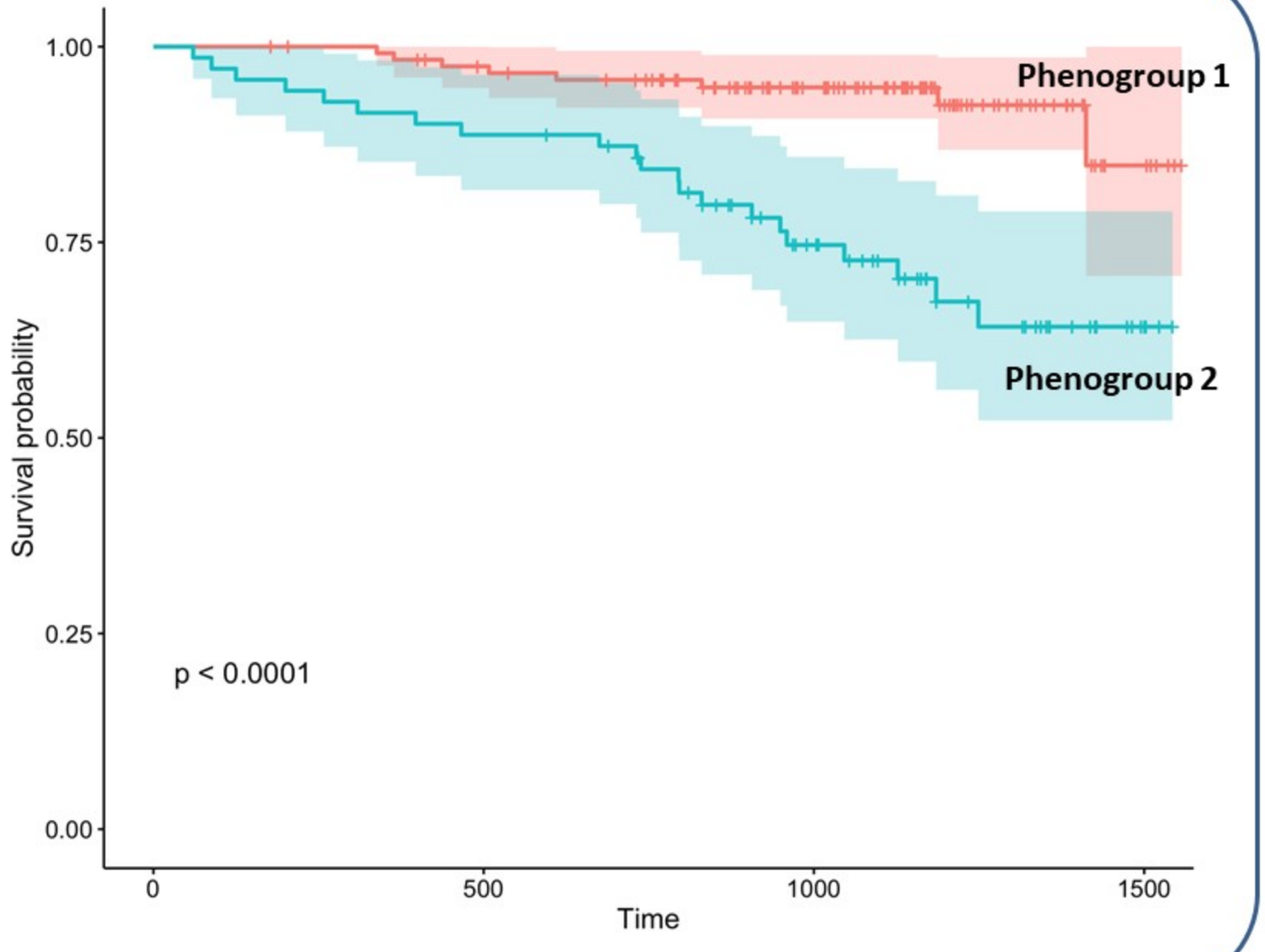
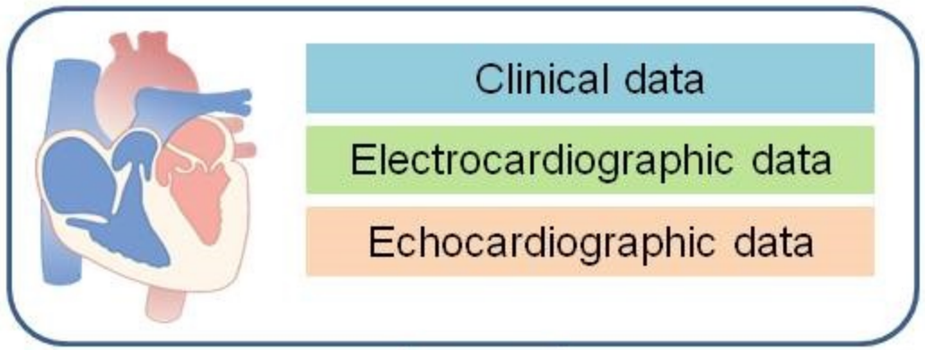

