Phenotyping of heart failure with preserved ejection faction using electronic health records and echocardiography

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Aims	Patients presenting symptoms of heart failure with preserved ejection fraction (HFpEF) are not a homogenous population. Different phenotypes can differ in prognosis and optimal management strategies. We sought to identify phenotypes of HFpEF by using the medical information database from a large university hospital centre using machine learning.
Methods and results	We explored the use of clinical variables from electronic health records in addition to echocardiography to identify different phenotypes of patients with HFpEF. The proposed methodology identifies four phenotypic clusters based on both clinical and echocardiographic characteristics, which have differing prognoses (death and cardiovascular hospitalization).
Conclusion	This work demonstrated that artificial intelligence–derived phenotypes could be used as a tool for physicians to assess risk and to target therapies that may improve outcomes.

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Graphical Abstract

- **Heart Failure with preserved ejection fraction is heterogeneous and patients are not all in the cardiological pathway**

=> Phenotyping these patients from the electronic health records and echocardiographic data set of one Hospital

① hospital warehouse with all the data from all the patients	Interrogations of the warehouse and use of machine learning capabilities	**4 clusters** (based on both clinical and echocardiographic characteristics) with differing prognoses

Introduction

The prevalence of heart failure with preserved ejection fraction (HFpEF) is increasing.[1] It represents a heterogeneous syndrome with different clinical phenotypes.[2,3] Using different phenotypes to identify patients more at risk of HF hospitalizations may be useful in tailoring the follow-up for individual patients as well as being able to provide more individualized prognosis. Research investigating treatments that modify disease outcomes[4] has so far been disappointing, and the characterization of different phenotypes may allow us to better target treatments that may improve the outcomes for patients with HFpEF.[5]

This study uses both the clinical variables available in electronic health records (EHR) and echocardiographic parameters to classify patients with HFpEF into phenotypical groups who share similar physiological profiles. Finally, we attempted to link these phenogroups to outcomes. The combined endpoint is death and/or cardiovascular hospitalization.

Methods

Study population and data source

The EHOP Clinical Data Warehouse (CDW) of Rennes University Hospital Center (RUHC) contains clinical notes, drug prescriptions, laboratory tests, and administrative data.[6,7] It also includes diagnoses coded using the French version of the International Classification of Diseases (ICD-10). With this technology, it was possible to screen the population of the RUCH to identify patients suffering from HFpEF. The patients were defined to have a HFpEF according to the reports made by their physicians (these are supposed to apply the definitions coming from the guidelines). We then extracted and analysed individual EHR data of these patients. In addition, echocardiographic data were also available; we focused on records performed between January 2017 and December 2018.

A list of relevant clinical and echocardiographic variables was established. We extracted clinical as well as echocardiographic variables. For clinical variables, we extracted information from the data warehouse using either structured data (ICD-10 codes, laboratory results, etc.) or key words (heart failure with preserved ejection fraction, heart failure with left ventricular ejection fraction ≥50%). The echocardiographic parameters consisted only in structured data. In the face of extreme values, the individual patient file was reviewed to check these were correct. The large size of the cohort allowed us to split it into two data sets (50/50): a first one named training set and a second independent data set named replication data set. The first one has been used to perform unsupervised clustering, train, and optimize the predictive models using artificial intelligence (AI). The second one has been used to predict phenotypes similarly to what we could do in real life.

Statistical modelling

We performed a two-step cluster analysis to identify common characteristics among patients. As a first step, we performed principal component analysis (PCA using the R package FactoMineR[8]) following by a spectral clustering to the 11 first coordinates of the PCA (using SNFtool R package).

Outcomes were obtained from both data available from the CDW and from the National Institute of Statistics and Economic Studies. We matched first name, surname, date of birth, and town of birth if available. We collected admissions under cardiology from the CDW. We carried out a survival analysis using Kaplan–Meier curves and the log-rank test on mortality and admission to a cardiology or geriatric department.

