

Characterizing the heterogeneity of heart failure with preserved ejection fraction: moving beyond subgroups and distinguishing disease from risk

Fardad Soltani ^{1,2}, Nicholas Black^{1,2}, Joshua Bradley¹, Lucy Priestner^{1,2}, Naing Ko Ko³, Hannah Glasse⁴, Isabelle Milner⁴, Sarah Kreppel⁵, Matthias Schmitt², Gaetano Nucifora^{1,2}, Mark C. Petrie ⁶, Abdallah Al-Mohammad⁷, Gerry P. McCann⁸, R. Thomas Lumbers ^{9,10}, Janine Beezer¹¹, Maria F. Paton^{12,13}, Shaun Robinson¹⁴, Rebecca Hyland¹⁵, Nick Hartshorne-Evans ¹⁶, Laurence Humphreys-Davies¹⁷, Zahra Raisi-Estabragh^{18,19}, Steffen E. Petersen^{18,19,20}, William G. Newman^{21,22}, Theresa McDonagh²³, Jamil Mayet¹⁴, Simon G. Williams^{1,2}, David A. Jenkins²⁴, Andrew P. Morris^{25,26}, Niels Peek^{24,27}, and Christopher A. Miller ^{1,2,26,*}

¹Division of Cardiovascular Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, University of Manchester, Oxford Road, Manchester M13 9PL, UK; ²Department of Cardiology, Manchester University NHS Foundation Trust, Southmoor Road, Manchester M23 9LT, UK; ³Department of Cardiology, Wrightington, Wigan, and Leigh NHS Foundation Trust, Wigan, Greater Manchester, UK; ⁴Division of Medicine, Northern Care Alliance NHS Foundation Trust, Salford, Greater Manchester, UK; ⁵Division of Medicine, Lancashire Teaching Hospitals NHS Foundation Trust, Preston, UK; ⁶School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK; ⁷Division of Clinical Medicine, University of Sheffield, Sheffield, UK; ⁸Department of Cardiovascular Sciences and the National Institute for Health and Social Care Research (NIHR) Leicester Biomedical Research Centre, University of Leicester, Leicester, UK; ⁹Department of Cardiology, University College London Hospitals NHS Foundation Trust, London, UK; ¹⁰Institute of Health Informatics, Faculty of Population Health Sciences, University College London, London, UK; ¹¹South Tyneside and Sunderland Foundation Trust, Sunderland Royal Hospital, Kayll Road, Sunderland, UK; ¹²Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK; ¹³Department of Cardiology, Leeds Teaching Hospitals NHS Trust, Leeds, UK; ¹⁴Department of Cardiology, Imperial College Healthcare NHS Trust, London, UK; ¹⁵Cardiology Service, HCRG, BSW, England, UK; ¹⁶Pumping Marvellous, Preston, UK; ¹⁷Patient Advisory Panel, British Society for Heart Failure, London, UK; ¹⁸William Harvey Research Institute, NIHR Barts Biomedical Research Centre, Queen Mary University London, London, UK; ¹⁹Barts Heart Centre, St Bartholomew's Hospital, Barts Health NHS Trust, London, UK; ²⁰BHF Data Science Centre, Health Data Research UK, London, UK; ²¹Division of Evolution, Infection and Genomics, School of Biological Sciences, The University of Manchester, Manchester, UK; ²²Manchester Centre for Genomic Medicine, Manchester University NHS Foundation Trust, Manchester, UK; ²³Department of Cardiology, Kings College Hospital NHS Foundation Trust, London, UK; ²⁴Division of Informatics, Imaging and Data Science, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK; ²⁵Centre for Genetics and Genomics Versus Arthritis, Centre for Musculoskeletal Research, Division of Musculoskeletal and Dermatological Sciences, University of Manchester, Manchester, UK; ²⁶NIHR Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Oxford Road, Manchester M13 9WL, UK; and ²⁷The Healthcare Improvement Studies Institute (THIS Institute), Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK

Received 20 November 2025; revised 20 January 2026; accepted 12 February 2026; online publish-ahead-of-print 5 March 2026

Abstract

Aims

Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous syndrome commonly hypothesized to comprise discrete subtypes. This study aimed to characterize HFpEF heterogeneity using advanced data science techniques applied to deeply phenotyped, multi-modal cohorts.

* Corresponding author. Email: christopher.miller@manchester.ac.uk

© The Author(s) 2026. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

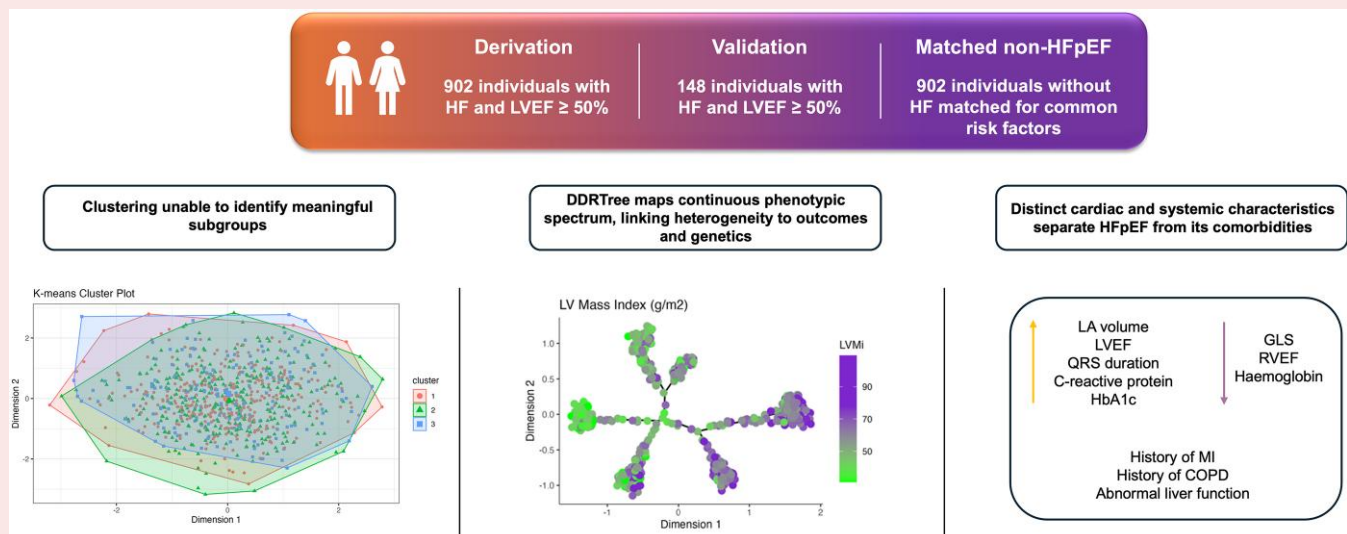
Methods and Results

A total of 902 patients with HF and a left ventricular ejection fraction $\geq 50\%$ were prospectively recruited and underwent detailed clinical, imaging, and genetic profiling. Clustering algorithms were first applied to derive discrete subgroups. To overcome rigid subgroup assignment, DDRTree was applied to map continuous phenotypic and outcome variation onto a two-dimensional tree. Genome-wide association studies (GWAS) identified variants associated with tree dimensions. Internal validation assessed stability, and external validation was conducted in a UK Biobank HFpEF cohort ($n = 148$). Sensitivity analyses included patients with mildly reduced ejection fraction ($n = 1154$). Logistic regression compared HFpEF with comorbidity-matched controls ($n = 902$). Whilst conventional clustering did not identify meaningful subgroups, DDRTree revealed a stable, interpretable tree structure, capturing continuous variation in cardiac structure and function, biomarkers and comorbidities. Over a median follow-up of 6.8 years, phenotypic complexes demonstrated differing risks of cardiovascular death, HF hospitalization, adverse renal outcome, and infection hospitalization. GWAS revealed a locus near *CRACD* associated with tree dimension one. Findings were reproducible in external and sensitivity analyses. A profile of cardiac and systemic characteristics that distinguish HFpEF from its associated comorbidities were identified.

