

Heart Failure Risk Phenotypes Based on a 2-Dimensional Tree Structure Derived from Clinical Characteristics and Associations with Disease Prevalence and Cardiovascular Mortality in the General Population

ABSTRACT

Background: Using the Discriminative Dimensionality Reduction Tree (DDRTree) algorithm, a 2-dimensional tree model was constructed based on conventional clinical indicators to identify heart failure (HF) risk phenotypes with different pathophysiological characteristics from the general adult population and evaluate their association with HF prevalence and cardiovascular mortality risk.

Methods: A representative sample of 24 205 general US adults from the National Health and Nutrition Examination Survey 1999–2018 was analyzed. Eleven routine clinical indicators from multiple physiological dimensions were fed into the DDRTree algorithm to project each of them in a 2-dimensional space. The resulting tree structure revealed distinct HF risk phenotypes whose links to outcome HF prevalence and cardiovascular mortality risk were quantified with weighted logistic regression and Cox proportional-hazard models.

Results: Discriminant Dimensionality Reduction Tree identified 3 HF risk phenotypes: normal, metabolic (characterized by upregulated glucose-metabolism markers), and inflammatory (characterized by abnormalities in inflammatory and hepatic-renal markers). After fully adjusting for confounding factors, the metabolic phenotype was significantly associated with the risk of HF compared with the normal phenotype (odds ratio [OR]=1.96, $P < .001$, 95% CI: 1.47–2.62), whereas it showed no significant correlation with the risk of cardiovascular death (hazard ratio [HR]=0.92, $P = .539$, 95% CI: 0.70–1.20). In contrast, the inflammatory phenotype was significantly correlated with both HF risk (OR=3.95, $P < .001$, 95% CI: 2.94–5.33) and cardiovascular mortality risk (HR=1.47, $P = .002$, 95% CI: 1.16–1.87).

Conclusions: This study elucidates potential risk phenotypes influencing HF and cardiovascular mortality, providing new insights for precise HF risk stratification and targeted preventive interventions in the general population.

Keywords: Cardiovascular diseases, heart failure, machine learning, mortality, nutrition surveys

INTRODUCTION

Heart failure (HF) is a complex clinical syndrome resulting from structural and functional abnormalities of the heart that impair ventricular pumping or filling capacity.¹ As the terminal stage of various cardiovascular diseases, HF has become an increasingly serious global health challenge. From 1990 to 2021, the number of patients with HF worldwide increased from 25.43 million to 55.50 million, and the age-standardized prevalence rose from 641.14 to 676.68 per 100 000.² Moreover, with population aging and the increasing prevalence of cardiovascular disease risk factors, the burden of HF is expected to further increase.^{2,3} Notably, despite continuous advances in therapeutic strategies, the long-term prognosis of patients with HF remains poor, with cardiovascular death accounting for approximately 70% of all deaths.⁴ This unfavorable prognosis is closely related to the marked pathological heterogeneity of HF. The pathogenesis, clinical manifestations,

ORIGINAL INVESTIGATION

Yuehuan Chen¹ 

Jing Wu² 

Xia Zang³ 

¹Department of Cardiovascular Medicine, Changxing People's Hospital, Huzhou, China

²Department of Nephrology and Geriatric Dermatology, Changxing People's Hospital, Huzhou, China

³Department of Cardiovascular Medicine, Changxing People's Hospital, Huzhou, China

Corresponding author:

Xia Zang,
✉ XxiaZzang@163.com

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and treatment responses of HF are influenced by the combined effects of multisystem factors, including metabolic disorders, hepatic and renal dysfunction, and inflammatory states.⁵⁻⁷ This complex multisystem interplay leads to substantial heterogeneity in disease trajectories among patients and also limits the effectiveness of traditional risk stratification.⁸ This challenging situation underscores the importance of precise identification and risk stratification of individuals at high risk for HF.

At present, the traditional taxonomy of HF mainly relies on left ventricular ejection fraction (LVEF), categorizing HF into HF with reduced LVEF (LVEF < 40%), HF with mildly reduced LVEF (LVEF 40%-49%), and HF with preserved LVEF (LVEF ≥ 50%).⁹ Although this approach is of important clinical relevance, it is essentially a coarse stratification based on a single dimension and fails to adequately capture the heterogeneity driven by the aforementioned multisystem physiological disturbances.¹⁰ Therefore, in clinical practice and the field of primary prevention, it is urgent to develop more refined risk phenotype classification systems that can reflect the complex multidimensional characteristics of HF.

The Discriminative Dimensionality Reduction Tree (DDRTree), as an innovative computational method, integrates dimensionality reduction with reversed graph embedding techniques, enabling high-dimensional data to be mapped into a low-dimensional space while simultaneously recovering and presenting their intrinsic tree-like branching structures.¹¹ This approach not only enables the mathematical reconstruction of continuous pseudo-trajectories simulating the progression of HF risk from a basal physiological state, but also effectively identifies distinct risk phenotypes distributed along divergent pathological branches.¹² This technique has demonstrated unique advantages in studies of heterogeneity in complex diseases such as diabetes and obesity, successfully delineating phenotypic landscapes with different metabolic characteristics and disease risks.^{13,14}

Although LVEF is crucial in clinical diagnosis, it mainly targets the population of already affected patients. In the field of primary prevention, it is urgent to identify individuals who have not yet been diagnosed but are on a high-risk evolutionary path. The study aims to use data from the adult

population in the National Health and Nutrition Examination Survey (NHANES) database to construct a 2-dimensional tree model based on routine clinical indicators. This study aims to reveal the latent phenotypic structure of HF risk and define a novel disease progression pattern from a normal physiological state to a pathological state, thereby identifying HF risk subtypes with different pathophysiological characteristics, evaluating their associations with HF prevalence and cardiovascular mortality risk, and providing a scientific basis for the precise prevention and management of HF.

