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RESEARCH ARTICLE

Machine learning approach to identify phenotypes in patients with ischaemic heart failure with reduced ejection fraction

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Aims Patients experiencing ischaemic heart failure with reduced ejection fraction (HFrEF) represent a diverse group. We hypothesize that machine learning clustering can help separate distinctive patient phenotypes, paving the way for personalized management.

Methods and results A total of 8591 ischaemic HFrEF patients pooled from the EPHESUS and CAPRICORN trials (64 ± 12 years; 28% women) were included in this analysis. Clusters were identified using both clinical and biological variables. Association between clusters and the composite of (i) heart failure hospitalization or all-cause death, (ii) cardiovascular (CV) hospitalization or all-cause death, and (iii) major adverse CV events was assessed. The derived algorithm was applied in the COMMANDER-HF trial ($n = 5022$) for external validation. Five clinical distinctive clusters were identified: Cluster 1 ($n = 2161$) with the older patients, higher prevalence of atrial fibrillation and previous CV events; Cluster 2 ($n = 1376$) with the higher prevalence of older hypertensive women and smoking habit; Cluster 3 ($n = 1157$) with the higher prevalence of diabetes and peripheral artery disease; Cluster 4 ($n = 2073$) with relatively younger patients, mostly men and with the higher left ventricular ejection fraction; Cluster 5 ($n = 1824$) with the younger patients and lower CV events burden. Cluster membership was efficiently predicted by a random forest algorithm. Clusters were significantly associated with outcomes in derivation and validation datasets, with Cluster 1 having the highest risk, and Cluster 4 the lowest. Mineralocorticoid receptor antagonist benefit on CV hospitalization or all-cause death was magnified in clusters with the lowest risk of events (Clusters 2 and 4).

Conclusion Clustering reveals distinct risk subgroups in the heterogeneous array of ischaemic HFrEF patients. This classification, accessible online, could enhance future outcome predictions for ischaemic HFrEF cases.

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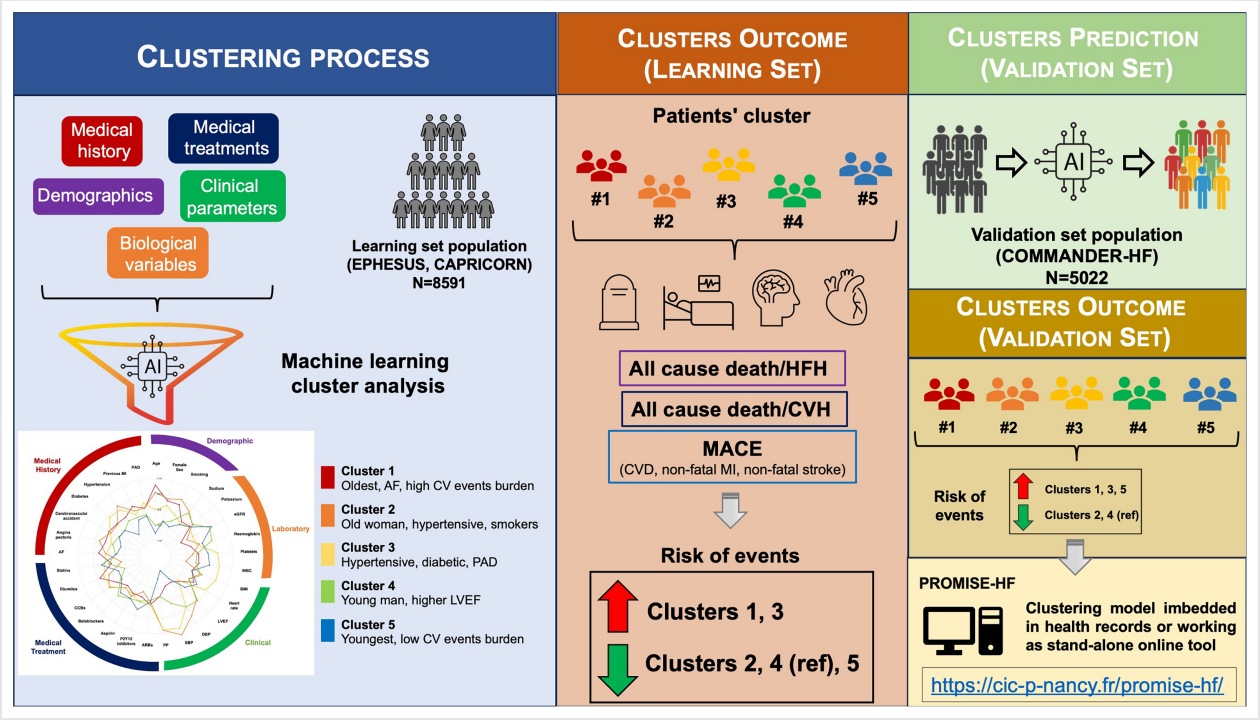
Graphical Abstract



Summary of the machine learning clustering methodology and results of the study. Clusters are identified using machine learning approach in the learning set population evaluating specific combinations of multiple characteristics. Then identified clusters are predicted and tested in the learning set to evaluate their association with outcomes. Finally, the reproducibility of the results of cluster analysis is tested in an external cohort (validation set). AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CV, cardiovascular; CVD, cardiovascular death; CVH, cardiovascular hospitalization; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HFH, heart failure hospitalization; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; MI, myocardial infarction; PAD, peripheral artery disease; PP, pulse pressure; SBP, systolic blood pressure; WBC, white blood cell.

Keywords Machine learning • Clustering • HFrEF • Clinical outcomes • Ischaemic heart disease

Introduction

Although long-term survival after myocardial infarction (MI) has improved over the last four decades, mainly due to reperfusion therapy and evidence-based treatments, ischaemic heart disease remains a leading cause of morbidity and mortality worldwide with a high global disease burden.[1–3] In recent years, there has been a plateau in the reduction of mortality rates, particularly among patients with heart failure (HF) after MI that face a particular high risk of adverse events.[4,5] A better understanding of the characteristics associated with worst outcomes in ischaemic HF (either soon after or distantly from MI) could refine the treatment targets of specific subset of patients at highest risk, possibly improving prognosis, and help in selecting a study population with enough events to provide robust outcome analysis. In the recent PARADISE-MI (Prospective ARNI versus ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events after Myocardial Infarction) trial, a neutral result was blamed on the low primary event rate.[6] Indeed, events rates are continuously declining in post-MI trials since the advent of the first renin–angiotensin system blockers, as demonstrated in the SAVE (Survival And Ventricular Enlargement)[7] and the VALIANT (Valsartan in Acute Myocardial Infarction)[8] trials (i.e. mortality was 8.5% at 2 years in the ramipril arm of PARADISE-MI compared with 20% in the VALIANT trial).