Conclusions

HFpEF risk and disease course reflect a variable interplay of pathophysiological processes in each individual. This study provides a biologically plausible framework to guide a more personalized approach to HFpEF.

Graphical Abstract



Keywords

Heart failure • Heart failure with preserved ejection fraction • Data science

Introduction

Heart failure with preserved ejection fraction (HFpEF) is the most common type of heart failure (HF).¹ The widespread clinical adoption of natriuretic peptide testing and emergence of evidence-based therapies are resulting in greater recognition of HFpEF.^{2,3} As the population ages and metabolic risk factors become more prevalent, its impact is expected to rise considerably.

The term 'HFpEF' originated as a description of exclusion, in order to distinguish from HF with low ejection fraction. Consequently, HFpEF comprises a highly heterogeneous group of patients, encompassing multiple disease mechanisms, a range of risk factors and associated conditions, and variable disease course and outcomes.⁴ Reclassifying HFpEF into more homogenous, discrete subgroups, as a basis for developing

more effective diagnostics, risk prediction, and therapeutics, has been a focus of research for nearly a decade. However, studies have been limited by sparse patient characterization or small retrospective cohorts, typically with single modal and minimal disease mechanism data.^{5–11} Findings have not translated clinically.

More recently, novel data science techniques that are able to take account of continua of phenotypic and genetic heterogeneity, have been applied to other complex, chronic diseases. For example, in type 2 diabetes, these methods have simplified heterogeneity, identified causal processes, and predicted disease progression and treatment response.¹²

In this study, we applied three conventional clustering approaches and DDRTree, a data dimensionality reduction technique, to deeply phenotyped, multi-modal data to reduce HFpEF from a complex, multi-dimensional disorder into interpretable models, as a basis for visualizing

the heterogeneity, investigating how phenotypic variation drives disease outcomes, identifying genetic determinants of the heterogeneity, and identifying features that distinguish HFpEF from its associated comorbidities. As contemporary trials often include patients with HF with mildly reduced ejection fraction (HFmrEF), we repeated our investigations in a cohort that included these patients.

Methods

Cohorts and phenotype data

Derivation cohort

Consecutive adult patients between 13 June 2016 and 21 May 2024, meeting the European Society of Cardiology Guideline criteria for HFpEF,¹³ including symptoms and/or signs of HF; N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥ 125 pg/ml; and a left ventricular ejection fraction (LVEF) $\geq 50\%$, were prospectively recruited via two routes: (i) Patients undergoing clinical cardiovascular magnetic resonance (CMR) imaging (prospective cohort study, NCT02326324) and (ii) patients assessed in a HFpEF clinical service (prospective cohort study, NCT05383287), both at Manchester University NHS Foundation Trust, UK. Patients with a diagnosis of any of the following were excluded: complex congenital heart disease, Fabry disease, hypertrophic cardiomyopathy, amyloidosis, iron overload, acute myocarditis, and stress-induced cardiomyopathy.

Baseline characteristics, including medical history, physical status, biochemistry and haematology laboratory data, electrocardiogram, and echocardiogram data were identified from medical records. CMR images were analysed for measurements of cardiac structure and function in accordance with international recommendations.¹⁴ Pericardial fat area was measured from CMR four-chamber cine images using a previously described automated method [images with poor segmentation quality (Dice score <0.7) were not included].¹⁵ Pulmonary capillary wedge pressure was derived from CMR measurements as described previously.¹⁶ Blood samples were collected and stored at -80°C until DNA extraction. All baseline data collection was blinded to outcome data.

Validation cohort

Individuals with prior HF and LVEF $\geq 50\%$ on CMR were identified from UK Biobank. HF diagnosis was determined from self-reported condition, International Classification of Diseases 10th revision (ICD-10) Summary Diagnoses, and first occurrences data fields ([Supplementary Table S1](#)). Baseline characteristics, corresponding to those in the derivation cohort, were recorded.¹⁷ The ICD-10 codes used to determine medical history data are listed in [Supplementary Table S2](#).

Matched non-HFpEF cohort

Utilizing the derivation cohort, a propensity-score matched (based on age, sex, body mass index, estimated glomerular filtration rate, hypertension, atrial fibrillation, and diabetes status) group of individuals without a diagnosis of HF (see [Supplementary Table S3](#) for exclusion criteria search terms) at the time of CMR assessment, and LVEF $\geq 50\%$, were identified from UK Biobank. Baseline characteristics data were obtained as described above.

Sensitivity analysis cohort

Consecutive adult patients with LVEF 40–49% (i.e. HFmrEF¹⁸) and otherwise meeting the same inclusion and exclusion criteria as the derivation cohort, were prospectively recruited via the same routes as the derivation cohort. This group of patients were combined with the derivation cohort for the purpose of a sensitivity analysis.

Outcomes

Outcome data were obtained from NHS England. Reflecting the heterogeneous disease course of HFpEF, several outcomes were evaluated: cardiovascular death, HF hospitalization, a composite of renal hospitalization or renal death, hospitalization for infection, and cancer death. The date of last follow-up was 1 November 2024, for the derivation and sensitivity analysis cohorts, and 31 October 2022, for the validation and matched

non-HFpEF cohorts, respectively. Detailed definitions and ICD-10 codes for each outcome are provided in the [Supplemental Methods](#) and [Supplementary Table S4](#).

Statistical analysis

Extended descriptions of all statistical analyses are provided in the [Supplemental Methods](#). Statistical analyses were conducted using R (version 4.4.1). Missing data were handled using random forest imputation. The overall proportion of missing data in the derivation cohort was low (11%). Highly correlated variables were removed prior to further analysis.

Clustering

To identify discrete HfPEF subgroups, three clustering algorithms were applied to the phenotype data from the derivation cohort: Density-Based Spatial Clustering and Application with NOISE (DBSCAN), Gaussian mixture modelling, and k-means clustering. Factor analysis of mixed data was applied to the data prior to clustering. Cluster stability was evaluated by calculating mean jaccard indices over repeated iterations of the clustering algorithms using bootstrapped replicates.

Data dimensionality reduction

To characterize the phenotypic spectrum of HFpEF without defining discrete subgroups, we applied DDRTree, a novel data dimensionality reduction technique that generates a two-dimensional (2D) map of patients' phenotypic profiles in the form of a tree structure.¹² In this map, individuals with similar profiles cluster along branches, and individuals with extremes of each profiles form the branch tips. Each branch thus represents a gradient of phenotypic similarity, rather than discrete subgroups. Internal validation was performed by calculating the Jaccard index over 1000 iterations of the algorithm.

Phenotype distribution

Phenotype variables were overlaid onto the tree to allow the variation in phenotypes to be assessed visually. In addition, phenotype distribution was quantified by regressing each phenotype against tree dimensions and plotting the regression coefficients and 95% confidence intervals. NT-proBNP values underwent log transformation prior to regression modelling.