METHODS

Study Design and Data Source

This study performed cross-sectional analyses and mortality follow-up analyses using pooled data from 10 cycles of the NHANES spanning 1999 to 2018. Cross-sectional analyses were conducted to assess the associations of distinct HF risk phenotypes and 11 clinical indicators with prevalent HF. Mortality follow-up analyses, based on NHANES linked mortality files, were used to evaluate the relationships between the aforementioned HF risk phenotypes, 11 clinical indicators, and cardiovascular mortality. The NHANES database is funded by the National Center for Health Statistics (NCHS) and employs a complex, multistage probability sampling design. Its samples are representative and can reliably reflect the health and nutritional status of the noninstitutionalized population in the United States. To account for the complex sampling design of NHANES and to ensure the representativeness of the results, Mobile Examination Center (MEC) weights were applied in this analysis, specifically the 2-year MEC examination weight (WTMEC2YR), scaled by 1/10 for the combined data from 10 cycles. In addition, all data collection protocols of the NHANES database were approved by an institutional review board. All participants provided written informed consent. No separate ethical approval was required for this study.

Given that the questionnaire asked for HF-related information, this study initially included data associated with HF from 1999 to 2018 ($n=101316$). After excluding individuals younger than 20 years ($n=46235$), those with missing core variables ($n=27699$), and those with extreme outliers in core variables ($n=3177$), a total of 24205 participants were ultimately included in the analysis. Details of the inclusion and exclusion criteria for the study population are shown in Figure 1.

Study Variables

Core Clinical Indicators (Independent Variables)

Based on previously published methods, 23 clinical indicators were initially selected from multiple physiological dimensions, including glucose metabolism, obesity, lipid metabolism, liver function, renal function, and inflammation.¹³ To avoid substantial sample selection bias, variables with a missing proportion greater than 40% were first excluded to reduce the impact of sample selection bias on weighted analysis results. During this process, some indicators, such as low-density lipoprotein cholesterol, triglycerides, homeostasis model assessment of insulin resistance (HOMA-IR),

HIGHLIGHTS

- Discriminative Dimensionality Reduction Tree-based modeling identified 3 distinct heart failure (HF) risk phenotypes: normal, metabolic, and inflammatory.
- The metabolic phenotype, driven by glucose dysregulation, increases HF prevalence risk but not cardiovascular mortality.
- The inflammatory phenotype, linked to liver-renal dysfunction, strongly associates with both higher HF prevalence and cardiovascular mortality.
- These findings enable precise HF risk stratification and targeted prevention beyond traditional classification systems.

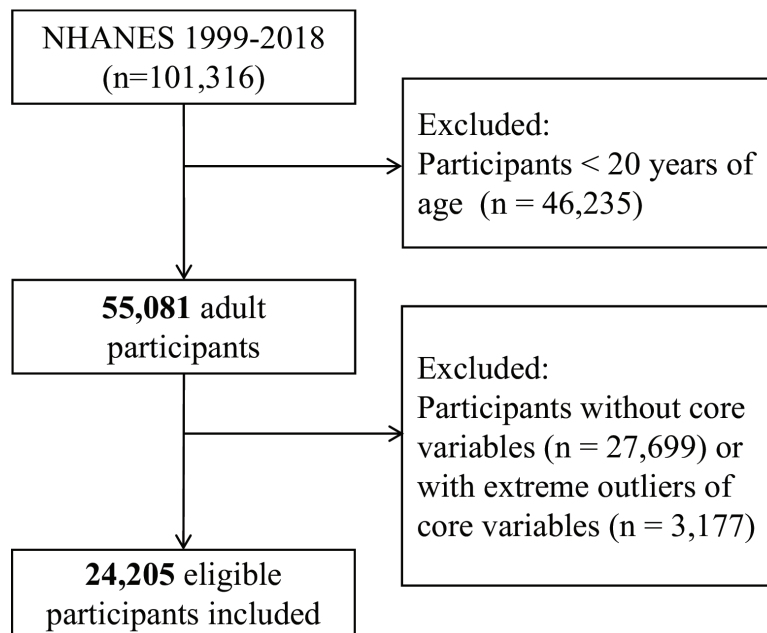


Figure 1. Flowchart showing the inclusion and exclusion of participants.

and fasting blood glucose, were not included in the final model due to a high proportion of deletions (approximately 56%-78%).

Subsequently, forward stepwise regression analysis was performed on the remaining variables using the MASS (Modern Applied Statistics with S) package in R to screen for the combination of variables most strongly associated with HF risk. According to the final model, based on the criteria of a variance inflation factor < 5 and $P < .05$, the following 11 core clinical indicators were identified: liver and kidney function indicators: glutamic oxaloacetic transaminase/glutamic pyruvic transaminase (AST/ALT), gamma-glutamyltransferase (GGT), estimated glomerular filtration rate (eGFR); metabolism and obesity indicators: glycosylated hemoglobin type A1c (HbA1c), waist circumference (WC), diastolic blood pressure (DBP), high-density lipoprotein (HDL); inflammation and hematological indicators: platelet count (PLT), C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR).¹⁵

Outcome Variables

Heart failure and cardiovascular mortality were defined as dependent variables. Heart failure was diagnosed using a multiple choice question (MCQ160B) from the questionnaire, which asks, "Someone ever told you had congestive heart failure?"¹⁶

Cardiovascular mortality data were obtained from the NCHS National Death Index, with follow-up updated through December 31, 2019. Cause of death was determined according to the International Classification of Diseases, 10th Revision. Cases with underlying cause-of-death codes 100-109, 111, 113, and 120-151 were defined as cardiovascular deaths.¹⁷

Covariates

Demographics and health-related information were collected from the NHANES household interviews, including age, sex, race/ethnicity, educational level, marital status, family poverty income ratio (PIR), smoking status, drinking status, and physical activity level. Race/ethnicity was categorized as Mexican American, non-Hispanic White, non-Hispanic Black, and other races. Educational level was classified into 2 categories: <12 years and ≥ 12 years. Marital status was categorized as married/living with a partner or other. Alcohol consumption status was defined based on items ALQ101, ALQ110, ALQ120Q, and ALQ120U from the NHANES Alcohol Use (ALQ) questionnaire, and participants were classified as current drinkers (>1 drink/month) or non-drinkers. Physical activity level was categorized into 2 levels based on self-reported metabolic equivalent of task (MET)-minutes per week: <600 MET-min/week and ≥ 600 MET-min/week.