As the final aim was to classify new patients, then we used supervised machine learning algorithms to predict the phenogroups defined by the unsupervised clustering algorithm. We optimized three algorithms: support vector machine (SVM), logistic regression, and random forest (RF). To avoid overfitting, we split the training data set into two sub-data sets (train and test). We trained the algorithms on the first set, and we evaluated their performance on the second one. We measured the performance by computing area under the receiver operating characteristic curve (AUC) and accuracy and the variable importance of each method by using permutations.[9]

Finally, we replicated the analysis on the *replication* data set. We predicted clusters with the best machine learning model and studied survival and characteristics of patients across the predicted clusters.

All analyses were performed using R version 3.6.0.

Table 1 Table of characteristics and *P*-values to compare clusters on training data set

Characteristic	1, $N = 506$[a]	2, $N = 235$[a]	3, $N = 216$[a]	4, $N = 324$[a]	*P*-value[b]
Age	74 (11)	51 (14)	69 (13)	75 (11)	<0.001
Sex (woman)	142 (28%)	41 (17%)	90 (42%)	203 (63%)	<0.001
BMI	27.5 (4.9)	25.7 (4.2)	24.6 (3.6)	25.1 (3.8)	<0.001
Serum creatinine	131 (84)	79 (23)	81 (21)	78 (23)	<0.001
NT-proBNP [log (ng/L)]	7.11 (0.96)	5.48 (0.85)	6.59 (0.81)	6.49 (0.92)	<0.001
Haemoglobin	11.95 (1.81)	13.63 (1.56)	11.42 (1.75)	12.21 (1.64)	<0.001
Renal impairment	386 (76%)	107 (46%)	174 (81%)	139 (43%)	<0.001
Diabetes	254 (50%)	40 (17%)	41 (19%)	55 (17%)	<0.001
Pulmonary hypertension	96 (19%)	6 (2.6%)	19 (8.8%)	13 (4.0%)	<0.001
Atrial fibrillation	292 (58%)	49 (21%)	114 (53%)	85 (26%)	<0.001
Peripheral artery disease	132 (26%)	13 (5.5%)	22 (10%)	6 (1.9%)	<0.001
Mitral regurgitation	192 (38%)	33 (14%)	48 (22%)	64 (20%)	<0.001
RV dysfunction	81 (16%)	10 (4.3%)	167 (77%)	6 (1.9%)	<0.001
LVH	402 (79%)	133 (57%)	135 (62%)	157 (48%)	<0.001
LBBB	201 (40%)	30 (13%)	68 (31%)	63 (19%)	<0.001
Hypertension	409 (81%)	72 (31%)	137 (63%)	185 (57%)	<0.001
GLS	−16.81 (2.41)	−18.58 (2.52)	−17.65 (2.21)	−18.97 (2.14)	<0.001
LVEF	0.62 (0.07)	0.63 (0.06)	0.61 (0.06)	0.65 (0.07)	<0.001
Indexed LA vol	49 (16)	31 (9)	36 (12)	38 (12)	<0.001
LVPWs	14.90 (1.99)	14.20 (1.90)	13.91 (1.37)	13.84 (1.21)	<0.001
e′	0.073 (0.020)	0.101 (0.019)	0.085 (0.021)	0.073 (0.016)	<0.001
E/e′	14.3 (5.3)	7.7 (2.2)	11.2 (4.1)	12.4 (4.0)	<0.001
sPAP	39 (10)	34 (6)	33 (7)	36 (7)	<0.001
TAPSE	21.0 (3.9)	22.5 (3.6)	16.1 (3.3)	22.4 (3.6)	<0.001

RV, right ventricular; LVH, left ventricular hypertrophysexe; LBBB, left bundle branch block; BMI, body mass index; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; LAvol, left atrial volume; LVPWS, left ventricular posterior wall in systole; sPAP, systolicpulmonay arterial pressure; TAPSE, tricuspid annular plan systolic excursion.