External validation

To evaluate the reproducibility of the tree structure and phenotype distribution, the DDRTree algorithm was *de novo* applied to the external validation cohort. As some key variables from the derivation cohort were unavailable in the external validation cohort, the DDRTree algorithm was re-applied to the derivation cohort using only the variables common to both cohorts.

Outcome analysis

Individual probabilities of developing each outcome were calculated using Fine-Gray competing risks models. All models included age, sex, hypertension, diabetes status, and all the variables used to derive the tree. Outcome distribution was visualized by plotting individual probabilities of each outcome at 5 years onto the tree. In addition, separate models for each outcome were constructed using only the tree dimensions (Dimension 1 and Dimension 2) as covariates. Given the exploratory nature of these analyses, *P*-values were not adjusted for multiple comparisons across outcomes. There were insufficient events in the external validation cohort to allow meaningful outcome analysis in this cohort ([Supplementary Table S5](#)).

To illustrate the clinical relevance, and the utility for selecting patients for trial entry, a proof-of-concept risk model was developed to estimate 3-year risk of a composite of cardiovascular death or HF hospitalization in the derivation cohort. An R Shiny web application was developed to allow interactive exploration of the risk calculator.

Genetic analysis

To explore the genetic contribution to the phenotypic heterogeneity, genome-wide association studies (GWAS) were conducted to identify single-nucleotide polymorphisms (SNPs) associated with the DDRTree dimensions. A significant association between SNPs and a tree dimension would indicate that those SNPs contribute to the phenotypic features

Table 1 Baseline characteristics of the 902 patients with HFpEF in the derivation cohort

	Derivation cohort (n = 902)
Demographics	
Age (years)	67 (11.9)
Male	481 (53.3%)
White ethnicity	830 (92%)
Past medical history	
Hypertension	625 (69.3%)
Diabetes	184 (20.4%)
Hypercholesterolaemia	551 (61.1%)
Atrial fibrillation	235 (26.1%)
Myocardial infarction	274 (30.4%)
Stroke or TIA	93 (10.3%)
Peripheral vascular disease	71 (7.9%)
Asthma	100 (11.1%)
COPD	101 (11.2%)
Obstructive sleep apnoea	23 (2.5%)
Ever smoked	497 (53.1%)
Physical status	
Body mass index (kg/m ²)	29.5 (6.4)
NYHA class	
Class I	320 (35.5%)
Class II	304 (33.7%)
Class III	218 (24.2%)
Class IV	60 (6.7%)
Laboratory results	
Haemoglobin (g/dL)	134 (15)
MCV (fL)	91.2 (6.3)
Haematocrit (L/L)	0.4 (0)
Red cell distribution width (%)	13.9 (1.4)
White cell count (10 ⁹ /L)	7.3 [6.1, 8.8]
Sodium (mmol/L)	139.2 (2.9)
Potassium (mmol/L)	4.4 (0.4)
Urea (mmol/L)	5.9 [5.1, 7]
Creatinine (μmol/L)	80.6 [71, 94]
eGFR (ml/min/1.73 m ²)	74 [61, 87]
Albumin (g/L)	38.2 (3.5)
Alkaline phosphatase (U/L)	83 [74, 95]
Total bilirubin (μmol/L)	10 [8, 12.9]
Alanine transaminase (U/L)	24.2 [19, 29.1]
HbA1c mmol/mol	42.4 (7.9)
C-Reactive protein (mg/L)	6.6 [4, 9.7]
NT-proBNP (pg/mL)	387 [196.4, 894.4]
Electrocardiography	
LBBB	52 (5.8%)
RBBB	52 (5.8%)
QRS duration (ms)	101.2 (18.8)
QTc duration (ms)	434.7 (31.6)
Echocardiography	
Average E/e' ratio	9.9 (2.5)
TV peak gradient (mmHg)	24.1 [21.9, 27.4]

Continued

Table 1 Continued

	Derivation cohort (n = 902)
Cardiac MRI	
LV ejection fraction (%)	62 [56, 68]
LV end-diastolic volume index (mL/m ²)	78 [67, 88]
LV end-systolic volume index (mL/m ²)	29 [22, 37]
LV mass index (g/m ²)	55.5 [44.5, 65]
LV global longitudinal strain (%)	−17.4 (3.7)
LA biplanar area index (cm/m ²)	14.2 (3.2)
LA volume index (mL/m ²)	99.1 [76, 119.9]
Pulmonary capillary wedge pressure (mmHg)	16 (3.1)
RV ejection fraction (%)	60.1 [55, 66]
RV end-diastolic volume index (mL/m ²)	74.6 [63, 85.8]
RV end-systolic volume index (mL/m ²)	29 [22, 37]
TAPSE (mm)	20.6 (4.3)
RA area index (cm/m ²)	12.8 (3.1)
Extracellular volume (%)	27.2 (4.3)
Pericardial fat area (cm ²)	27.5 [22.4, 33.1]

Values are n (%) or mean ± standard deviation or median ± interquartile range.

BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; LA, left atrium; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LV, left ventricle; MCV, mean corpuscular volume; MRI, magnetic resonance imaging; NYHA, new york heart association; NT-proBNP, N-terminal pro B-type natriuretic peptide; QTc, corrected QT; RA, right atrium; RBBB, right bundle branch block; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; TIA, transient ischaemic attack; TV, tricuspid valve.

that vary along that dimension. Associations between SNPs and the DDRTree dimensions were tested using linear regression under an additive genetic model implemented in PLINKv1.9 (–linear). Genome-wide significant association was defined by $P < 5 \times 10^{-8}$.

Distinguishing HFpEF from its associated comorbidities

To identify characteristics that distinguish HFpEF from the multiple comorbidities that are associated with HFpEF, the derivation and matched non-HFpEF cohorts were combined, and two analyses were conducted. First, multivariable logistic regression was performed to determine the relationship between phenotypic variables and HF status. Second, the DDRTree algorithm was applied blinded to HF status and outcomes, to examine whether patients with HFpEF display unique characteristics that cluster them among comorbidity-matched individuals. HF status and outcomes (individual probabilities at 5 years of: cardiovascular death, and HF hospitalization) were overlaid onto the derived tree.

Sensitivity analysis

The analyses were repeated in the sensitivity analysis cohort.

Results

The derivation cohort comprised 902 patients with HFpEF (807 patients undergoing CMR, 85 patients undergoing assessment in a HFpEF clinical service). Baseline characteristics are presented in [Table 1](#). Mean age was 67 ± 12 years and 481 (53.3%) were male. Median LVEF was 62% [interquartile range (IQR) 56–68%].