Data Analysis

This study applied weighted analytical approaches to account for the complex sampling design of the NHANES database. A total of 11 core clinical indicators covering multiple physiological domains including renal function, liver function, metabolism, hematology, lipid profiles, and inflammation were selected, namely eGFR, AST/ALT ratio, GGT, HbA1c, WC, DBP, PLT, HDL, CRP, NLR, and MLR. Outliers exceeding 3 SDs from the mean of each indicator were excluded prior to standardization. All indicators were then standardized via Z-score transformation. Linear regression models were constructed with each standardized clinical indicator as the dependent variable and age and sex as covariates, and model residuals were extracted. The matrix composed of residuals from the 11 clinical indicators was subjected to dimensionality reduction and phenotype identification using DDRTree.

Discriminant Dimensionality Reduction Tree served as the core algorithm in the present work, which projects the high-dimensional residual matrix onto a 2-dimensional space defined by Dim1 and Dim2 through reversed graph embedding. A key advantage of DDRTree is its capability to recover the intrinsic tree-branching structure of datasets; this algorithm is widely adopted in bioinformatics for constructing pseudo-trajectories. Although DDRTree-based phenotype identification relies on cross-sectional baseline data, the algorithm leverages interindividual variations in clinical characteristics to characterize the continuous distribution and potential transition relationships of distinct risk phenotypes within the low-dimensional space. Such pseudo-trajectories do not represent real clinical follow-up trajectories but rather inferred phenotypic progression pathways derived from static population-wide characteristic distributions. Based on trajectory patterns and spatial autocorrelation analyses, 3 predominant HF risk phenotypes were identified: the normal phenotype exhibited low glycometabolic and inflammatory markers alongside elevated HDL levels; the metabolic HF risk phenotype was primarily characterized by elevated metabolic markers including HbA1c and WC with mild inflammatory elevation; the inflammatory HF risk phenotype displayed markedly increased inflammatory and liver function markers accompanied by reduced HDL concentrations. To verify the discriminability of these phenotypes, the K-means clustering algorithm was further implemented. Initial cluster centers were predefined based on the 2-dimensional tree-branching trajectory, and all study participants were reclassified into 3 clusters. Means and distribution ranges of core variables within each cluster were calculated to facilitate clinical feature description and visualization. Linear regression models were utilized to assess associations between the 11 core clinical indicators and the 2 latent DDRTree dimensions, with regression coefficients and corresponding 95% CIs reported. Moran's I statistic was applied to evaluate spatial autocorrelation of each clinical marker across the DDRTree 2-dimensional space. Weighted logistic regression models were subsequently built to quantify associations of Dim1 and Dim2 with prevalent HF status, and an HF risk landscape was generated using predicted probabilities derived from these models.

Weighted statistics were used to describe baseline characteristics and demographic profiles across distinct risk phenotype groups. Categorical variables were presented as sample sizes with weighted percentages, while continuous variables were summarized as weighted mean $\pm$ SD. Weighted logistic regression models estimated associations between individual HF risk phenotypes and prevalent HF, and weighted Cox proportional hazards models evaluated relationships between HF risk phenotypes and cardiovascular mortality. Two sequentially adjusted multiple regression models alongside a crude model were constructed for all phenotype-level regression analyses: the crude model incorporated no covariates; model 1 adjusted for age, sex, race/ethnicity, educational duration, and marital status; model 2 additionally adjusted for drinking status, smoking status, and leisure-time physical activity on the basis of model 1.

To further assess mutually adjusted associations between each core clinical indicator and prevalent HF, weighted multiple logistic regression was performed with prevalent HF as the dependent variable, simultaneously incorporating raw continuous values of eGFR, AST/ALT ratio, GGT, HbA1c, WC, DBP, PLT, HDL-C, CRP, NLR, and MLR. All variable-level regression analyses used untransformed continuous measurements of each marker, with results expressed as odds ratios (ORs) and 95% CIs. Each OR reflects the relative change in the odds of prevalent HF per 1-unit increment in the corresponding indicator while holding all other markers constant in the model.

Weighted multiple Cox proportional hazards regression was conducted to evaluate mutually adjusted associations between each core clinical marker and cardiovascular mortality. The PERMTH_INT variable (person-months of follow-up from the NHANES interview date) from NCHS linked mortality data, was designated as the follow-up time variable, and cardiovascular death served as the outcome event. Raw continuous values of the 11 aforementioned clinical indicators were entered simultaneously into the Cox models, with results reported as hazard ratios (HRs) and 95% CIs. Each HR represents the relative change in the instantaneous risk of cardiovascular death per 1-unit increase in the respective marker, independent of all other covariates included in the model. Cox regression analyses exclusively adopted cardiovascular death as the endpoint because NHANES linked mortality files lack time-to-event data for incident HF.

All statistical analyses were performed using R software version 4.5.0. Two-tailed statistical tests were applied throughout, and $P < .05$ was defined as the threshold for statistical significance.

RESULTS

Phenotypic Characteristics and Gradients of the 2-Dimensional Tree Structure

Based on 11 clinical indicators, including eGFR, AST/ALT, GGT, HbA1c, WC, DBP, PLT, HDL-C, CRP, NLR, MLR, etc., the DDRTree algorithm is used to map the high-dimensional clinical data of 24 205 participants in the NHANES study to a 2-dimensional space and constructed a 2-dimensional tree-like evolutionary structure of HF risk. As shown in Figure 2, the data of these 11 HF-related indicators were overlaid in the tree diagram, visually presenting the phenotypic variation characteristics of HF risk: the high values (yellow) of the indicators were mainly distributed in the distal branches of the tree structure, while the middle values (blue) were concentrated in the proximal region. This distribution pattern presented a phenotype gradient that spread outward from the center of the tree, simulating the pseudo-time trajectory of individuals evolving from physiological ground states to different pathophysiological states.