[a]*n* (%); mean (SD).

[b]Pearson's χ^2 test; Kruskal–Wallis rank-sum test.

Figure 1 Flowchart of patient selection. ML, machine learning.
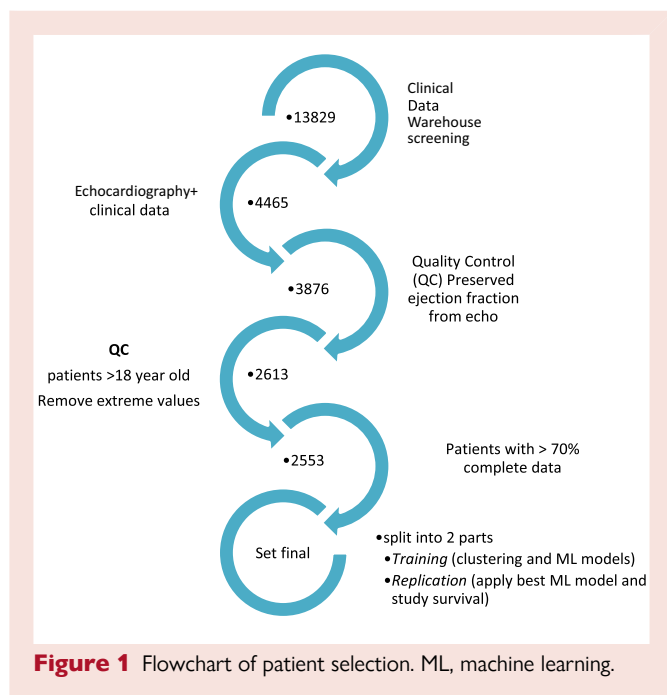
Results

Baseline characteristics

The flowchart of patient selection is presented in *Table 1*. The final sample eligible included around 2500 patients with echocardiograms and with HFpEF (*Figure 1*). The variables included in the two-step cluster analysis were both clinical (18 variables) and echocardiographic (8 variables).

Identification of four phenogroups

We selected four clusters with the unsupervised clustering algorithm on the *training* set. The groups are relatively well balanced with 506, 235, 216, and 324 individuals, respectively, and we clearly identified distinct patterns (*Figure 2*). The characteristics for the four phenotypes are given in *Table 1*. *Figure 3* summarizes the main characteristics of the phenotypes.