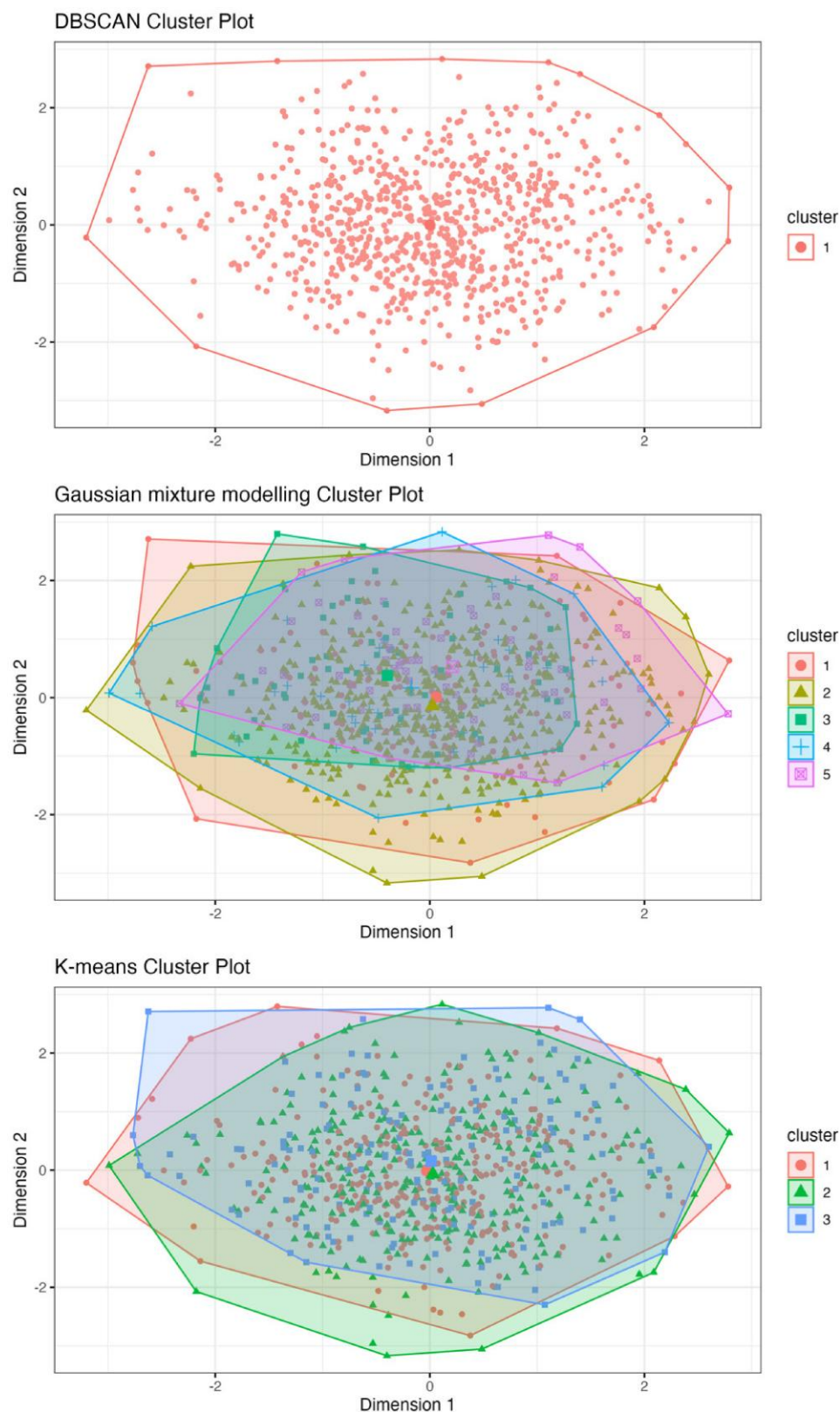


Figure 1 Cluster plots using the phenotype data from patients with HFpEF. Three clustering algorithms were applied: (A) Density-based spatial clustering and application with NOISE (DBSCAN); (B) Gaussian mixture modelling; (C) k-means clustering. Each point in each plot represents one individual. Dimensions represent the principal components explaining the largest variation in data. HFpEF, heart failure with preserved ejection fraction

Phenotype deconvolution

Clustering techniques were unable to identify meaningful clusters (Figure 1). DBSCAN yielded a single cluster, while Gaussian mixture modelling and k-means identified overlapping clusters with weak stability (Gaussian: mean Jaccard coefficients 0.33, 0.54, 0.39, 0.65, 0.27 across 50 iterations; k-means: mean Jaccard coefficients 0.60, 0.71, 0.40 across 1000 iterations).

We therefore applied DDRTree, a dimensionality reduction method that maps individuals according to phenotypic similarity, which demonstrated good stability of the tree structure, with a median Jaccard index of 0.84 (IQR 0.81–0.87).

Phenotypic heterogeneity

Phenotypic distribution varied across the tree structure (Figure 2, Table 2, and Supplementary Figures S1–S4). Symptom severity, the presence of hypertension and the presence of myocardial infarction were uniformly distributed. In contrast, individuals located in the right part of the tree had more LV hypertrophy and myocardial fibrosis, evidence of more systemic inflammation, higher LV filling pressures, lower LVEF, worse renal function, higher prevalence of atrial fibrillation and higher NT-proBNP. Individuals located in the lower part of the tree had higher body mass index, larger pericardial fat area, higher haemoglobin A1c, and higher prevalence of diabetes. Those in the left part of the tree had lower LV mass, higher LVEF, and lower NT-proBNP.

External validation

The external validation cohort comprised 148 individuals (Supplementary Table S6). Mean age was 67.4 ± 6.6 years and 103 (69.6%) were male. Median LVEF was 56% (IQR 52–58%). The tree derived using the DDRTree algorithm demonstrated good stability, with a median Jaccard index of 0.82 (IQR 0.79–0.84). The tree structure was different in shape to the derivation cohort but displayed consistent patterns of phenotypic distribution (Supplementary Figures S5–S8 and S9–S12). For example, individuals with higher LV mass, higher LV filling pressures, and higher prevalence of atrial fibrillation were located towards the upper part of the tree, whereas those with higher body mass index, larger pericardial fat area, higher haemoglobin A1c, and higher prevalence of diabetes were located in the left part of the tree.

Outcome heterogeneity

Median follow-up duration in the derivation cohort was 6.8 years (IQR 5.7–7.4). Cardiovascular death occurred in 60 (6.7%) patients, cancer death in 43 (4.8%) patients, and all-cause death in 181 (20%) patients. HF hospitalization occurred in 74 (8.2%) patients, renal hospitalization or renal death in 28 (3.1%) patients, and hospitalization for infection in 177 (19.6%) patients. Whereas the probability of cancer death was uniformly distributed across the tree, the risks of cardiovascular death, HF hospitalization, and adverse renal outcome were higher for individuals with more myocardial fibrosis and a higher prevalence of atrial fibrillation located in the right part of the tree (Figure 3). Each unit increase in tree dimension 1 was associated with a higher risk of cardiovascular death [hazard ratio (HR) 1.80, 95% confidence interval (CI) 1.32–2.46, $P < .001$], HF hospitalization (HR 2.10, 95% CI 1.55–2.84, $P < .001$), and renal death or hospitalization (HR 1.54, 95% CI 1.09–2.19, $P = .015$). The risk of hospitalization for infection/sepsis was higher for individuals in the lower part of the tree, with each unit decrease in tree dimension 2 associated with higher risk (HR 0.58, 95% CI 0.46–0.75, $P < .001$).

Demonstrating individual risk in relation to phenotype

A proof-of-concept risk calculator was developed to estimate 3-year risk of a composite of cardiovascular death or HF hospitalization

(https://hfpef-outcome-prediction.shinyapps.io/hfpef_calculator/; for demonstration purposes only). There were a total of 118 events. The proportional hazards assumption was satisfied. Model performance was acceptable (optimism-corrected C-index 0.779; Integrated Calibration Index of 0.022; E_{90} of 0.038; median calibration slope of 0.94). Optimism-adjusted model coefficients and decile calibration plots are provided in Supplementary Table S7 and Supplementary Figure S13, respectively.