Linear regression analysis clarified the pathophysiological connotations of the 2 core dimensions of DDRTree and revealed the different driving directions of HF risk evolution (Figure 3 A). Dim1 (metabolism liver kidney axis): AST/ALT, GGT, and HbA1c had the highest contribution to this

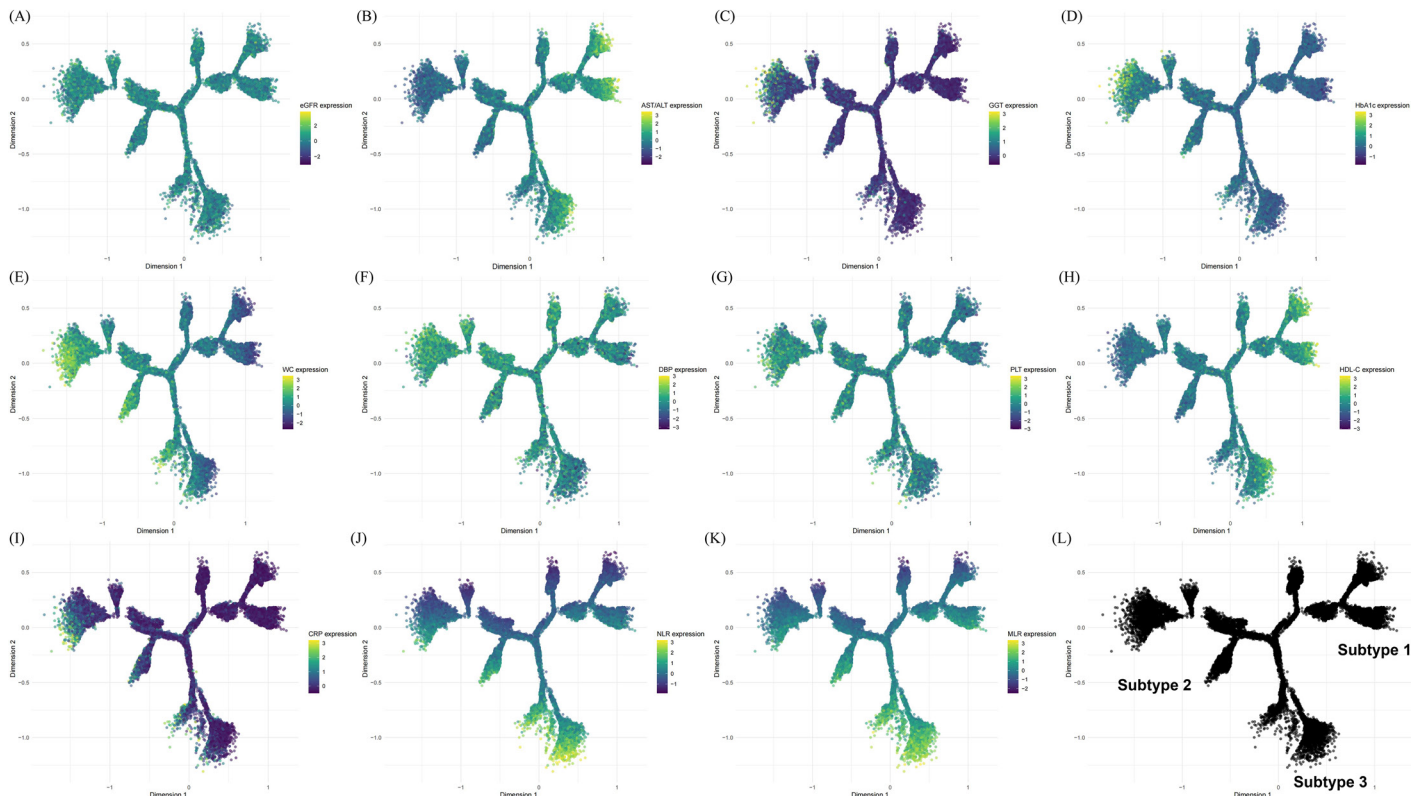


Figure 2. A visual representation of the phenotypic characteristics. DDRTree was used to reduce the 11 clinical variables residualized for age and sex into a non-linear tree structure. The values of clinical variables are overlaid on the tree structure to visualize the distribution of each variable over the reduced tree structure. Each point in the figure represents 1 individual. AST/ALT, glutamic oxaloacetic transaminase/glutamic pyruvic transaminase; CRP, C-reactive protein; DBP, diastolic blood pressure; DDRTree, Discriminative Dimensionality Reduction Tree; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyltransferase; HbA1c, glycosylated hemoglobin type A1C; HDL-C, high-density lipoprotein cholesterol; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLT, platelet count; WC, waist circumference.

dimension. This indicates that Dim1 mainly characterizes the risk evolution pathway driven by glucose metabolism disorders and impaired liver and kidney function. Dim2 (systemic inflammatory axis): Inflammation-related indicators such as CRP, NLR, and MLR exhibit stronger explanatory power. This reflects that Dim2 mainly represents the risk evolution pathway driven by systemic inflammation and immune activation. In addition, the spatial autocorrelation analysis (Moran's I) results showed that all core indicators exhibited significant non-random clustering patterns in the DDRTree space (all $P < .001$), with liver and kidney function indicators and inflammation indicators showing the most prominent clustering (Figure 3 B). This validates the robustness of the DDRTree structure in characterizing HF risk heterogeneity, demonstrating that the structure can effectively identify risk evolution directions with different biological characteristics.