Validation of follow-up outcomes

After performing survival analysis, we observed that clusters have significantly different survival curves for death or HF hospitalization.[4] Cluster 1 has the highest risk of death or cardiology hospitalization (*Figure 4*).
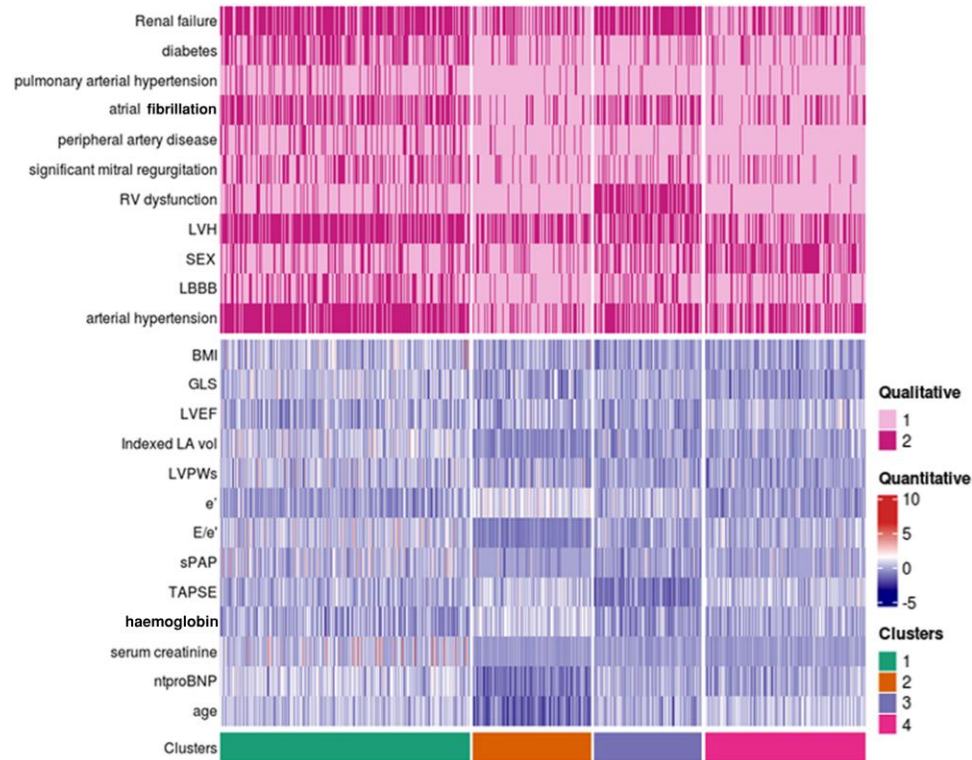
Figure 2 Heatmap of clinical and echocardiographic variables across different patients. Relative value is indicated by colour: high level (red), median level (white), and low level (blue) for quantitative variable. For qualitative, 1 means no and 2 means yes, except for sex where 1 matches to man and 2 matches to woman. RV, right ventricular; LVH, left ventricular hypertrophysexe; LBBB, left bundle branch block; BMI, body mass index; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; LAvol, left atrial volume; LVPWS, left ventricular posterior wall in systole; sPAP, systolicpul-monay arterial pressure; TAPSE, tricuspid annular plan systolic excursion.
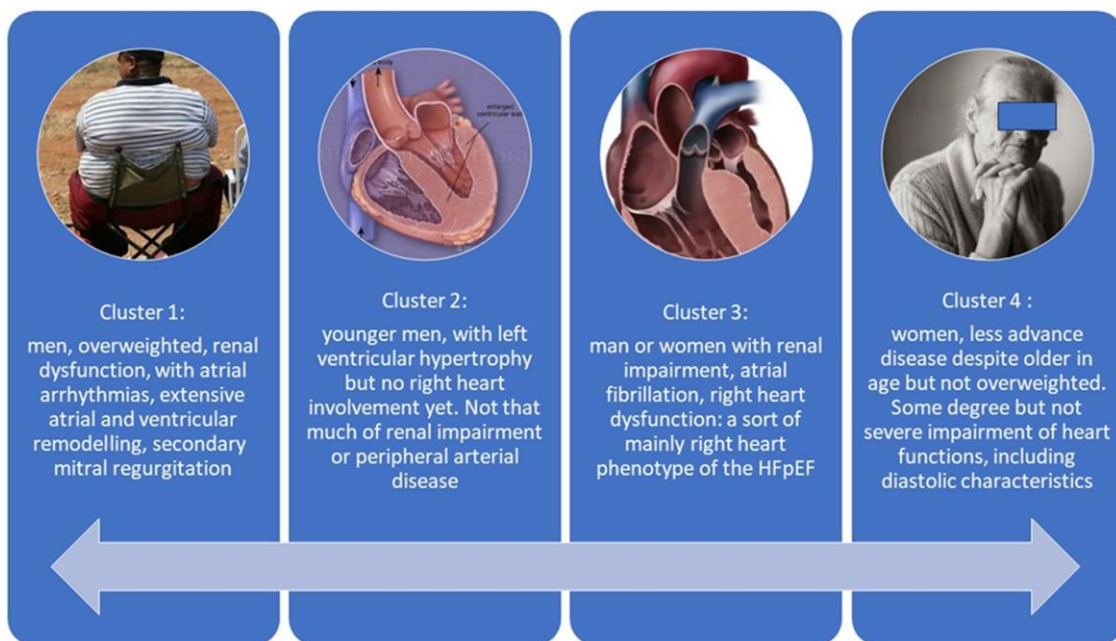

Figure 3 Schematic description of the clusters. HFpEF, heart failure with preserved ejection fraction.