Genetic drivers of the phenotypic heterogeneity

Genotyping was performed in 486 individuals from the derivation cohort, which comprised the primary GWAS analysis, and in a further 149 individuals in the sensitivity cohort. After quality control, 566 samples (320 males and 246 females) and 774 519 SNPs (autosomes and X chromosome) were retained, with a genotyping rate of 99.85%. GWAS were conducted in 396 individuals for whom tree dimension values were available after quality control. A locus on chromosome 4, near CRACD (rs114184876) reached genome-wide significance ($P = 2.8 \times 10^{-8}$) for tree dimension 1 (Supplementary Figure S14). Several other loci demonstrated suggestive associations for both dimensions ($P < 5 \times 10^{-5}$, Supplementary Table S8).

Distinguishing HFpEF from its associated comorbidities

After combining the derivation and matched non-HFpEF (Supplementary Table S9) cohorts, multivariable logistic regression identified independent predictors of HFpEF to include larger left atrial volume, higher LVEF, more impaired LV global longitudinal strain, lower right ventricular ejection fraction, longer QRS duration, previous myocardial infarction, history of COPD, higher C-reactive protein, lower haemoglobin, abnormal liver function, and higher haemoglobin A1c (Table 3). A secondary analysis including variables used for matching revealed similar results (Supplementary Table S10). When the DDRTree algorithm was applied to the combined cohorts, individuals with HFpEF clustered to the right of the tree, suggesting a distinct phenotypic profile compared to matched non-HFpEF individuals (Figure 4).

Median follow-up duration for the combined cohorts was 5.9 years (IQR 4.0–7.1). Annualized rates of cardiovascular death (1% vs 0.2%), HF hospitalization (1.2% vs 0.1%), and all-cause death (3% vs 0.7%), were higher in individuals with HFpEF compared to the matched individuals without HFpEF. Overlaying individual probabilities of experiencing each outcome illustrated that risks were higher for patients with HFpEF, located in the right side of the tree (Figure 4).

Sensitivity analysis including patients with HFmrEF

The sensitivity analysis cohort comprised 1154 patients (Supplementary Table S11). Whilst the tree derived from the sensitivity analysis cohort had a different morphology to that derived from the derivation cohort, the pattern of phenotypic variation across the tree was consistent (Supplementary Figures S15–S18, median Jaccard index 0.75 (IQR 0.73–0.76)). The distributions of outcome risks were also very similar (Supplementary Figure S19). The sensitivity analysis cohort GWAS included 532 genotyped individuals. The CRACD locus remained among the strongest associations for tree dimension 1, although it did not surpass the genome-wide significance threshold ($P = 6.8 \times 10^{-6}$; Supplementary Figure S20). Several other loci demonstrated suggestive associations for both dimensions ($P < 5 \times 10^{-5}$; Supplementary Table S12).

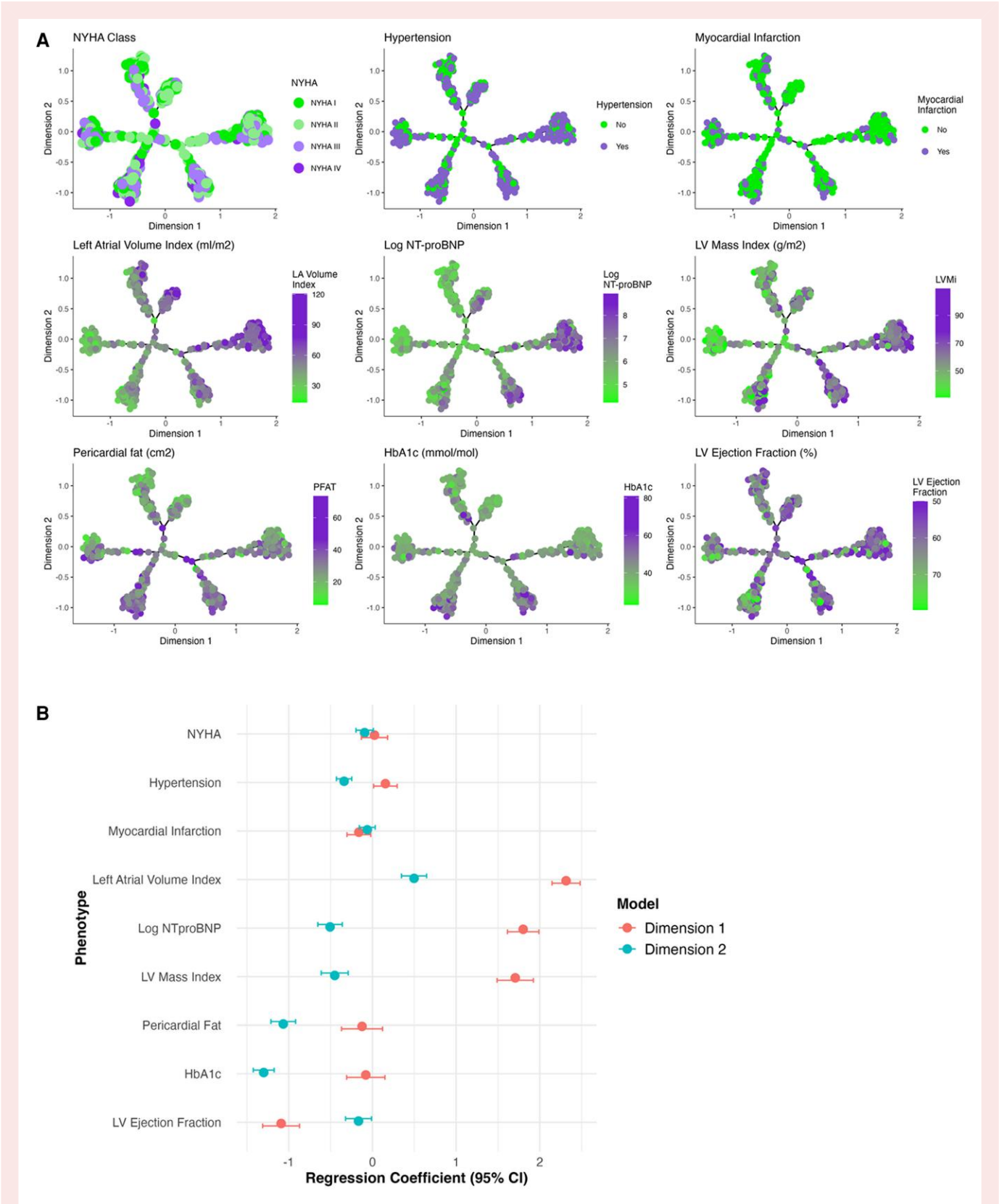


Figure 2 A visual representation of the phenotypic characteristics of 902 patients with HFpEF. (A) DDRTree with reverse graph embedding was applied to reduce the highly dimensional phenotypic data to form a two-dimensional tree structure. Phenotype variables are overlaid onto the tree to visualize the distribution of phenotypes. Each point represents one individual. (B) Linear regression estimates (with 95% confidence interval, CI) between the DDRTree dimensions and phenotypes, showing the relationship between phenotypes and dimensions. HbA1c, Haemoglobin A1c; HFpEF, heart failure with preserved ejection fraction; LA, left atrium; LV, left ventricle; LVMi, left ventricular mass index; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; PFAT, pericardial fat

Table 2 Key phenotype-dimension associations

Dimension 1	Dimension 2
Higher LV mass	Increased pericardial fat
Higher NTproBNP	Higher HbA1c
Lower LVEF	Higher BMI
Worse renal function (lower eGFR)	Higher prevalence of diabetes
Greater myocardial fibrosis (ECV)	
Higher prevalence of atrial fibrillation	
Higher LV filling pressures (E/e')	
Higher systemic inflammation (CRP)	

Each column lists the dominant phenotypes associated with the corresponding DDRTree dimension.