Heterogeneity of Heart Failure–Related Outcomes

Visual analysis via Risk Landscape construction was performed to uncover the associations between the 2 latent dimensions and prevalent HF. As illustrated in Figure 4 A, the prevalence probability of HF was unevenly distributed across the tree structure, exhibiting distinct topological heterogeneity. The prevalence probability rose continuously as individuals moved from the proximal segments (baseline

physiological state) toward the distal branches of the tree. Notably, the lower branch aligned with Dim2 (systemic inflammation axis) contained the densest concentration of high-risk samples (yellow region), visually demonstrating a continuous gradient of HF prevalence probability within the DDRTree space. Quantitative analyses (Figure 4 B) further validated the statistical significance of these relationships. Weighted regression models revealed that both Dim1 and Dim2 were significantly associated with prevalent HF. The effect size of Dim2 was substantially larger than that of Dim1, suggesting that the systemic inflammation-related dimension may exert a stronger association with prevalent HF than the metabolism–hepatorenal dimension.

Overview of Clinical Characteristics of Heart Failure Phenotypes

Next, different HF risk phenotypes were defined through DDRTree clustering analysis and used visualization analyses to reveal the distribution of their clinical characteristics. As shown in Figure 5, the clustering analysis classified HF samples into normal, metabolic HF, and inflammatory HF risk phenotypes. Each phenotype exhibited distinct patterns across the 11 core clinical variables: the normal phenotype showed overall low or near-average levels of indicators; the metabolic HF risk phenotype was primarily characterized

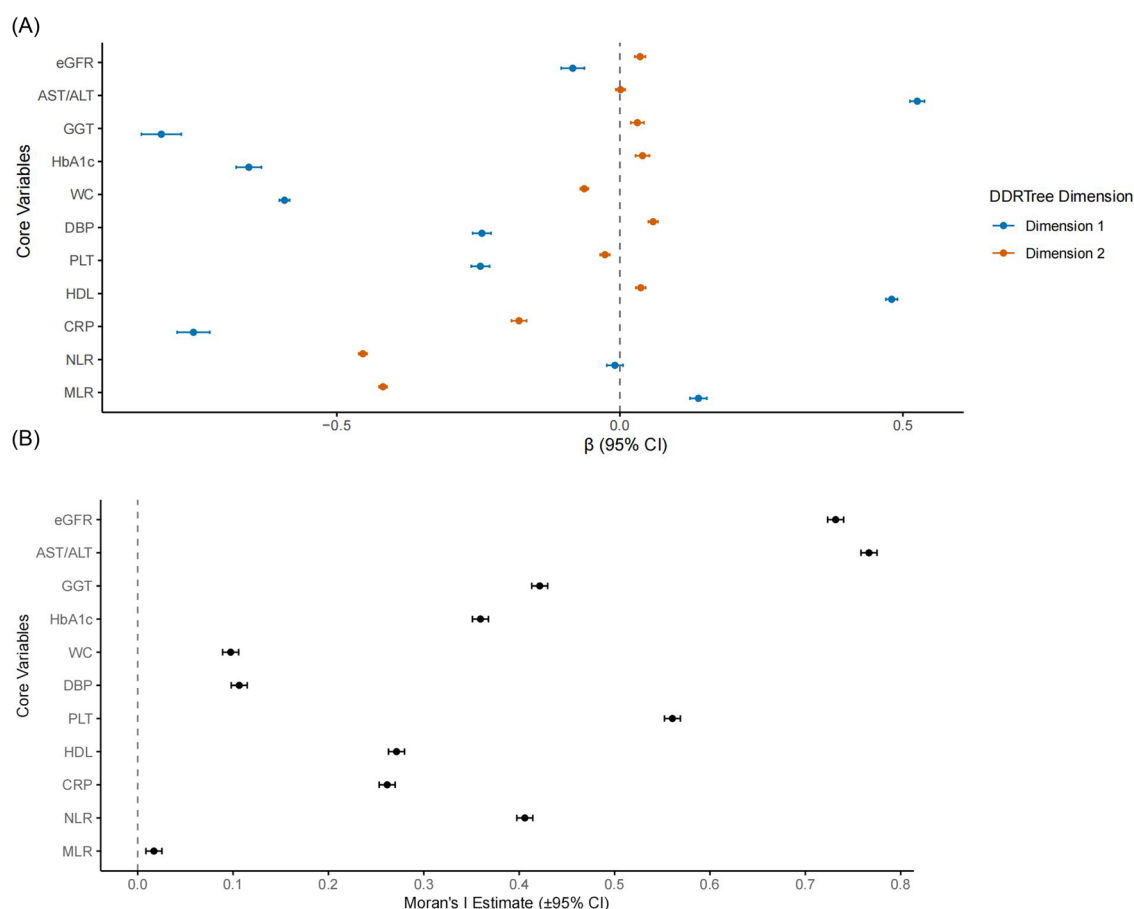


Figure 3. Associations between DDRTree dimensions and core clinical variables. (A) Linear regression estimates (95% CI) showing the relationship between each of the 11 clinical variables and the DDRTree dimensions. (B) Spatial autocorrelation analysis of the 11 variables, illustrating their clustering patterns in the DDRTree space. The x-axis represents Moran's I statistic, with higher values representing variables that are more strongly autocorrelated; all values were at $P < .001$. DDRTree, Discriminative Dimensionality Reduction Tree.

by elevated glucose metabolism-related indicators; and the inflammatory HF risk phenotype was marked by significantly elevated inflammatory indicators (e.g., CRP, NLR) and reduced liver and kidney function, suggesting clear differences in metabolic and inflammatory characteristics among the phenotypes.

Comparison of Baseline Characteristics of Heart Failure Phenotypes

To further explore the differences among HF risk phenotypes, the baseline characteristics of each phenotype population were compared. As shown in Table 1, the normal phenotype, metabolic HF phenotype, and inflammatory HF phenotype groups included 8996, 10029, and 5180 subjects, respectively. Compared with participants in the normal phenotype group, subjects in the metabolic and inflammatory phenotype groups were older and had higher proportions of males, married/cohabiting individuals, and those with a PIR ranging from 1.3 to 3.5. Meanwhile, these 2 groups showed lower proportions of non-Hispanic Black participants, individuals with less than 12 years of education, and those engaging in physical activity ≥ 600 MET-min/week. Furthermore, the inflammatory phenotype group had a larger share of subjects aged

≥ 60 years and non-Hispanic White individuals but a smaller proportion of current smokers relative to the other 2 groups. All intergroup differences described above reached statistical significance (all $P < .001$).