Predictions of clusters with machine learning methods

The second part of this study consisted of building a comprehensive model able to predict the phenogroups of patients. Logistic multinomial regression, SVM, and RF[10] models were used on raw data as predictors and clusters as predicted output.

Optimization of machine learning models was been performed on the training set (75%) in addition to bootstrapping. We then evaluated the models on the test set (25%). The performances of these models were very satisfying with an AUC >0.95 and an accuracy >0.80 (Table 2). We retained the logistic multinomial model that provides better performance on the two criteria to classify patients.

We computed the variable importance of the three models by permutation method. The most important variables seem to be right ventricular (RV) dysfunction, then age and sex.

The replication was conducted on the independent data set (replication data set) where we used the logistic regression to predict the groups of these new patients. We recovered the similar characteristics and survival curves than for the training set (see Supplementary material online, Table S1). All results are displayed in the Supplementary material (see Supplementary material online, Table S1 and Figure S2).

Discussion

Heart failure with preserved ejection fraction is a challenging disease entity that represents a large proportion of the patients with HF symptoms.[11] Up to the recent months, there have been disappointing results in clinical trials for this group of patients who have an unmet need for treatments that alter disease outcomes.[12,13] It has been highlighted that this HFpEF syndrome is regrouping different types of patients.[3] In this study, we looked at a large population of HFpEF patients treated in a referral hospital and identified four clusters of HFpEF patients using machine learning based on clinical and echocardiographic features. This is important for several reasons; it demonstrates the heterogeneity of HFpEF patients, the possibility to identify specific disease targets that lead to improved outcomes, and to provide individualized prognosis and follow-up plans.[14]

Traditionally, HFpEF has been treated as one large group, and other studies[2] have also confirmed different phenogroups exist under the umbrella of HFpEF.[14–16] The use of AI to define and group the patients is promising as it can be done quickly and can be transitioned into care at the bedside. This study provides evidence that AI can be used to define groups of patients that differ in their clinical characteristics and that these groups have different prognoses. Further validation of this method should be carried out as it offers an exciting prospect to provide more personalized care.[17,18]

Previous works using the clustering methods have been published and are summarized in Table 3.

Table 2 Accuracy and area under the receiver operating characteristic curve for the multinomial regression, random forest, and support vector machine models

Partition	Metric	Multinomial regression	RF	SVM
Training	Accuracy	0.97	0.99	0.92
	AUC	1	1	0.96
Testing	Accuracy	0.94	0.83	0.89
	AUC	1	0.97	0.95

AUC, area under the receiver operating characteristic curve.