Machine learning-based clustering may provide unbiased separation of subgroups of patients with similar characteristics and outcomes among populations with heterogeneous underlying features. This approach has been previously used in cardiovascular (CV) research to explore populations with well-known heterogeneity, such as patients with HF with preserved ejection fraction[9] or community-based cohorts.[10] By improving our ability to identify

Table 1 Variables used for clustering

Demographic	Medical history	Medical treatment	Clinical	Laboratory
Age	Angina pectoris	$P2Y_{12}$ inhibitors	BMI	eGFR
Sex	Atrial fibrillation	Angiotensin II receptor blockers	Heart rate	Haemoglobin
Smoker status	Cerebrovascular accidents	Aspirin	LVEF	Platelet count
	Diabetes	Beta-blockers	Diastolic blood pressure	Potassium
	Hypertension	Calcium channel blockers	Systolic blood pressure	Sodium
	Previous myocardial infarction	Diuretics	Pulse pressure	White blood cell count
	Peripheral artery disease	Statins		

BMI, body mass index; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction.

subgroups of patients with distinct clinical features and outcomes, machine learning clustering has the potential to drive more personalized and effective treatment strategies for CV diseases.

This study sought to identify clinically and prognostically homogeneous clinical clusters of patients with ischaemic HF with reduced ejection fraction (HFrEF), with the potential of defining high-risk patients who might benefit from novel preventive interventions.

Methods

Study groups

The high-risk MI initiative consists of a previously published cohort of pooled patient data derived from four clinical trials.[11] Briefly, the main objectives of the project were to provide a comprehensive and statistically robust analysis of long-term clinical outcomes in high-risk survivors of MI. The datasets included in this pooling initiative were as follows: the CAPRICORN (Effect of Carvedilol on Outcome After Myocardial Infarction in Patients With Left Ventricular Dysfunction) trial,[12,13] EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study),[14,15] OPTIMAAL (Optimal Trial in Myocardial Infarction With Angiotensin II Antagonist Losartan),[16,17] and VALIANT.[8,18] Full details of total enrolled patients, the inclusion and exclusion criteria for each trial, the endpoints, and the results have previously been published.[11] Each trial enrolled patients with left ventricular systolic dysfunction, HF, or both between 12 h and 21 days after acute MI. The respective chairpersons of the steering committees of the four trials initiated the pooling project.

The COMMANDER-HF (Rivaroxaban in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease) trial was a multicentre, randomized, double-blind, placebo-controlled, event-driven trial that evaluated the safety and efficacy of rivaroxaban compared with placebo among patients with chronic HFrEF, a recent episode of worsening HF and underlying coronary artery disease.[19]

The studies were all conducted in accordance with the Declaration of Helsinki and were approved by site ethics committees. All participants gave written informed consent to participate in the studies.

For the present analysis, the high-risk MI pooled cohort worked as learning set. The OPTIMAAL and VALIANT trials were excluded from the analysis because data on left ventricular ejection fraction (LVEF) in the former, and laboratory information (white blood cells, haemoglobin, platelets, plasma sodium and potassium) in the latter, were missing. The COMMANDER-HF trial population worked as validation set.

Machine learning approach: cluster analysis and decision tree construction

Cluster identification was based on demographic data, treatment information, medical history, and biological data known to impact prognosis in patients with ischaemic HF (*Table 1*), as previously described.[20] To ensure high data integrity and to minimize the impact of missing data on the robustness of the analysis, the selection was further refined to include only those variables with less than 30% missing data across derivation cohorts. Strong correlations between the chosen variables were excluded before the analysis (online supplementary *Figure S1*). The impact of each variable on cluster structure and its contribution to defining distinct clusters were evaluated using leave-one-out analysis and discriminative analysis (online supplementary *Table S1*).

To identify clinical patterns, we used latent class model (LCM) clustering analysis with VarSelLCM R package due to its proven effectiveness in handling mixed data types, as previously demonstrated by our group.[21] The optimal cluster number was based on examining Bayesian information criterion (BIC), across solutions from two to eight clusters. To ensure a satisfactory balance between model performance and interpretability, we selected the number of clusters at the point where BIC improvements diminished significantly with additional clusters (online supplementary *Figure S2*). Moreover, to preserve statistical robustness relative to the learning cohort size, we set a minimum cluster size of 1000 patients. Each patient in the data set was labelled with a corresponding cluster.

To predict clusters on new datasets, a random forest and a decision tree classifier (from WEKA)[22] were trained. Considering the number of variables and the number of patients, the number of trees in the forest was set at 100 and the minimal number of patients per leaf in the decision tree was defined as 15% of the smallest cluster size. The models were first evaluated by 10 repetitions of 10-fold cross-validation and then the random forest model was applied for validation to the COMMANDER-HF dataset. The performance of our classification models was tested using the receiver operating characteristic (ROC) curve and the F-measure, a harmonized metric of precision and recall that ranges from 0 (no reliability) to 1 (perfect accuracy). The source code of all analyses performed within this project including the random forest model is available in GitLab.

Outcomes

The main outcomes were: (i) the composite of HF hospitalization or all-cause death events, (ii) the composite of CV hospitalization or all-cause death, and (iii) the 3-point major adverse CV events (MACE)

outcome (including CV death, non-fatal MI, or non-fatal stroke). Additionally, we evaluated all-cause death, CV death, and the composite of HF hospitalization or CV death. Multiple HF hospitalizations, defined as at least two HF hospitalizations during follow-up or one HF hospitalization followed by death, were also explored. Endpoints were independently adjudicated in the respective trials.

Statistical method

Categorical variables were described as frequencies (percentages), whereas continuous variables are described as median (25th–75th percentile). Comparisons of participant characteristics across clusters were analysed using analysis of variance (ANOVA), Kruskal–Wallis, and chi-squared test or Fisher's exact test, as appropriate. To assess the associations between clusters and clinical outcomes, time to event analysis were performed using a Cox regression model and adjusted for age and sex. Hazard ratios (HR) are presented with their 95% confidence intervals (CI). Survival probabilities were estimated using the Kaplan–Meier method. Heterogeneity of the treatment effect for eplerenone (in the EPHESUS population) and for low-dose rivaroxaban (in the COMMANDER-HF population) was evaluated by assessing treatment interactions across clusters in expanded Cox models.

Continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated to assess the added prognostic value of clusters for the main endpoints on top of the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) score.[23]

All analyses were performed using R software version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). The two-tailed significance level was set at $p < 0.05$ except for the analyses of interactions. Given the low power of interaction tests, the significance level was set at $p < 0.10$.

Results

Clusters characteristics

A total of 8591 patients were included in the development cohort analysis, comprising 1959 patients from the CAPRICORN trial and 6632 patients from the EPHESUS trial. The two populations were quite similar in terms of key clinical and demographic characteristics, although the EPHESUS cohort showed a higher prevalence of comorbidities, such as diabetes, hypertension, and atrial fibrillation, as well as higher rates of CV drug treatments (including antiplatelet agents, antihypertensive medications, and HF drugs) (online supplementary *Table S2*). No significant differences were found in the distribution of cluster membership between the cohorts (online supplementary *Table S3*).