Association of Heart Failure Phenotypes with Prevalence of Congestive Heart Failure

Subsequently, the associations between each risk phenotype and prevalent HF were further explored. As presented in Table 2, in fully adjusted model 2, participants with the metabolic phenotype exhibited approximately doubled odds of prevalent HF relative to those with the normal phenotype (fully adjusted OR=1.96, $P < .001$, 95% CI: 1.47–2.62). Individuals with the inflammatory phenotype showed 3.95-fold higher odds of prevalent HF compared with the normal phenotype (OR=3.95, $P < .001$, 95% CI: 2.94–5.33), indicating substantial disparities in HF risk across distinct phenotypes. In weighted multiple logistic regression models at the individual marker level, elevated AST/ALT ratio, GGT, HbA1c, WC, CRP, NLR, and MLR were associated with greater odds of prevalent HF, whereas higher eGFR, DBP, PLT, and HDL-C correlated with reduced odds of prevalent HF (Supplementary Table 1).

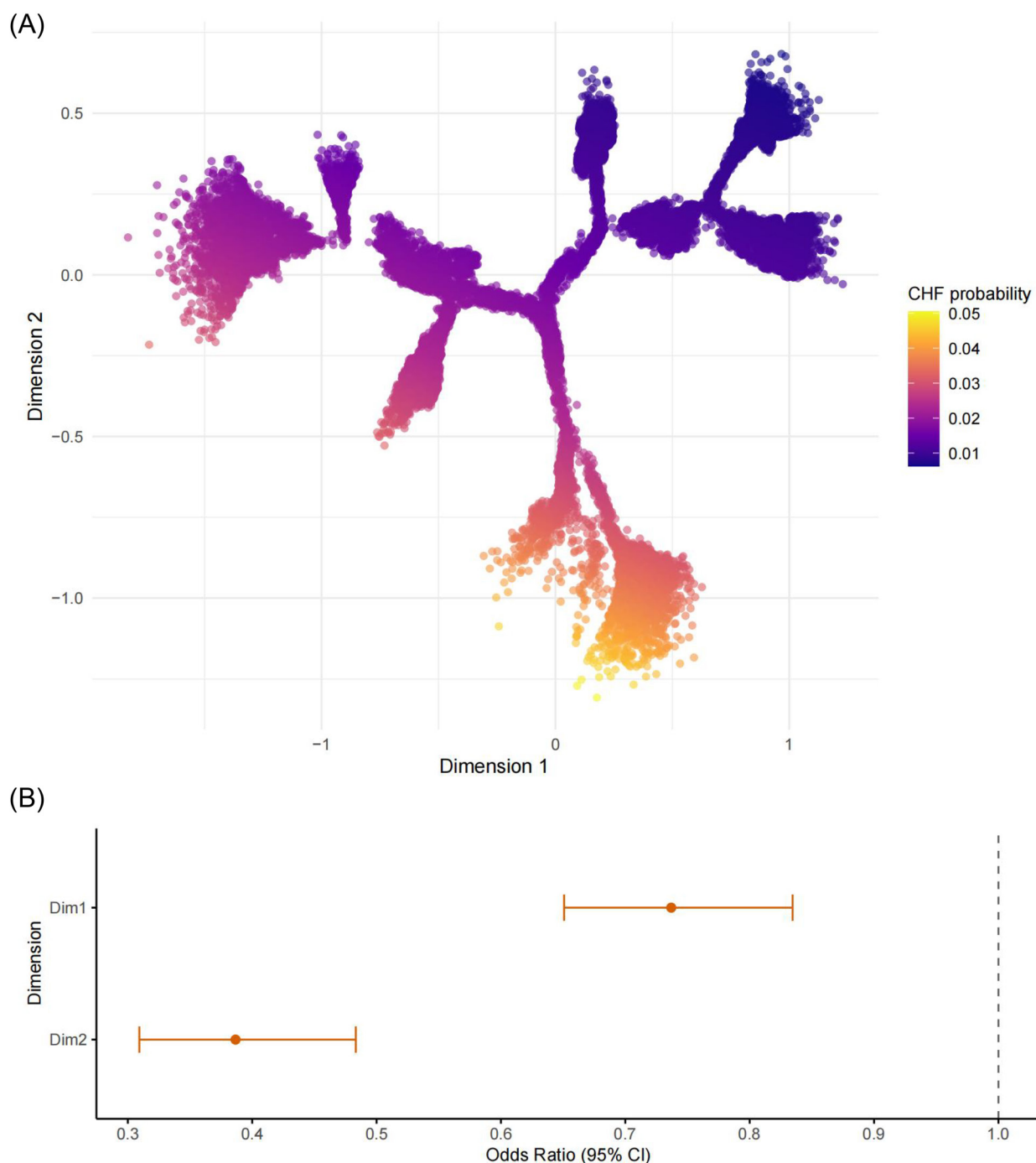


Figure 4. Heterogeneity of HF prevalence across the DDRTree space. (A) Predicted probability of HF prevalence; probabilities were generated from logistic regression models constructed with DDRTree dimensions. (B) Odds ratios and 95% CIs for the associations of Dim1 and Dim2 with HF prevalence, estimated using weighted logistic regression models. DDRTree, Discriminative Dimensionality Reduction Tree; Dim 1, dimension 1; Dim 2, dimension 2; HF, heart failure.