BMI, body mass index; CRP, c-reactive protein; ECV, extracellular volume; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; LV, left ventricle; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide.

Discussion

In this study, we applied a novel dimensionality reduction approach to deeply phenotyped, multi-modal data to better characterize and understand the heterogeneity of HFpEF. In contrast to conventional clustering techniques, which failed to identify meaningful subgroups, the data dimensionality reduction approach exposed the spectrum of phenotypic variation in individuals with HFpEF. The two-dimensional representation provided by DDRTree, which was robust across two independent cohorts, enabled visualization of the phenotype and outcome heterogeneity, identifying phenotypic complexes that associate with different outcomes. It also enabled investigation of genetic drivers underlying the phenotypic heterogeneity, with findings suggesting that the heterogeneity may be in part genetically determined. In addition, we discovered a profile of cardiac and systemic characteristics that distinguish HFpEF from its associated comorbidities. Our findings challenge the prevailing hypothesis that HFpEF comprises discrete subgroups and instead, consistent with the 'palette model' described in type 2 diabetes and other complex heterogeneous diseases,¹⁹ suggest individual patient disease course and likely treatment response reflect a combination of pathophysiological processes that are present to a greater or lesser extent in each individual. The findings provide a biologically plausible basis for developing a more personalized approach to diagnosing, risk stratifying and treating patients with HF in the context of an LV ejection fraction that is not markedly reduced ([Graphical Abstract](#)).

What constitutes HF in the context of an LV ejection fraction that is not markedly reduced remains unclear. People in the typical HFpEF age range that report breathlessness, peripheral oedema, or fatigue often have multiple reasons for their symptoms, and structural and functional cardiac abnormalities are common.⁴ Natriuretic peptide levels are often elevated as a consequence of age and comorbidities. A key reason for identifying patients with HF with reduced ejection fraction (HFrEF), and a central rationale for patients with HFrEF being managed by cardiology teams, is that the disease course is such that most patients (approximately 80%) experience cardiovascular death.²⁰ This is not the case for patients with HFpEF, where the majority of patients (50–55% in randomized controlled trials, more than 60% in observational studies) experience death due to other causes e.g. cancer, infection, respiratory illness.^{2,21} Sodium-glucose co-transporter-2 inhibitors, non-steroidal mineralocorticoid receptor antagonists and glucagon-like peptide-1 agonist-based interventions have moved the field forward substantially, but numbers needed to treat are high and no therapies significantly reduce cardiovascular mortality. Trialling potential HF

interventions, and measuring their effect via impact on cardiovascular death, in patients whose symptoms and natriuretic peptides levels may be the consequence of other factors, and who are unlikely to suffer cardiovascular death, introduces considerable noise.

Factors such as these have driven extensive research aiming to identify distinct subgroups of patients with HFpEF with more homogenous disease mechanisms, disease course and outcomes. Some studies, including our own, have identified potential subgroups, however phenotype data have generally been sparse and not reflective of the complex phenotypes of real patients, resulting in subgroups that are superficial.^{5–10} Few have included disease mechanism data. Furthermore, aside from specific causes of HF in the context of an LV ejection fraction that is not markedly reduced (e.g. hypertrophic cardiomyopathy, amyloidosis), discrete subgroups are not really observed in clinical practice; in keeping with this, discrete clustering techniques have generally resulted in inconsistent, unstable subgroups with considerable overlap, as we found here.

In contrast, the DDRTree data dimensionality reduction technique provided a more biologically plausible, and more robust, representation of HFpEF, revealing a structured continuum of phenotypic characteristics. Clear differences in disease mechanisms, associated conditions, and outcomes were identified, despite uniform symptom severity, demonstrating that symptom burden in this context is a poor marker of underlying disease and co-morbidity profile, risk of adverse outcome, and nature of outcome. Whilst hypertension and myocardial infarction were uniformly distributed, pathophysiological mechanisms such as myocardial fibrosis and left ventricular hypertrophy, and structural and functional abnormalities, such as left atrial size and diastolic function, showed considerable heterogeneity, being particularly evident in individuals in the right part of the tree. The findings show parallels with prior discrete cluster-based analyses, with the right branch aligning with a cardiorenal phenotype and the lower branches aligning with a metabolic phenotype. In this way, the continuous 'palette' model helps reconcile previously identified phenotypes, which rather than being distinct entities instead represent extremes along continuous biological spectra. Collectively, these findings support the hypothesis that there are as yet undefined molecular mechanisms responsible for the phenotypic variation that could provide a basis for novel biomarkers and therapeutic targets.

In keeping with other observational studies, two-thirds of deaths were non-cardiovascular.²¹ Individuals with greater adverse cardiac remodelling, higher natriuretic peptide levels and more systemic inflammation, located in the right part of the tree, were more likely to experience cardiovascular death and HF hospitalization. Individuals with higher body mass index, more pericardial adipose tissue and higher haemoglobin A1c, located in the lower part of the tree, were at increased risk of hospitalization for infection/sepsis. These patterns likely reflect underlying pathophysiology: the findings potentially support the concept that an inflammation-metabolic driven HFpEF has a different predominant risk (infection, perhaps related to immuno-metabolic dysfunction), than a fibrosis-cardiac remodelling-driven HFpEF which leads to classical cardiovascular events. Importantly, these findings also suggest that it may be possible to enrich trial entry with patients that are at higher risk of cardiovascular death than which are currently enrolled into HFpEF trials. More fundamentally, by identifying phenotypic complexes that associate with adverse cardiovascular outcome, it may be possible to refine HFpEF into 'cardiovascular HFpEF' and 'non-cardiovascular HFpEF', akin to cardiac and non-cardiac chest pain, providing the opportunity for cardiovascular drug discovery and trials, and clinical cardiology resource, to focus on those patients with the highest cardiovascular need. Building on these observations, we developed a risk calculator to estimate 3-year risk of cardiovascular death or HF hospitalization. Whilst only internally validated, this tool demonstrates how variation in outcomes within the HFpEF population could be translated into an approach with clinical and trial entry utility.