Cluster analysis identified five clinically relevant groups with different phenotypes: Cluster 1 ($n = 2161$), was the larger and included the older patients (73 [68–78] years) with the higher prevalence of atrial fibrillation (22%) and CV events burden (previous MI: 40%; cerebrovascular accidents: 14%), and a low LVEF (31 [25–36] %); Cluster 2 ($n = 1376$), also included old patients (71 [65–76] years), the higher prevalence of women (46%), smoking habit (64%), and arterial hypertension (85%), associated with relatively high LVEF (36 [34–39] %) and pulse pressure (60 [50–65] mmHg); Cluster 3 ($n = 1157$) included patients with the larger prevalence of diabetes (50%), arterial hypertension (77%) and peripheral artery disease (19%), along with an elevated pulse pressure (60 [48–70] mmHg); Cluster 4 ($n = 2073$) included mostly middle-aged (58 [51–65] years) men (89%) with the higher LVEF (37 [34–39] %); Cluster 5 ($n = 1824$) included the younger patients (55 [48–61] years) with the lower pulse pressure (39 [30–40] mmHg) and systolic blood pressure (101 [100–110] mmHg), along with the lower prevalence of previous CV events (previous MI: 18%; cerebrovascular accidents: 3.1%). Patients in Cluster 1 were also the most treated with diuretics (71%), meanwhile beta-blockers were more prevalent in Cluster 4 (81%) and calcium channel blockers in Cluster 2 (13%) (*Figure 1*; *Table 2*).

Association of clusters with clinical outcomes in the learning set

During a median follow-up of 16 (12–20) months, 1299 (15%) patients died (87% for CV causes), 2014 (15%) patients had an HF hospitalization or all-cause death event, 3909 (46%) patients had a CV hospitalization or all-cause death event, 2314 (26%) experienced a MACE, and 1133 (13%) patients had an HF hospitalization or CV death event.

Patients exhibiting characteristics of Cluster 1 had a significantly higher risk of experiencing a range of adverse events including HF hospitalization or all-cause death (HR 2.89 [95% CI 2.45–3.41], $p < 0.001$), CV hospitalization or all-cause death (HR 1.74 [95% CI 1.56–1.93], $p < 0.001$), and MACE (HR 2.02 [95% CI 1.71–2.39], $p < 0.001$), as well as all-cause death (HR 2.36 [95% CI 1.93–2.89], $p < 0.001$), CV death (HR 2.52 [95% CI 2.02–3.13], $p < 0.001$) and the composite of HF hospitalization and CV death (HR 3.05 [95% CI 2.57–3.63], $p < 0.001$), compared to Cluster 4 (lowest risk). A similar increased risk for all the composite outcomes was observed for Cluster 3, while an intermediate event risk was associated with Cluster 5. On the contrary, the lower risk (HF hospitalization or all-cause death: HR 1.53 [95% CI 1.27–1.84], $p < 0.001$; CV hospitalization or all cause death: HR 1.13 [95% CI 1.00–1.27], $p = 0.05$; MACE: HR 1.34 [95% CI 1.11–1.62], $p = 0.002$; all-cause death: HR 1.37 [95% CI 1.09–1.71], $p = 0.007$; CV death: HR 1.40 [95% CI 1.09–1.78], $p = 0.008$; and the composite of HF hospitalization and CV death: HR 1.56 [95% CI 1.28–1.89], $p < 0.001$) was observed in patients showing the characteristics of Cluster 2 (*Figures 2* and *3*; online supplementary *Figures S3* and *S4*). This risk pattern, with Cluster 1 having the highest risk and Clusters 2 and 4 the lowest, was also evident for the outcome of multiple HF hospitalizations (online supplementary *Table S4*).

Clusters significantly improved prognostic performance on top of the MAGGIC score for all the main explored endpoints (all $p < 0.0001$) (online supplementary *Table S5*).

Effect of eplerenone and low-dose rivaroxaban on clusters

The evaluation of treatment effect in the EPHESUS population showed no significant interaction between eplerenone and clusters

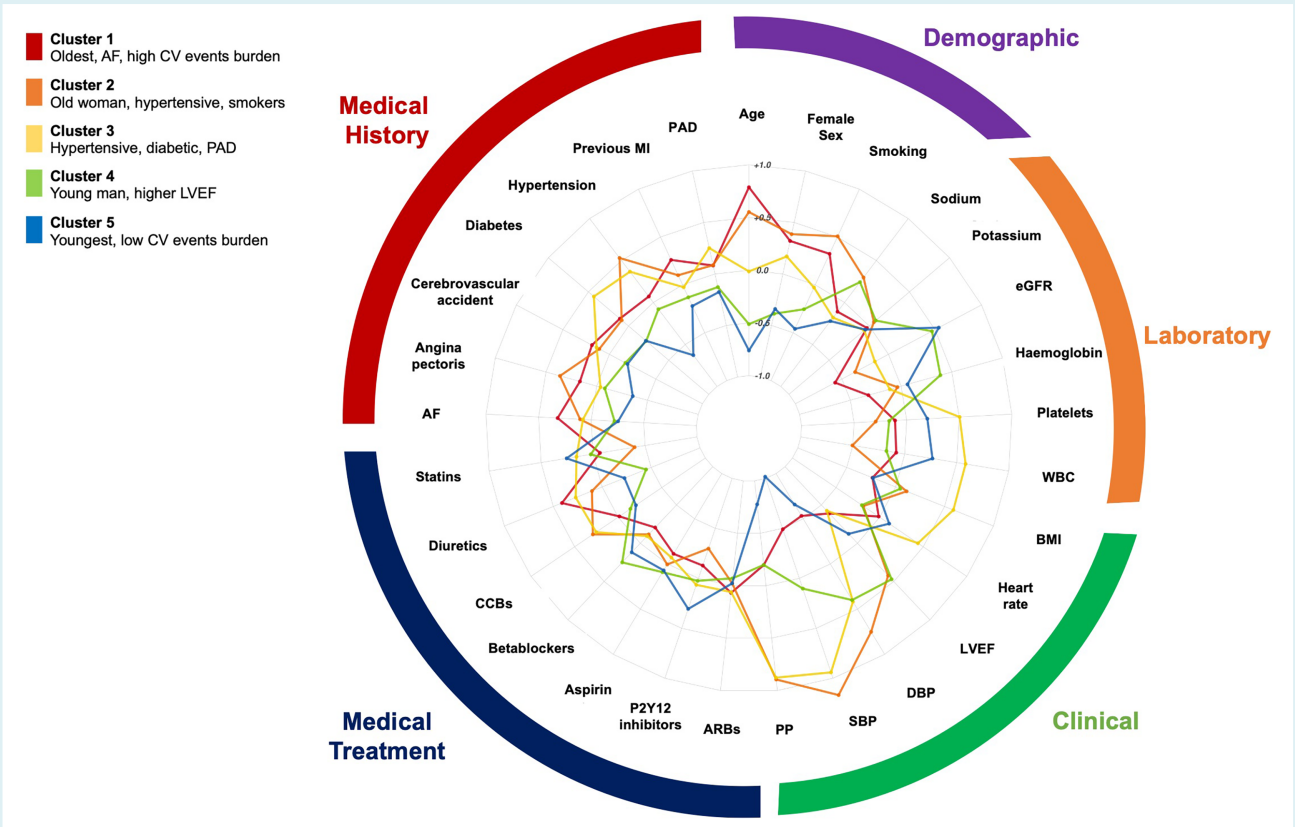


Figure 1 Radar charts illustrating the differences in demographic, clinical, biological, anamnestic and treatment variables across the five clusters. The points most distant from the centre indicate higher values (expressed as standard deviations from the mean). AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CV, cardiovascular; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral artery disease; PP, pulse pressure; SBP, systolic blood pressure; WBC, white blood cells.

for the composite endpoint of HF hospitalization or all-cause death and the MACE, as well as for all-cause death, CV death and the composite of HF hospitalization or CV death (all p for interaction > 0.10). On the contrary, eplerenone had a heterogeneous effect on clusters for the composite outcome of CV hospitalization or all-cause death (p for interaction $= 0.021$), with a stronger risk-reducing effect on Cluster 4 (HR 0.76 [95% CI 0.65–0.90], $p = 0.001$) and Cluster 2 (HR 0.82 [95% CI 0.68–0.98], $p = 0.033$) (*Figure 4* and online supplementary *Figure S5*).