Association of Heart Failure Phenotypes with Cardiovascular Mortality

In addition, the relationship between HF phenotypes and cardiovascular mortality were further analyzed. As summarized in Table 3, after full adjustment for confounders in model 2, the metabolic HF phenotype demonstrated no significant difference in the risk of cardiovascular death relative to the normal phenotype (HR = 0.92, $P = .539$, 95% CI:

0.70-1.20). In contrast, participants with the inflammatory HF phenotype exhibited an approximately 47% higher risk of cardiovascular death compared with those with the normal phenotype (HR = 1.47, $P = .002$, 95% CI: 1.16-1.87). In weighted multiple Cox regression models at the individual marker level, elevated AST/ALT ratio, HbA1c, and MLR were associated with increased cardiovascular mortality risk, whereas higher eGFR, DBP, and PLT were linked to reduced cardiovascular

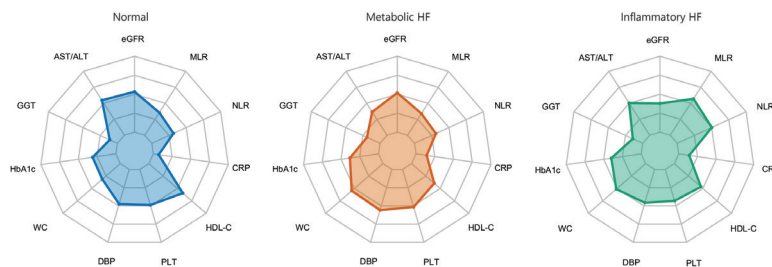


Figure 5. Clinical feature profiles of heart failure (HF) phenotypes. Radar plots depicting the distribution of 11 core clinical variables across the 3 DDRTree-defined HF phenotypes: normal, metabolic HF, and inflammatory HF. Each plot shows the relative magnitude of each variable, highlighting distinct metabolic and inflammatory patterns among the phenotypes. DDRTree, Discriminative Dimensionality Reduction Tree.

mortality risk. No statistically significant associations with cardiovascular mortality were observed for GGT, WC, HDL-C, CRP, and NLR (Supplementary Table 2).

DISCUSSION

This study utilized the NHANES database, integrated 11 routine clinical biomarkers, and applied the DDRTree algorithm to construct a low-dimensional phenotypic framework associated with HF, thereby identifying 3 HF risk phenotypes: normal, metabolic, and inflammatory. The key findings are summarized as follows. First, significant heterogeneity existed across phenotypes in clinical profiles, prevalent HF status, and cardiovascular mortality risk. Compared with the normal phenotype, both the metabolic and inflammatory phenotypes were linked to elevated odds of prevalent HF, while the inflammatory phenotype additionally conferred higher cardiovascular mortality risk. Second, the 2 primary dimensions extracted by DDRTree captured features related to metabolism and hepatorenal function as well as systemic inflammation, indicating that clinical heterogeneity in HF may arise from distinct multisystem pathophysiological processes. Third, multiple regression analyses at the biomarker level revealed divergent association patterns of hepatic and renal function, glycometabolism, adiposity, inflammatory, and hematological markers with prevalent HF and cardiovascular death. Collectively, this study uncovered heterogeneity in HF risk phenotypes through the integration of multi-dimensional clinical characteristics, providing novel evidence for HF risk stratification and identification of high-risk individuals in the general population.

International clinical consensus indicates that LVEF, as an assessment metric for HF patient risk and health status, has certain limitations. Particularly, when LVEF values exceed 45%, its prognostic and diagnostic value declines and it shows no clear correlation with the severity of cardiac dysfunction or clinical outcomes associated with higher values.¹⁸ To address the limitations of conventional single biomarkers in reflecting clinical heterogeneity of HF, the present study adopted the DDRTree algorithm to establish a 2-dimensional phenotypic space using 11 continuous clinical variables, and identified 2 variation axes with distinct pathophysiological signatures. Dimension 1 primarily represented markers of hepatorenal function (GGT, eGFR, AST/ALT ratio) and glycometabolic traits (HbA1c, WC), whereas Dimension 2 mainly

captured innate immune activity and systemic inflammatory status (CRP, NLR, MLR). This structure is highly consistent with the current understanding of the multisystem involvement in HF.^{19,20} Specifically, GGT, as a marker of oxidative stress, is elevated in association with endothelial dysfunction and adverse outcomes.²¹ Decreased eGFR reflects early activation of the cardiorenal interaction, which may exacerbate cardiac remodeling through sodium and water retention and pro-fibrotic mechanisms.²² An elevated AST/ALT ratio indicates more severe systemic congestion, myocardial injury, and oxidative stress in HF patients, thereby increasing mortality risk.²³ A previous study also reported that variability in HbA1c is associated with rehospitalization and mortality risk in HF patients.²⁴ Waist circumference is independently and positively associated with HF risk in the elderly population.²⁵ In addition, inflammatory indicators such as CRP and NLR have been widely confirmed to be closely associated with the occurrence and progression of HF.²⁶ Taken together, the multi-dimensional phenotypic framework established in this study suggests that HF-related risk may involve the combined contribution of several core physiological processes, including metabolic disorders, hepatorenal dysfunction, and systemic inflammation.

The metabolic HF phenotype was primarily characterized clinically by increased HbA1c and WC. Hemoglobin type A1c, as a key indicator reflecting medium- to long-term glycemic control, is increased to indicate glucose metabolism disorder.²⁷ Meanwhile, increased WC, as a surrogate marker for central obesity, is significantly associated with visceral fat, collectively indicating an obesity-related metabolic abnormality.^{28,29} Both factors are independent risk factors for HF, and when coexisting, they exhibit a synergistic effect on risk enhancement.³⁰ Mechanistically, hyperglycemia can impair cardiomyocyte function through multiple pathways, including induction of myocardial metabolic remodeling, promotion of advanced glycation end-product accumulation, and exacerbation of oxidative stress.^{31,32} By inhibiting fatty acid oxidation, promoting toxic lipid accumulation, impairing mitochondrial function, and disrupting metabolic regulatory factors, dysregulated lipid metabolism may drive abnormalities in myocardial structure and function, thereby elevating HF-related risk.³³ Regression results at the biomarker level also demonstrated that both HbA1c and WC were positively associated with prevalent HF, further supporting the critical