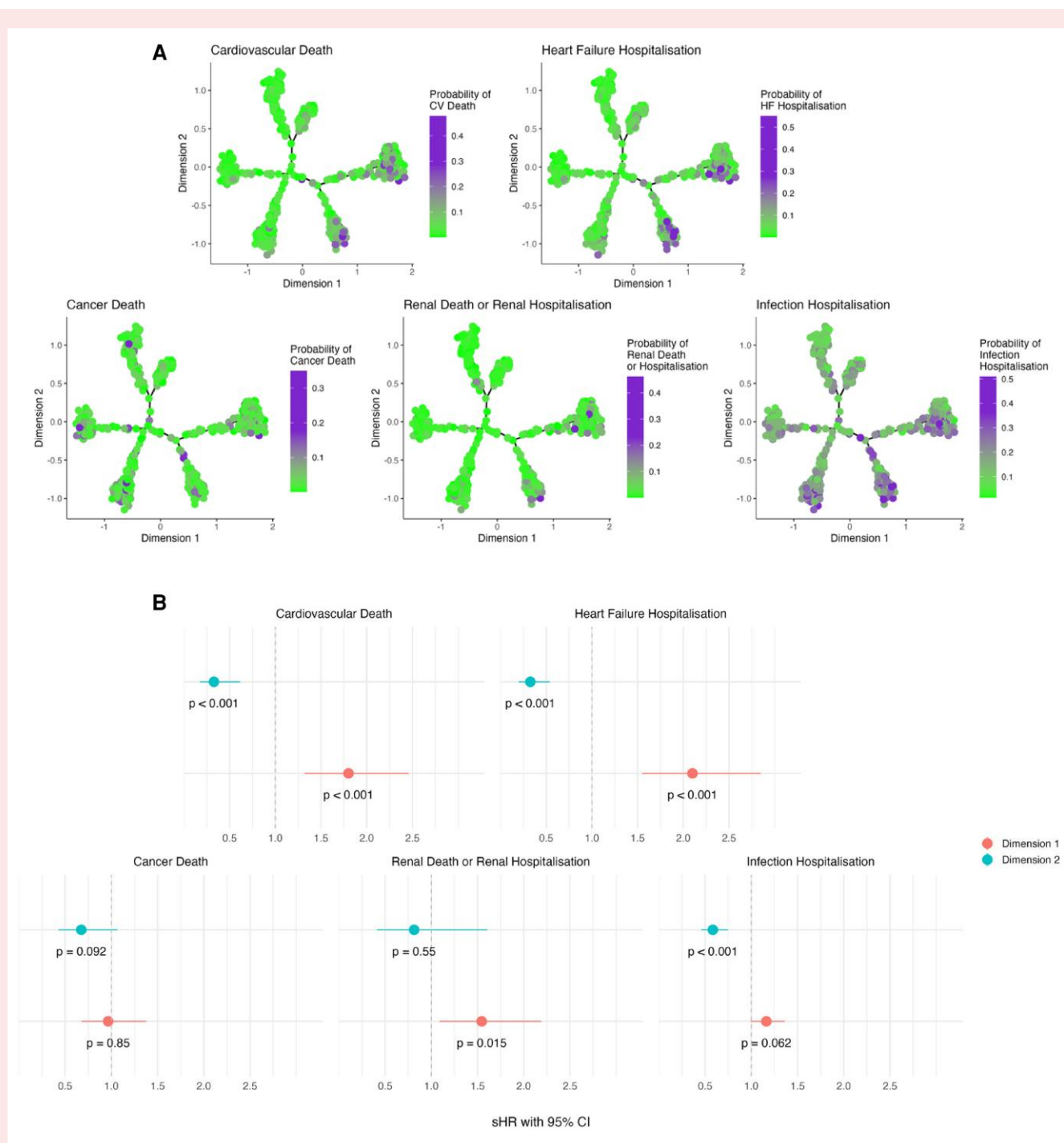


Figure 3 A visual representation of the variability of outcomes in patients with HFpEF. (A) Probabilities of developing each outcome at 5 years were calculated for each individual and overlaid onto the tree structure. (B) Sub-hazard ratios (HR) with 95% confidence intervals (CI) of DDRTree dimensions for each outcome. HFpEF, heart failure with preserved ejection fraction

Genetic investigations in HFpEF have been hampered by the phenotypic heterogeneity, with a recent study concluding that it is 'paramount' to resolve the phenotypic heterogeneity before the genetic architecture of HFpEF can be determined.²² In keeping with this, our study highlights the potential for phenotypic continua, such as those captured by the two dimensions of the representation of the phenotypic variation, to serve as quantitative traits for investigating causal

processes. Our exploratory analyses identified a locus near *CRACD* to be associated with tree dimension 1. *CRACD* encodes a capping protein inhibiting regulator of actin dynamics, which has not previously been linked to cardiovascular biology, but its role in actin regulation may be relevant to cardiac disease, indeed, individuals further along the dimension 1 axis displayed more cardiac dysfunction. Several other loci were identified that had suggestive associations with both tree

Table 3 Phenotypic characteristics that distinguish HFpEF from age, sex and co-morbidity-matched individuals without HF

Variable	Odds ratio ^a	Lower 95% CI	Upper 95% CI	Wald statistic	P value
(Intercept)	1.33	0.91	1.97	1.48	.14
Myocardial infarction	2.16	1.02	4.68	1.98	.048
COPD	6.74	1.49	29.39	2.5	.012
Ever smoked	1.52	0.89	2.6	1.53	.125
Haemoglobin	0.52	0.36	0.75	−3.43	.001
Mean corpuscular volume	1.32	1.05	1.64	2.4	.016
Red cell distribution width	0.91	0.63	1.31	−0.51	.613
White cell count	0.93	0.69	1.29	−0.42	.674
Urea	0.93	0.78	1.18	−0.83	.408
Albumin	0.03	0.02	0.05	−12.73	<.001
Alkaline phosphatase	0.87	0.66	1.14	−0.99	.323
Bilirubin	2.17	1.61	2.98	4.92	<.001
Alanine transaminase	1.57	1.23	1.99	3.74	<.001
C-reactive protein	2.92	1.93	4.58	4.75	<.001
HbA1c	1.5	1.14	1.97	2.95	.003
QRS duration	1.97	1.47	2.66	4.52	<.001
QTc duration	1.46	1.11	1.94	2.66	.008
LV ejection fraction	12.51	7.65	21.51	9.61	<.001
LV end-diastolic volume index	6.67	4.1	11.27	7.37	<.001
LV mass index	0.99	0.65	1.52	−0.04	.971
LV global longitudinal strain	0.4	0.27	0.59	−4.57	<.001
LA volume index	1.85	1.34	2.58	3.7	<.001
RV ejection fraction	0.56	0.39	0.8	−3.18	.001
RV end-diastolic volume index	0.14	0.09	0.22	−8.21	<.001
Pericardial fat area	1.11	0.83	1.47	0.73	.466

Determined using multivariable logistic regression modelling. P values <.05 in bold lettering.

CI, confidence interval; COPD, chronic obstructive pulmonary disease; LA, left atrium; LV, left ventricle; QTc, corrected QT; RV, right ventricle.

^aOdds ratio per 1 standard deviation increase in continuous variables.

dimensions, such as *XIRP2*, which is linked to both cardiomyopathy and arrhythmogenesis,²³ and *TEK*, an important regulator of endothelial function that has been implicated in angiogenesis and vascular calcification.²⁴ Given the multifactorial nature of HFpEF, including the likely substantial contribution of structural, metabolic, inflammatory, and environmental factors, genetic variation likely explains only a proportion of the observed phenotypic heterogeneity. Further investigations with larger sample sizes are required.

Taken together, our findings suggest that the pathogenesis of HFpEF is consistent with the 'palette model' of complex disease described in type 2 diabetes, in which multiple pathophysiological mechanisms may be present in each individual to a greater or lesser extent, and their cumulative impact determines the HFpEF phenotype, disease course, drug response, and outcome of that individual.¹⁹ Our investigation followed many of the methods that Nair et al. used to characterize the heterogeneity of type 2 diabetes in line with the model.¹² Also in keeping with the model, rather than any one characteristic distinguishing HFpEF from its associated comorbidities, a spectrum of cardiac and systemic (particularly metabolic) characteristics was identified. A strength of our investigation is the extensive matching of the non-HFpEF cohort with the HFpEF cohort across multiple key comorbidities.