No significant interaction was found between low-dose rivaroxaban treatment and clusters for all the explored end points (online supplementary *Figures S6* and *S7*).

Predicting cluster membership with random forest

After 10-fold cross-validation was performed, promising results were obtained for both the decision tree and random forest models. A respectable ROC area under the curve (AUC) of 0.91 was achieved by the decision tree model, indicating its ability to accurately allocate patients into the respective cluster. Furthermore, an F-measure of 0.71 suggested reasonably balanced performance in terms of precision and recall.

However, it is important to note that the random forest model outperformed the decision tree model in terms of predictive performance. The random forest model yielded an impressive ROC AUC of 0.94, indicating higher discriminatory power, and an excellent F-measure of 0.84 (online supplementary *Table S6*), highlighting a strong balance between precision and recall. With these superior results, the random forest model was chosen for further predictions, as it is expected to provide accurate and reliable predictions.

Both models (decision tree and random forest) are available on a Gitlab repository (https://gitlab.com/cic-p/hrmi_clustering).

External validation of the random forest model in the COMMANDER-HF population

Participant characteristics according to cluster phenotypes in the COMMANDER-HF cohort are presented in *Table 3*. Overall, the relative clusters' characteristics were like that shown in the learning

Table 2 Baseline characteristics according to clusters in the high-risk myocardial infarction cohort (CAPRICORN and EPHESUS cohorts)

Variable	Patients, *n*	Cluster 1 (*n* = 2161)	Cluster 2 (*n* = 1376)	Cluster 3 (*n* = 1157)	Cluster 4 (*n* = 2073)	Cluster 5 (*n* = 1824)	*p*-value
Demographic							
Age, years	8591	73 (68–78)	71 (65–76)	64 (55–72)	58 (51–65)	55 (48–61)	<0.001
Female sex, *n* (%)	8591	925 (43)	630 (46)	417 (36)	227 (11)	238 (13)	<0.001
Current smokers, *n* (%)	8580	1193 (55)	884 (64)	441 (38)	560 (27)	310 (17)	<0.001
Medical history, *n* (%)							
Diabetes	8591	753 (35)	465 (34)	575 (50)	411 (20)	365 (20)	<0.001
Atrial fibrillation	8591	485 (22)	213 (15)	169 (15)	100 (4.8)	68 (3.7)	<0.001
Angina pectoris	8591	1226 (57)	916 (67)	539 (47)	923 (45)	560 (31)	<0.001
Cerebrovascular accidents	8591	299 (14)	160 (12)	144 (12)	78 (3.8)	57 (3.1)	<0.001
Previous MI[a]	8591	854 (40)	445 (32)	309 (27)	456 (22)	327 (18)	<0.001
Peripheral artery disease	8591	302 (14)	194 (14)	224 (19)	152 (7.3)	106 (5.8)	<0.001
Hypertension	8591	1346 (62)	1168 (85)	889 (77)	1137 (55)	508 (28)	<0.001
Clinical							
BMI, kg/m^2	8518	26.0 (24.0–29.0)	27.0 (25.0–31.0)	29.0 (25.0–34.0)	27.0 (25.0–30.0)	26.0 (24.0–29.0)	<0.001
Pulse pressure, mmHg	8569	45 (40–50)	60 (50–65)	60 (48–70)	45 (40–50)	39 (30–40)	<0.001
Diastolic BP, mmHg	8569	70 (60–70)	80 (75–85)	80 (70–86)	80 (70–80)	65 (60–70)	<0.001
Systolic BP, mmHg	8569	110 (105–120)	140 (130–145)	135 (122–145)	120 (118–126)	101 (100–110)	<0.001
Heart rate, bpm	8561	74 (68–82)	72 (67–80)	80 (70–90)	72 (66–80)	76 (68–84)	<0.001
LVEF, %	8565	31 (25–36)	36 (34–39)	31 (25–36)	37 (34–39)	34 (29–37)	<0.001
Laboratory							
eGFR, ml/min/1.73 m^2	7609	57 (46–67)	60 (50–72)	64 (50–78)	76 (65–89)	78 (67–89)	<0.001
Potassium, mmol/L	7830	4.30 (4.00–4.60)	4.40 (4.10–4.70)	4.30 (3.90–4.60)	4.40 (4.10–4.70)	4.30 (4.00–4.60)	<0.001
Sodium, mmol/L	7839	139.0 (136.0–141.0)	140.0 (138.0–143.0)	139.0 (136.0–141.0)	140.0 (138.0–142.0)	139.0 (136.0–141.0)	<0.001
White blood cells, 1000/mm^3	7785	8.10 (6.70–9.90)	7.10 (5.90–8.40)	9.70 (7.70–12.30)	7.90 (6.50–9.50)	9.00 (7.40–11.10)	<0.001
Haemoglobin, g/L	6580	12.70 (11.70–13.80)	13.20 (12.10–14.40)	13.10 (11.80–14.40)	14.00 (13.00–14.90)	13.50 (12.40–14.60)	<0.001
Platelets, 1000/mm^3	7709	238 (194–290)	224 (190–271)	274 (215–371)	236 (196–286)	257 (204–327)	<0.001
Medical treatment, *n* (%)							
$P2Y_{12}$ inhibitors	8586	386 (18)	147 (11)	301 (26)	504 (24)	660 (36)	<0.001
Aspirin	8586	1776 (82)	1187 (86)	968 (84)	1850 (89)	1615 (89)	<0.001
Statins	8586	731 (34)	244 (18)	518 (45)	791 (38)	900 (49)	<0.001
ARBs	8586	64 (3.0)	23 (1.7)	33 (2.9)	21 (1.0)	31 (1.7)	<0.001
Beta-blockers	6627	1039 (60)	633 (64)	617 (65)	1268 (81)	1059 (75)	<0.001
CCBs	8586	129 (6.0)	184 (13)	144 (12)	60 (2.9)	25 (1.4)	<0.001
Diuretics	8586	1540 (71)	770 (56)	744 (64)	587 (28)	718 (39)	<0.001
Loop diuretics	8591	1425 (66)	604 (44)	670 (58)	495 (24)	672 (37)	<0.001

ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction.
[a]Before study randomization.

dataset. In particular, Cluster 1 (*n* = 1545) was the larger and encompassed the older patients (73 [67–78] years), with the most impaired renal function (estimated glomerular filtration rate [eGFR] 56 [45–70] ml/min/1.73 m^2) and a low LVEF; Cluster 2 (*n* = 1199) also included old patients with the higher prevalence of arterial hypertension (86%); Cluster 3 (*n* = 561) included patients with the higher body mass index (28.8 [25.2–34.3] kg/m^2) and the lower LVEF (26 [22–35] %), together with the larger prevalence of diabetes (55%); Cluster 4 (*n* = 1172) included middle-aged patients with the higher LVEF (37 [33–39] %) and a large prevalence of previous MI (81%); Cluster 5 (*n* = 554) was the smaller and included the younger patients (57 [53–61] years), mainly male (84%), with relatively preserved renal function and lower prevalence of hypertension (53%).