A
True Positive Percentage
False Positive Percentage
AUC: 0.809 (0.747–0.870)
0.0
0.2
0.4
0.6
0.8
1.0
B
True Positive Percentage
False Positive Percentage
AUC: 0.839 (0.753–0.925)

Fig 4


Silhouette Width
0.10
0.15
0.20
0.25
1
2
3
4
5
6
7
8
Number of clusters

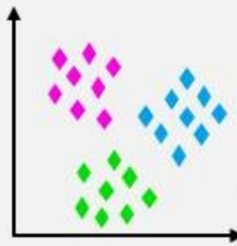

Survival probability
1.00
0.75
0.50
0.25
0.00
0
500
1000
1500
Time
Phenogroup 1
Phenogroup 2
p < 0.0001

Central illustration



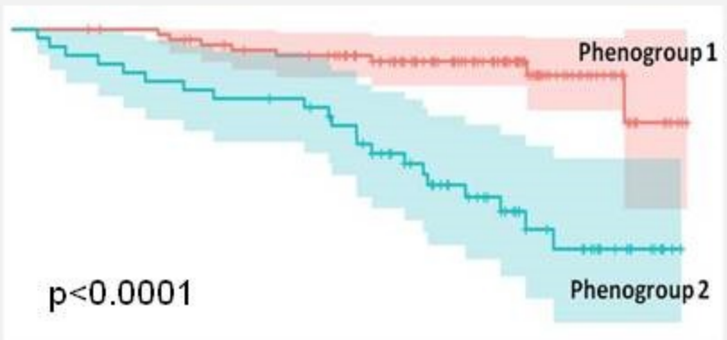
Unsupervised Machine Learning

k-medoid Clustering



Significant difference in RV size and function among groups

Patients' phenotyping



Supervised Machine Learning

Selection of features
Boruta algorithm

Predictors of CRT-response

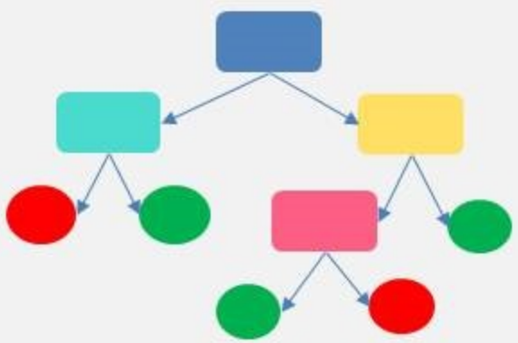
16 main features: 50% from RV size/function

Predictors of Prognosis

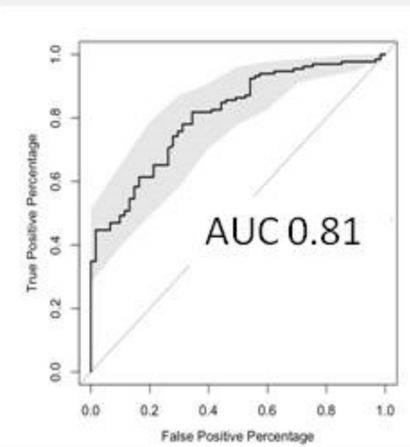
11 main features: 36% from RV size/function

TAPSE is the most important feature

Random Forest
Features' classification



Predictors of CRT-response



Predictors of prognosis