We included the sensitivity analysis to (i) provide insight into contemporary trial populations, which typically include patients with HFmrEF and (ii) start to progress from arbitrary descriptive

categories to an approach that focuses on the underlying biology, integrating ejection fraction alongside other variables, analogous to cancer where traditional anatomic descriptors have given way to precise molecular descriptors that yield insight into causal mechanisms.²⁵ This continuous framework also accommodates the upper end of the ejection fraction range; supranormal ejection fraction has increasingly been recognized as a distinct HFpEF phenotype, characterized by unique contractility-related genetic signatures, altered ventricular-arterial coupling, and higher cardiovascular risk.^{26–28}

This study has several important limitations. Many patients in the derivation cohort were recruited as part of a prospective cohort undergoing clinical CMR imaging, which introduces selection bias. Similarly, the matched non-HFpEF controls were identified from the UK Biobank imaging sub-cohort, which may also introduce selection bias. That said, CMR provided extensive, highly granular data and unique pathophysiological insight, such as myocardial fibrosis and pericardial adipose tissue. The UK Biobank cohorts were identified using ICD-10 codes, potentially leading to misclassification. Only a small number of people in UK Biobank had a diagnosis of HF and an LV ejection fraction $\geq 50\%$, and the resulting small number of outcomes precluded outcome analysis. Not all phenotyping variables from the derivation cohort were available in UK Biobank. The relatively narrow ejection fraction distribution in UK Biobank also limited validation of the full ejection fraction continuum, especially at the high ejection fraction extreme. The genetic analyses were limited by

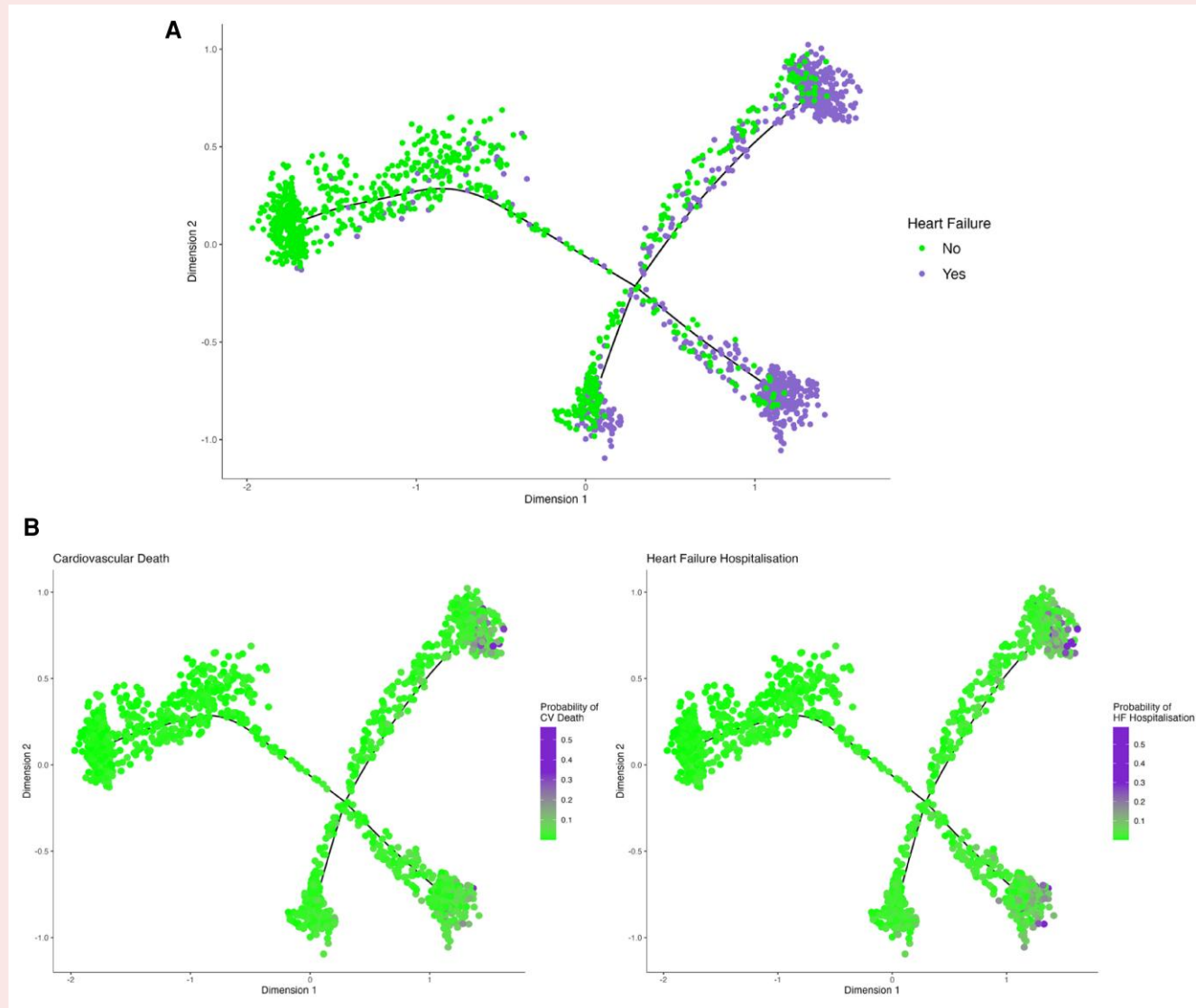


Figure 4 Visualizing the distinction between HFpEF and its associated comorbidities. The DDRTree algorithm was applied to a cohort combining patients with HFpEF and age, sex, left ventricular ejection fraction and co-morbidity-matched individuals without HF, blinded to HF status and outcomes. Each point represents one individual. Black lines indicate the latent tree structure learned by the DDRTree algorithm. (A) Heart failure status overlaid onto tree structure. (B) Probabilities of developing each outcome at 5 years for each individual overlaid onto the tree structure. HF, heart failure; HFpEF, heart failure with preserved ejection fraction

sample size and restricted to individuals of European ancestry. Large scale, co-ordinated, prospective studies, collecting extensive, multi-modal phenotype and genetic data, and including external validation cohorts with adequate sample size and phenotyping, are required to understand the pathobiology of HFpEF, discover more specific diagnostics and targeted interventions, and efficiently trial new therapies. The objectives of initiatives, such as UK HFpEF, HeartShare, and CAPTURE-HFpEF, are in line with these ambitions.^{29,30}

In conclusion, the findings of this study provide a novel approach to understanding the heterogeneity of HFpEF. By integrating high-dimensional, multi-modal data, we uncovered a structured spectrum of phenotypic, genetic and outcome variation. The findings provide a biologically plausible basis for developing a more personalized approach to HFpEF, and support a shift towards mechanism-focused research in large scale, deeply phenotyped cohorts.

Acknowledgements

The authors acknowledge the support of the NIHR BHF Cardiovascular partnership for providing infrastructure support and facilitating collaborative cardiovascular research. This research has been conducted using the UK Biobank Resource under application number 182118.

Supplementary Data

Supplementary data are available at [European Journal of Heart Failure](https://www.ejhf.com) online.

Declarations

Disclosure of Interest

A.A.M. has received honoraria from Alnylam, Boehringer Ingelheim, and Pharmacosmos. S.E.P. has undertaken consultancy for Circle

30. CAPTURE-HFpEF. <https://www.herlevhospital.dk/capture-heart/Sider/default.aspx>.
Date accessed 2 August 2025.