Overall, during a median follow-up of 20 (12–32) months, 1102 (22%) patients died (48% for CV causes), 1966 (39%) patients had an HF hospitalization or all-cause death event, 2537 (51%) patients had a CV hospitalization or all-cause death event, 1121 (22%) patients experienced a MACE, and 2537 (51%) patients had a HF hospitalization or CV death event in the COMMANDER-HF cohort.

Like the learning set findings, in the validation set patients showing the characteristics of Cluster 1 and Cluster 3 had the highest risk of adverse clinical outcomes compared to Cluster 4 (reference; lowest risk). The risk of experiencing an adverse outcome was modest in patients featured with the characteristics of Cluster 2, while was higher for Cluster 5 compared to the learning set (*Figures 2* and *3*, online supplementary *Table S4*).

Discussion

In this study, a machine learning approach was useful for identifying clinical phenotypes of ischaemic HFrEF associated with an enhanced risk of adverse outcomes. Compared to Cluster 4 (middle-aged patients with relatively high LVEF), older patients with low LVEF and high burden of previous CV events (Cluster 1) and those with multiple comorbidities (Cluster 3) showed the highest risk of clinical events. On the contrary, older female

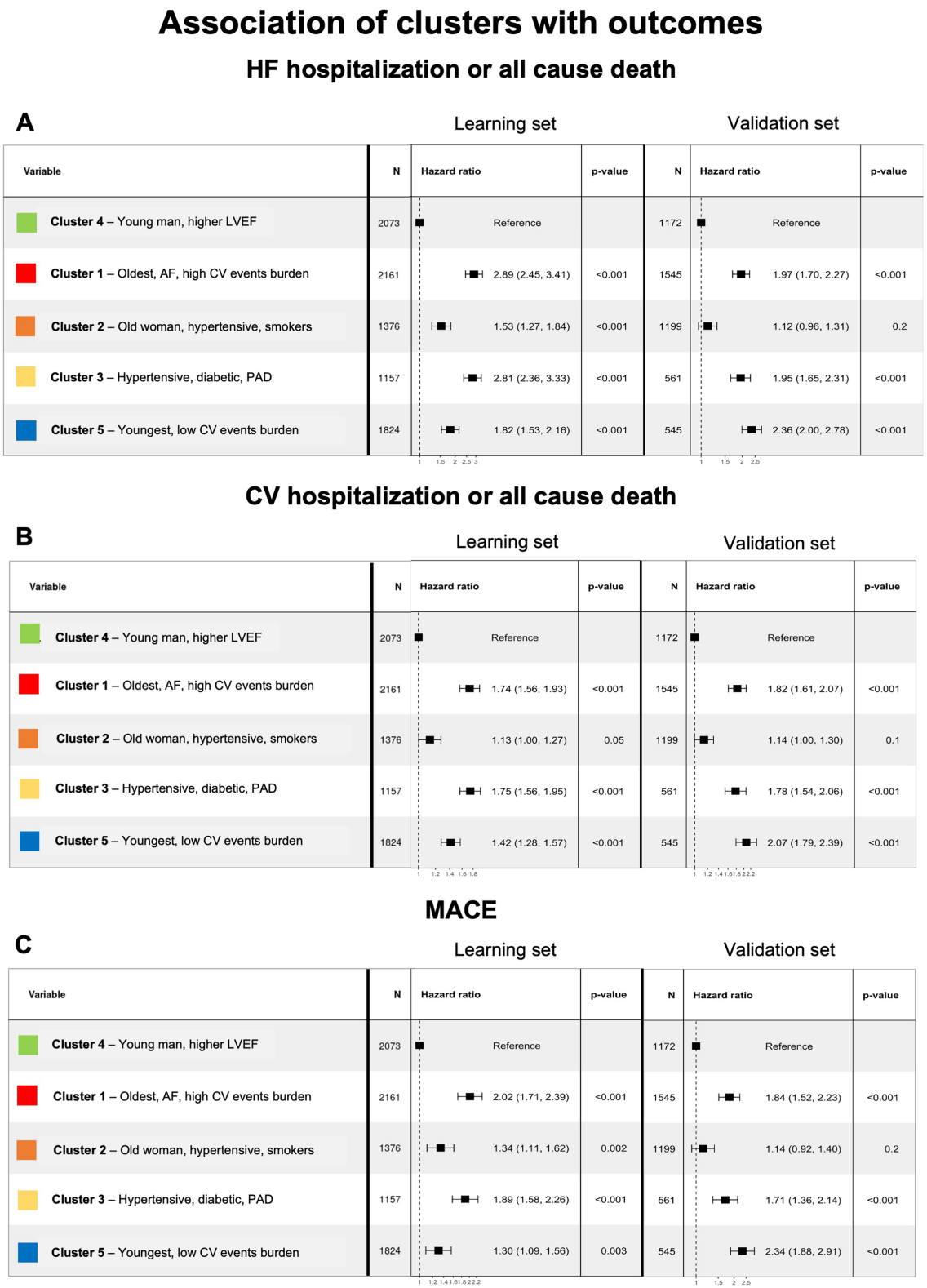


Figure 2 Risk of (*A*) heart failure (HF) hospitalization or all-cause death, (*B*) cardiovascular (CV) hospitalization or all-cause death, and (*C*) major adverse CV events (MACE) by clusters in the learning and in the validation set. Cluster 4 was used as reference. AF, atrial fibrillation; LVEF, left ventricular ejection fraction; PAD, peripheral artery disease.