Among the four phenogroups we identified, there was a striking difference in outcomes that points to real differences between the clusters (Figure 5). Cluster 1 had more advanced cardiac disease noted on echo parameters and a higher prevalence of comorbidities including peripheral vascular disease and atrial fibrillation (AF). This was reflected in the survival curves with the poorest survival of 80% at 2 years in this group. Cluster 2 that was a group of predominantly younger men, with a lower proportion of risk factors and surprisingly normal diastolic function despite a high prevalence of AF. These patients would probably benefit from an aggressive management of comorbidities and lifestyle measures to prevent progressive cardiac dysfunction (survival 92% at 2 years).
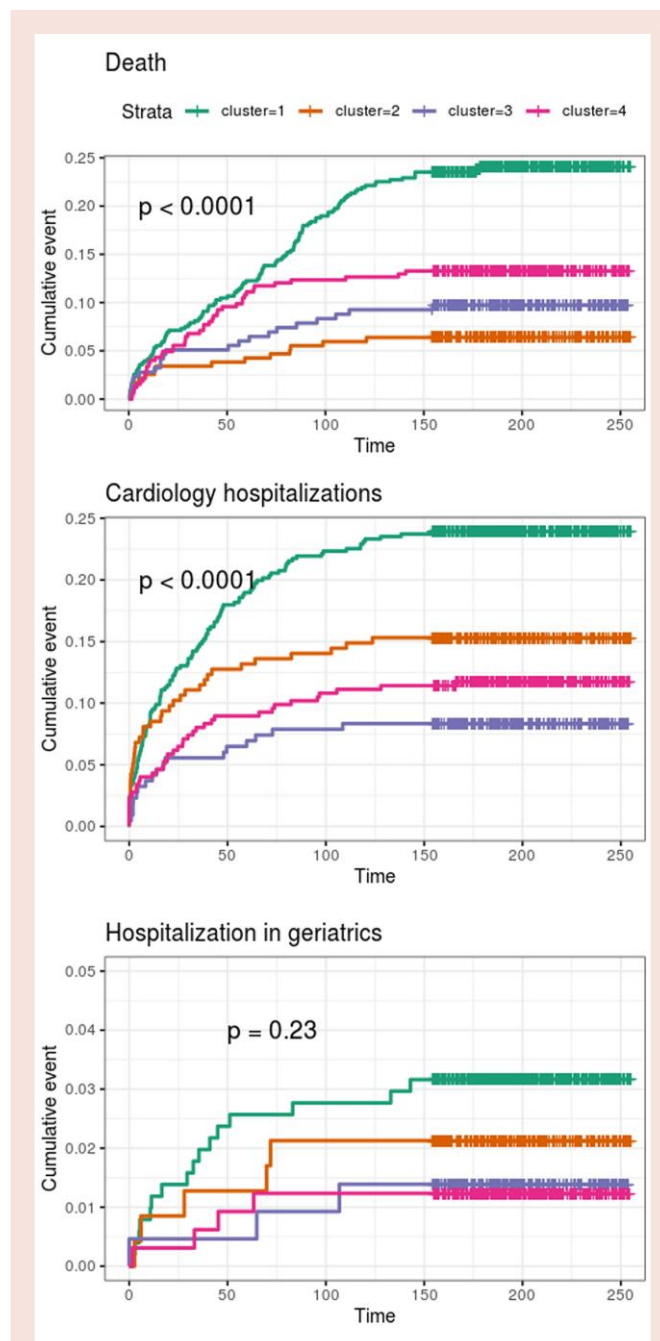

Figure 4 Variable importance of multinomial regression, support vector machine, and random forest models.

Table 3 Main results of previous phenotyping studies in the field of heart failure with preserved ejection fraction

Study	Shah et al. 2015[3]	Cohen et al. 2020[24]	Schrub et al. 2020[16]	Gu et al. 2021[19]	Uijl et al. 2021[12]	Kyodo et al. 2023[20]
Population, number of patients	397 patients + 107 patients (validation cohort), 56 variables (clinical, biological, echocardiography)	3442 patients from the TOPCAT Study. Multiple biomarkers, TTE, arterial tonometry	356 patients from the KaRen cohort (French + Norwegian). No validation cohort. 55 variables (clinical + biological + TTE)	970 patients initially + 290 patients (validation cohort). 11 variables (clinical + biological + TTE)	6909 patients in Sweden (female 52%). No echocardiographic variables	365 patients from a Japanese HF register + 230 patients (validation cohort). 24 variables (clinical + biological + TTE)
Number of clusters/ phenogroups	3	3	3	3	5	3
Cluster characteristics	1: young patients, obesity, few cardiac damage; 2: intermediate age, many risk factors, altered relaxation; 3: AF, CKD, older patients	1: younger patients, low NYHA class; 2: women, less LV remodelling, low CV risk factors; 3: women, LVH, biomarkers of AF and inflammation, severe MR	1: young men, low AF, CKD, many smoking, low CV risk factors; 2: older, LA dilatation, remodelling but intermediate LA AF, vascular calcification; 3: obesity, CV dilatation, and MR; 3: elderly risk factors, CKD, LVH, high prevalence of	1: young patients, low comorbidities; 2: predominance, risk factors, less AF; 2: frequent AF and hypertension, low, older women, LVH, and diastolic diabetes; 3: old people with many dysfunction; 3: older male, major risk comorbidities; 4: obesity, diabetes, factors, ischaemic heart disease, hypertension; 5: CHD, renal failure	1: older patients with high BNP level, worse kidney function, history of myocardial infarction; 2: elderly women, high prevalence of AF, low risk factors; 3: young overweight males, frequent LVH
Cluster prognosis	Worst prognosis for Clusters 3 > 2 > 1 (CV hospitalization and death)	Worst prognosis for Clusters 3 > 2 > 1 (CV death, HF hospitalization, aborted cardiac arrest)	No statistical difference, tendency towards higher mortality in Cluster 3	Worst prognosis 3 > 2 > 1 (all-cause death)	Clusters 3 and 5 with the worst prognosis (mortality and HF hospitalization)	Cluster 1 with the worst prognosis (all-cause death or HF re-admission)