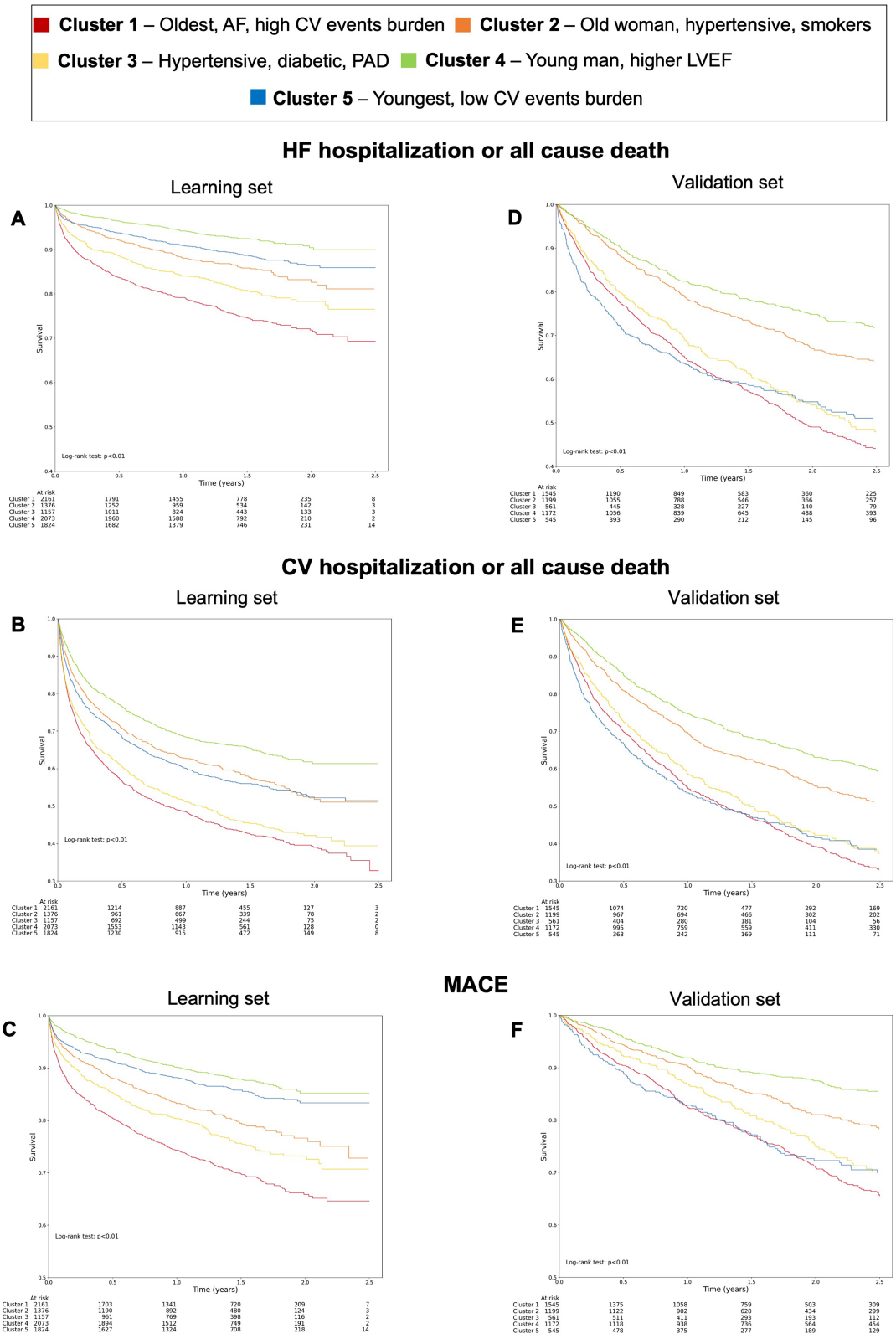


Figure 3 Kaplan–Meier survival estimates according to clusters for the composite endpoint of heart failure (HF) hospitalization or all-cause death, cardiovascular (CV) hospitalization or all-cause death and the major adverse CV event (MACE) outcome in the learning set (*A*–*C*) and the validation set (*D*–*F*). AF, atrial fibrillation; LVEF, left ventricular ejection fraction; PAD, peripheral artery disease.

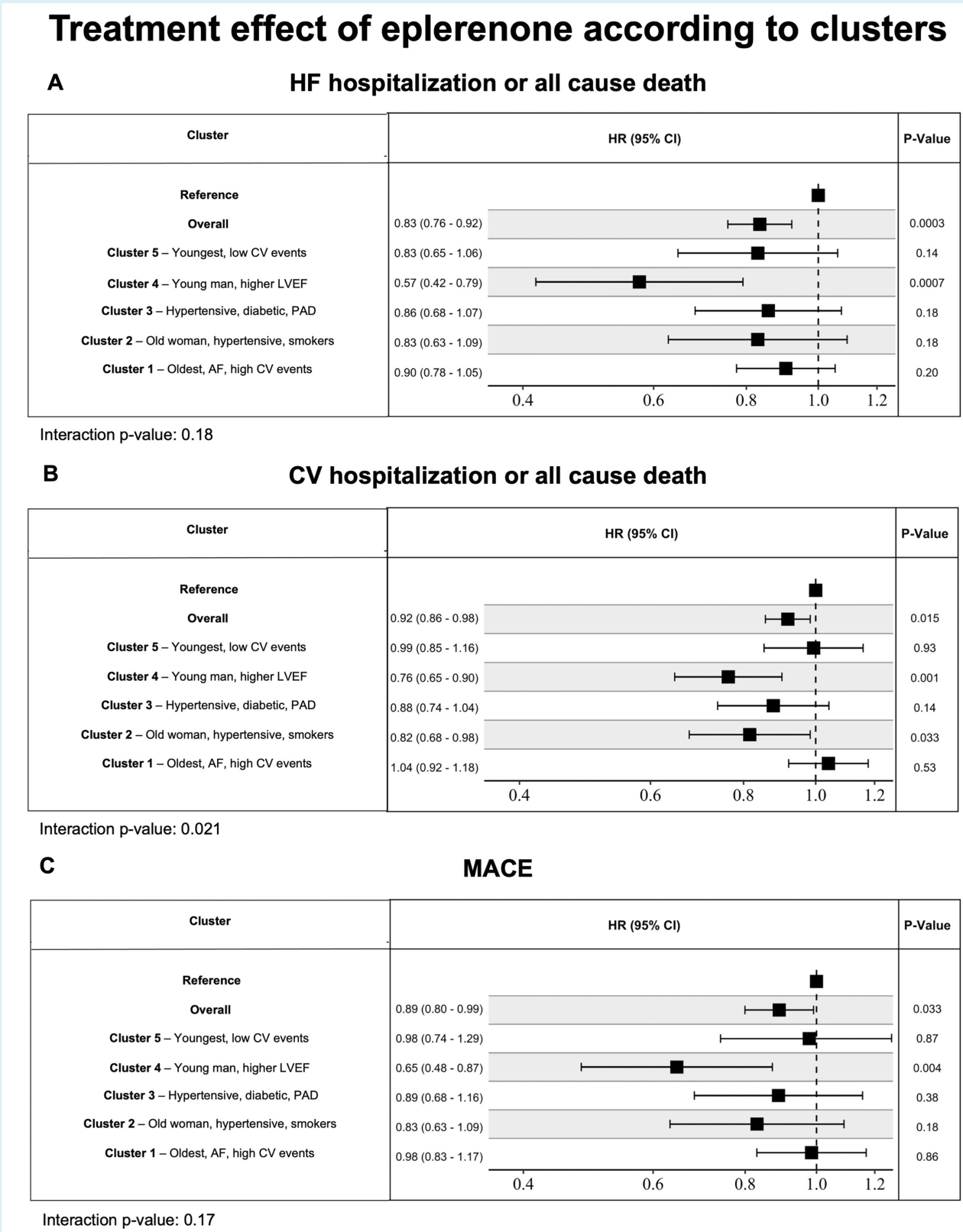


Figure 4 Treatment effect of eplerenone among clusters in the EPHESUS population for the composite endpoints of (*A*) heart failure (HF) hospitalization or all-cause death, (*B*) cardiovascular (CV) hospitalization or all-cause death, and (*C*) the major adverse CV event (MACE) outcome. AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; PAD, peripheral artery disease.

Table 3 Baseline characteristics according to the predicted clusters in the validation cohort (COMMANDER-HF)

Variable	Patients, *n*	Cluster 1 (*n* = 1545)	Cluster 2 (*n* = 1199)	Cluster 3 (*n* = 561)	Cluster 4 (*n* = 1172)	Cluster 5 (*n* = 554)	*p*-value
Demographic							
Age, years	5022	73 (67–78)	70 (64–76)	62 (56–71)	60 (55–65)	57 (53–61)	<0.001
Female sex, *n* (%)	5022	370 (24)	311 (26)	142 (25)	242 (21)	85 (16)	<0.001
Current smokers, *n* (%)	5022	205 (13)	210 (18)	85 (15)	178 (15)	90 (17)	<0.001
Medical history, *n* (%)							
Diabetes	5022	639 (41)	520 (43)	309 (55)	396 (34)	188 (34)	<0.001
Previous MI[a]	5022	1160 (75)	910 (76)	384 (68)	944 (81)	405 (74)	<0.001
Hypertension	5022	1120 (72)	1032 (86)	463 (83)	878 (75)	290 (53)	<0.001
Clinical							
BMI, kg/m^2	5018	25.7 (22.8–28.9)	27.7 (24.9–30.9)	28.8 (25.2–34.3)	28.0 (25.4–31.5)	26.1 (23.3–29.4)	<0.001
Pulse pressure, mmHg	5021	45 (40–50)	59 (51–62)	60 (51–70)	47 (40–50)	37 (30–40)	<0.001
Diastolic BP, mmHg	5021	69 (60–70)	80 (75–85)	80 (70–85)	78 (72–80)	67 (60–70)	<0.001
Systolic BP, mmHg	5021	112 (108–120)	138 (130–142)	138 (130–144)	122 (120–129)	104 (98–110)	<0.001
Heart rate, bpm	5019	70 (62–76)	70 (64–76)	74 (66–84)	70 (64–76)	74 (65–81)	<0.001
LVEF, %	5022	30 (24–35)	37 (34–39)	26 (22–35)	37 (33–39)	28 (21–34)	<0.001
Laboratory							
eGFR, ml/min/1.73 m^2	5022	56 (45–70)	65 (51–79)	67 (49–82)	76 (64–91)	78 (65–95)	<0.001
Potassium, mmol/L	664	4.40 (4.08–4.75)	4.39 (4.00–4.75)	4.42 (4.05–4.80)	4.40 (4.16–4.70)	4.40 (4.10–4.70)	0.8
Sodium, mmol/L	651	138.0 (135.6–141.0)	141.0 (138.0–143.0)	139.0 (137.0–142.0)	140.0 (137.8–141.0)	138.0 (135.0–139.0)	<0.001
White blood cells, 1000/mm^3	710	7.49 (6.15–9.28)	7.19 (6.30–8.70)	8.58 (6.82–10.40)	7.37 (6.05–8.93)	7.62 (6.43–10.40)	<0.001
Haemoglobin, g/L	5019	13.10 (11.80–14.30)	13.60 (12.40–14.70)	13.50 (12.10–14.80)	14.10 (13.00–15.20)	13.50 (12.30–14.79)	<0.001
Platelets, 1000/mm^3	4923	200 (164–245)	208 (177–253)	219 (178–270)	221 (186–263)	216 (177–258)	<0.001
Medical treatment, *n* (%)							
$P2Y_{12}$ inhibitors	5022	599 (39)	453 (38)	232 (41)	477 (41)	254 (47)	0.007
Aspirin	5022	1422 (92)	1116 (93)	515 (92)	1126 (96)	496 (91)	<0.001
Statins	5022	695 (45)	522 (44)	309 (55)	635 (54)	306 (56)	<0.001
ARB	5022	334 (22)	304 (25)	128 (23)	230 (20)	89 (16)	<0.001
Beta-blockers	5022	1409 (91)	1105 (92)	522 (93)	1101 (94)	505 (93)	0.1
Diuretics	5022	1539 (100)	1194 (100)	560 (100)	1164 (99)	542 (99)	0.7
Loop diuretics	5022	1463 (95)	1091 (91)	524 (93)	1072 (91)	516 (95)	<0.001

AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blockers; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; WBC, white blood cell.
[a]Before study randomization.

patients, smokers and hypertensives (Cluster 2) showed a low event rate. Younger patients with low pulse pressure and systolic blood pressure, and a lower prevalence of prior CV events (Cluster 5) had an increased risk of adverse outcomes compared to Cluster 4, though the magnitude of this risk differed between the learning set (lower) and the validation set (higher) (*Graphical Abstract*). Our findings suggest that machine learning clustering is an important and reproducible method to identify high-risk features in patients with HFrEF after MI at high risk of adverse events (learning set) and in admitted patients with worsening ischaemic HF (external validation set). From a practical perspective, unravelling key clinical variables more frequently associated with a heightened CV risk might prompt stricter follow-up and a more effective implementation of guideline-directed medical therapies in a broad population with HFrEF and ischaemic heart disease.

Clustering for risk stratification

Despite notable advancements in the prognosis of ischaemic cardiomyopathy in the last decades, patients who develop HF or left ventricular systolic dysfunction remain a vulnerable population facing unfavourable outcomes.[4] Among this population, the identification of high-risk features is critical to strategize further interventions. It is well-known that some clinical characteristics could be associated with a worse prognosis in patients with HFrEF. Indeed, pulse pressure was demonstrated to be an independent predictor of mortality showing a U-shaped relationship in a large HFrEF cohort, with a risk nadir at a pulse pressure of 50 mmHg.[24] A similar U-shaped association with adverse clinical events was previously demonstrated in patients with HFrEF for in-office systolic blood pressure[25] and for systolic blood pressure variability.[26] Comorbidities, such as chronic kidney disease, hypertension, or diabetes, interact with MI increasing short- and long-term mortality beyond that explained by their additive effects.[27] Finally, even in the era of primary percutaneous coronary intervention, left ventricular systolic dysfunction has been shown to be one of the most powerful predictors of CV outcome after MI.[28,29] Despite the demonstrated individual associations of these factors with an increased risk of CV events in post-MI patients with HF, the investigation on the effect of their interaction on clinical outcomes remains inadequately explored.

In the pursuit of improving the assessment and characterization of the heterogeneous population of HF patients, various strategies have been employed. Among them, clustering has emerged as a particularly promising approach, shedding light on the extensive heterogeneity in terms of outcomes and treatment response observed in patients with HFrEF, irrespective of the

ejection fraction.[30] In line, we observed that the association of outcome predictors in homogeneous clinical phenotypes, such as older age, lower LVEF and worst eGFR, or lower pulse pressure and systolic blood pressure, was associated with a significant increase in the risk of adverse events. Notably, in the case of the coexistence of features with opposite impact on adverse events (benefit vs. harm), clustering can estimate the global risk derived from the interaction of different characteristics. Just to cite an example, in our study Cluster 5 was associated with an increased risk of CV events compared to reference, mainly driven by the coexistence of low pulse pressure and systolic blood pressure, even if it includes relatively young patients (mean 55 years), a characteristic commonly associated with better post-MI outcomes.[31]

Risk scores are frequently used in patients with HF to predict outcomes. Notably, while risk scores are crucial for providing prognostic assessments at the population level (but with usually lower performance at an individual level), unsupervised machine learning techniques like clustering offer unique insights by identifying recurring patterns that define homogeneous subgroups. These subgroups may reveal populations more likely to respond uniformly to specific treatments, thereby facilitating more personalized care. Therefore, risk scores and machine learning models fulfil different but complementary roles. An illustrative example of the distinct nature of these two tools lies in the risk association for Cluster 5 in our study. The clustering approach effectively homogenized patients with similar characteristics, including those in Cluster 5, though the associated risk for this cluster varied in magnitude between the learning and validation sets. This discrepancy may stem from the distinct prognostic implications of Cluster 5 in patients post-HF admission, as seen in the COMMANDER-HF trial. Specifically, it suggests a heightened risk of rehospitalization in younger patients with ischaemic HFrEF, a finding that may reflect different risk dynamics in this particular patient subset.