CV, cardiovascular; AF, atrial fibrillation; CKD, chronic kidney disease; HF, heart failure; LA, left atrial; CV, cardiac cavities; CHD, chronic heart disease; LVH, left ventricular hypertrophy.

Figure 5 Survival outcomes—death, cardiology hospitalizations, and hospitalizations in geriatrics.
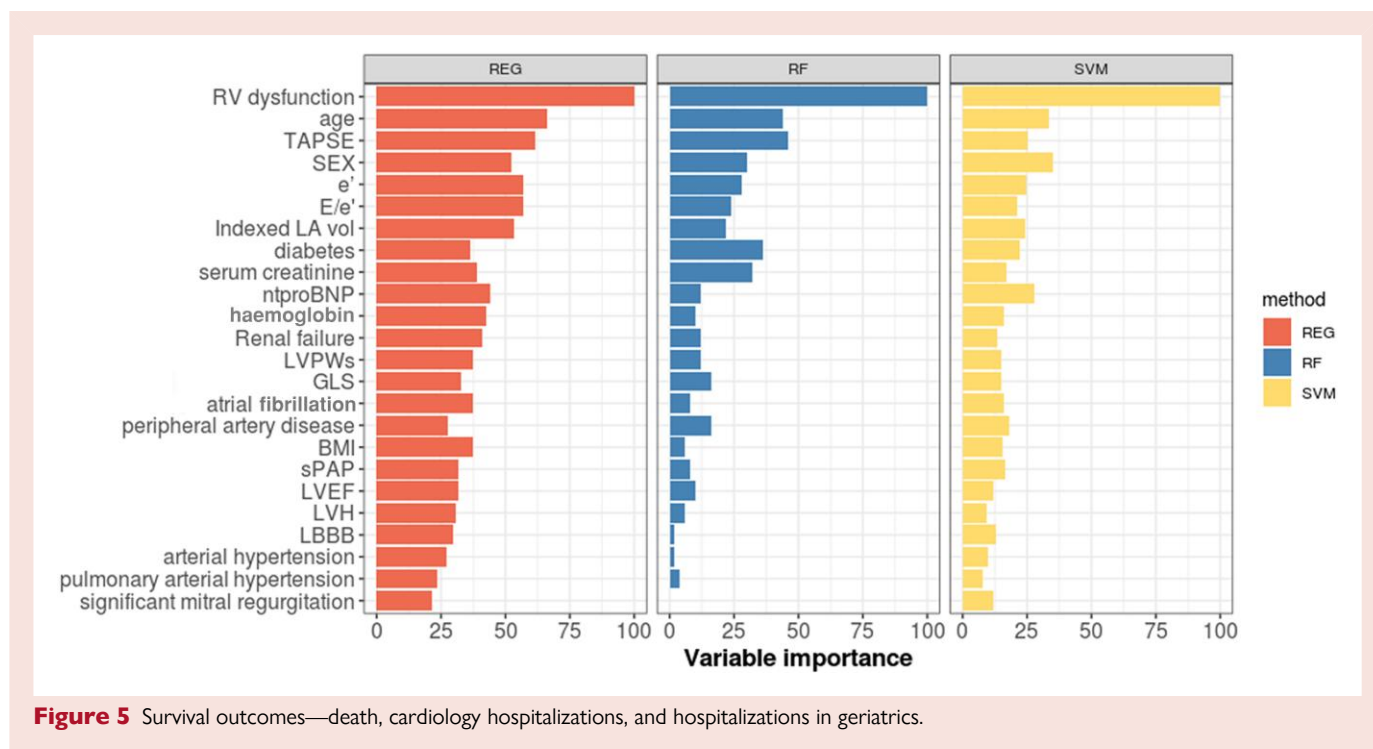
Previously, trials have taken all comers with a diagnosis of HFpEF, which may have led to the nulling of the effect of therapies and has left us with very little to offer in terms of treatment. Cluster 3, who are largely defined by the presence of RV dysfunction and >50% with AF, are likely to require substantially different care than the patients in Cluster 4, for example, as the patients in Cluster 4 are older, have a higher percentage of females, and have preserved RV function.[21–23] Using these phenogroups, the treatments could be targeted and this may hold the key to the development of disease-modifying therapies for this population where there exists a large space to improve outcomes.