Different treatment benefit across clusters

In our study, we showed a significant treatment interaction for eplerenone in two of the generated clinical clusters. The significant heterogeneity of HFrEF could also mirror in the widely different responses (in terms of left ventricular remodelling, quality of life, functional capacity, etc.) of individual patients to HF treatments commonly observed in clinical practice.[30,32] One of the primary causes for this phenomenon could be ascribed to the amalgamation of patients into general categories based on arbitrary LVEF thresholds, even if it is now increasingly recognized how this classification fails to capture the complexity of the HF syndrome.[33] Machine learning technologies have the potential to untangle this complexity by identifying distinct groups within populations that exhibit heterogeneous underlying features, thereby potentially deriving specific enhanced benefits (or harm) from a particular treatment. Therefore, this novel approach to HF patients could potentially pave the way for innovative and refined approaches to advance risk stratification, prediction, and treatment response.

Practical use of clusters

From a practical perspective, machine learning methods might gain importance in the future since they can provide an easy and immediate estimation of individual patient outcome, thereby enhancing the granularity of risk stratification beyond standard scores (i.e. MAGGIC score). Additionally, clustering models offer valuable insights at an individual level by adopting a phenotypic approach rather than focusing solely on risk assessment. This allows for the identification of distinct patient subgroups with shared characteristics, which can inform more personalized management strategies and improve our understanding of disease mechanisms beyond what traditional risk models can achieve. The random forest model we built could be imbedded in health record systems to provide an automated identification of cluster membership that most closely aligns with the individual patient and predicts his/her 2-year risk of clinical events, or even work as a stand-alone online tool (PROMISE-HF [Prognostication and Outcome Monitoring in Ischaemic HFrEF], available at the following website: https://cic-p-nancy.fr/promise-hf/).

This approach stands to transform the framework for designing and interpreting new clinical trials, since clustering techniques may select subgroups more prone to have a benefit from the treatment. This could become particularly relevant in the modern era where the improvement of therapeutic strategies led to a relevant decline of event rates in post-MI clinical trials, which could ultimately pose problems in interpreting results. To cite an example, the recent PARADISE-MI trial failed to show any difference in terms of CV death or incident HF between sacubitril/valsartan and ramipril in post-MI patients, largely due to the notably low mortality rate.[6] Similarly, in the REMI (Relation Between Aldosterone and Cardiac Remodelling After Myocardial Infarction) study, the adequate implementation of post-MI treatments significantly reduced the expected rate of adverse left ventricular remodelling, therefore requiring a recalibration of the pre-specified endpoints (i.e. baseline to follow-up change in left ventricular volumes was adjusted from 20% to 15%).[34] Clustering analysis could have enabled the selection of patients at the highest risk of events, allowing for the treatment to be tested on subgroup(s) that could attain the maximum benefit, thus avoiding the dilution of the treatment effect in the low-risk population. Although the research interest in clustering methods is exponentially growing, and several clustering experiences were previously published, a critical limitation to their use in the everyday clinical practice is their low power in predicting cluster in population other than the derivation. On the contrary, our clustering model demonstrated a high accuracy also in the validation cohort, making this tool appropriate for a wide population with ischaemic HFrEF.

In the future, clinical trials in HF might use cluster analysis to enrich the study population with patients at different levels of risk or even to assess heterogeneity of treatment effect. For example, regarding the latter, a first experience of this approach was conducted in the heterogeneous population of patients with HF and preserved ejection fraction. In this setting, even if the results of the primary analysis were neutral, clustering analysis of the I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction

Study) and TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial) trials demonstrated a significant risk-reduction effect on the primary outcome of irbesartan and spironolactone in patients within the diabetic obesity cluster.[35,36] To enhance our comprehension of the effectiveness of this approach, there is a need for clinical trials that specifically focus on assessing treatment response in relation to cluster phenotypes.

Limitations

The results of this study should be interpreted in the context of the following limitations. First, this was a non-pre-specified analysis of a pooled dataset from randomized clinical trials; therefore, causality cannot be inferred. Second, described machine learning clusters were developed in a specific population (ischaemic HFrEF patients); therefore, the findings reported here cannot be generalized to other patients without these characteristics. Third, the learning set and validation set comprise patients with slightly different baseline characteristics. Most significantly, all patients in the learning set have both HFrEF and a previous MI, whereas the validation set comprises patients with HFrEF and underlying coronary artery disease, 76% of whom have a previous MI; additionally, diuretic use varies significantly between the cohorts, with half of the learning set patients treated with diuretics compared to virtually all in the validation set, who received diuretics following a recent episode of worsening HF. The validation set also had a higher prevalence of comorbidities and was enriched with patients exhibiting elevated levels of natriuretic peptides to increase the event rate. While the clustering approach successfully homogenized patients with similar characteristics across all subgroups, these differences likely contributed to the observed variation in event risk association for Cluster 5 between the learning and validation sets. However, since the primary goal of clustering is to create homogeneous patient groups, and the risk of events was largely consistent across the two datasets (with Clusters 1 and 3 showing the highest risk, and Clusters 2 and 4 the lowest), the differences in baseline characteristics between the two cohorts should be viewed as a strength rather than a weakness, enhancing the generalizability of the study's findings to a broader spectrum of clinical profiles. Fourth, the inclusion of earlier trials in the learning cohort, which differed significantly in HF treatment compared to the more contemporary COMMANDER-HF trial, may have artificially increased the observed association between clusters and clinical outcomes. More generally, the relevance of our findings may be challenged by the legacy nature of the cohorts which do not include use of angiotensin receptor–neprilysin inhibitors or sodium–glucose cotransporter 2 inhibitors. Nevertheless, this situation exemplifies a common limitation in studies utilizing older databases for constructing risk prediction models, potentially not reflecting the most recent therapeutic acquisitions. Because we used a pooled cohort of studies from the HRMI initiative as the learning cohort, information on treatment doses possibly relevant to the outcomes (i.e. loop diuretics) was not available. Fifth, determining the optimal number of clusters is inherently complex and often subjective,[37] with no universal standard for selecting cluster count. This variability can lead to different clustering solutions depending on the method and data used, potentially impacting the robustness and interpretation of results. Although our chosen cluster number consistently balanced interpretability and statistical robustness, inherent uncertainty in identifying an exact optimal count persists. Finally, the selection of variables recorded during trials was carried out by the steering committee, choosing classical factors known to have an influence on outcomes in patients with ischaemic HF. Different experts may prioritize variables differently, leading to variations in the chosen set of variables and potentially affecting the clustering analysis results. Even if this could limit the interpretation of the results, our objective in this study was not merely define a set of patient clusters, but rather to illustrate the potential of machine learning algorithms to overcome the constraints imposed by conventional and simplistic phenotyping approaches in the context of HFrEF.

Conclusions

Machine learning algorithms have the potential to identify subgroups with homogeneous clinical characteristics and to accurately predict adverse outcomes among the heterogeneous population of patients with ischaemic HF. This easily accessible classification, available through an online software, has the potential to assist in predicting outcomes and potentially evaluating treatment response in the future.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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