Having the ability to accurately identify patients who are more likely to have recurrent hospital admissions and higher mortality is useful for both planning frequency of follow-up and to help the patient understand the meaning of the diagnosis of HFpEF specific to their context. The clusters we identified had a large variability in rates of hospitalization and death, and this information could be useful for tailoring the care for each patient. In the patients with high rates of HF hospitalizations, early development of HF action plans may help to reduce the frequency of hospitalization, which is important in considering the cost that these admissions represent.[23] Of note, according to the cluster, the location of the hospitalization is potentially different, and the risk of death is not occurring following the same trends than hospitalizations. Frailty is a component that has not been quantified but that might have been more prevalent in Cluster 4.

Limitations

The clinical variable extraction from health records is imperfect because of automatic extraction, and for a non-negligible number of patients, there was poor quality or missing data. This required clinicians to perform quality control of data, which is time costly, but it can be avoided by utilizing Natural language processing techniques.

Imputation of missing values was done using the k-nearest neighbors algorithm, which has limitations as these are not real data.

Perspectives

The utility of this method is that we reliably identified four different clusters of patients who differed in clinical and echocardiographic variables, and that these differences were associated with real differences in outcomes. This phenotypical clustering method could be used for clinical trials using targeted therapies for each phenogroup and may be the key in identifying disease-modifying therapy in HFpEF.

Conclusions

We developed a proof of concept of machine learning model to predict the phenotype of patients suffering from HFpEF using both clinical and echocardiography data from data warehouse of a large university hospital centre. The phenotypes displayed the heterogeneity that exists in patients with HFpEF and was linked to outcomes. The phenotyping of HFpEF could improve the characterization of patients and define the most appropriate treatments and the care pathways required for each patient.

Lead author biography

Clinical responsibility at the University Hospital of RENNES—general cardiology, valvular heart diseases and structural heart diseases, and head of the echocardiography laboratory; head of the imaging Core Lab at the CIC-IT INSERM 1414; member of the LTSI (laboratoire du traitement du signal et de l'image) INSERM 1099—University Rennes (www.ltsi.univ-rennes1.fr); secretary of the EACVI; and president of the French group for heart valve disease (at the SFC).

Data availability

The data underlying this article will be shared upon reasonable request to the corresponding author.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

Conflict of interest: CHU Rennes and Erwan DONAL are receiving research facilities from Abbott structural and General Electric Healthcare.

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