Table 1. Baseline Characteristics of the General Adult Population Across DDRTree-Defined Heart Failure Risk Phenotypes (NHANES 1999-2018)

	Overall n=24 205	Normal Phenotype n=8996 (38.6%)	Metabolic Phenotype n=10 029 (41.3%)	Inflammatory Phenotype n=5180 (20.1%)	P
Age	46.71 (16.62)	42.43 (16.43)	44.73 (13.68)	58.97 (16.65)	<.001
Age group					<.001
20-44 years (%)	10 522 (47.3)	5012 (58.4)	4642 (50.0)	868 (20.9)	
45-59 years (%)	5737 (28.6)	1819 (24.5)	3052 (34.5)	866 (24.3)	
60+ years (%)	7946 (24.1)	2165 (17.1)	2335 (15.5)	3446 (54.8)	
Sex (male) (%)	11 875 (49.0)	2922 (31.2)	5906 (61.6)	3047 (57.0)	<.001
Race/ethnicity					<.001
Mexican American (%)	4393 (8.4)	1406 (7.2)	2335 (11.6)	652 (4.4)	
Non-Hispanic Black (%)	4560 (9.9)	1991 (11.9)	1953 (10.3)	616 (5.3)	
Non-Hispanic White (%)	10 998 (69.4)	3806 (66.9)	3902 (65.1)	3290 (83.0)	
Other Hispanic (%)	2119 (5.1)	770 (5.1)	1013 (6.0)	336 (2.9)	
Other/multiracial	2135 (7.2)	1023 (9.0)	826 (7.0)	286 (4.4)	
Education duration (<12 years) (%)	18 041 (84.4)	6993 (86.1)	7257 (83.1)	3791 (83.9)	<.001
Marital status (%)	13 006 (57.1)	4302 (52.0)	5728 (60.1)	2976 (61.0)	<.001
PIR					<.001
<1.3 (%)	6388 (18.9)	2373 (19.1)	2760 (20.1)	1255 (15.8)	
1.3-3.5 (%)	8764 (36.5)	3158 (35.7)	3591 (36.0)	2015 (39.3)	
≥3.5 (%)	7073 (44.6)	2741 (45.3)	2830 (43.9)	1502 (44.9)	
Current drinking (%)	13 627 (58.9)	5039 (59.9)	5674 (58.5)	2914 (57.7)	.294
Current smoking (%)	5035 (21.1)	1953 (21.9)	2290 (23.0)	792 (15.7)	<.001
Physical activity (>600 METs/week) (%)	10 315 (45.6)	4052 (48.1)	4387 (45.3)	1876 (41.3)	<.001
Core clinical variables used to define HF risk phenotypes					
eGFR	87.80 (21.30)	92.36 (20.75)	90.89 (19.44)	72.70 (19.13)	<.001
AST/ALT	1.09 (0.30)	1.26 (0.27)	0.90 (0.22)	1.15 (0.28)	<.001
GGT	25.20 (19.66)	18.57 (13.78)	31.81 (22.68)	24.37 (18.08)	<.001
HbA1c	5.50 (0.59)	5.29 (0.41)	5.59 (0.63)	5.69 (0.69)	<.001
Waist circumference	98.31 (15.50)	85.81 (9.74)	107.35 (12.84)	103.76 (13.28)	<.001
DBP	70.98 (11.07)	68.34 (10.22)	75.00 (10.43)	67.80 (11.36)	<.001
PLT	253.46 (60.62)	252.88 (57.78)	264.44 (61.65)	232.04 (57.92)	<.001
HDL-C	1.38 (0.39)	1.65 (0.37)	1.15 (0.26)	1.33 (0.33)	<.001
CRP	3.16 (4.00)	1.92 (2.82)	3.93 (4.32)	3.93 (4.62)	<.001
NLR	2.09 (0.86)	1.87 (0.70)	1.88 (0.65)	2.95 (0.96)	<.001
MLR	0.27 (0.10)	0.25 (0.08)	0.24 (0.07)	0.38 (0.10)	<.001

AST/ALT, aspartate aminotransferase/alanine aminotransferase ratio; CRP, C-reactive protein; DBP, diastolic blood pressure; DDRTree, Discriminative Dimensionality Reduction Tree; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyltransferase; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; MET, metabolic equivalent of task; MLR, monocyte-to-lymphocyte ratio; NHANES, National Health and Nutrition Examination Survey; NLR, neutrophil-to-lymphocyte ratio; PIR, poverty income ratio; PLT, platelet count; WC, waist circumference.

roles of impaired glycometabolism and central obesity within the metabolic risk phenotype. However, their associations with cardiovascular mortality were not entirely concordant, implying differential effects of these 2 markers on HF prevalence versus long-term clinical outcomes.

Notably, although the metabolic phenotype was significantly associated with higher odds of prevalent HF, its association with cardiovascular mortality failed to reach statistical significance in the fully adjusted model. One

plausible explanation is that the adverse effects of metabolic disturbances on HF risk are predominantly mediated through long-term metabolic burden and myocardial remodeling, while the relationship between metabolic abnormalities and cardiovascular death may be confounded by multiple factors including disease severity, comorbidities, and therapeutic interventions.^{34,35} In contrast, the systemic inflammatory state characteristic of the inflammatory phenotype impairs cardiovascular outcomes by exacerbating myocardial injury, destabilizing atherosclerotic plaques, and

Table 2. Association Between Heart Failure (HF) Phenotypes and Congestive HF Prevalence

HF Phenotype	Cases/Participants	Crude Model		Model 1		Model 2	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Normal HF	81/8.996	Reference		Reference		Reference	
Metabolic HF	164/10.029	2.05 (1.56-2.70)	<.001	1.98 (1.48-2.65)	<.001	1.96 (1.47-2.62)	<.001
Inflammatory HF	376/5.180	10.16 (7.80-13.24)	<.001	3.96 (2.94-5.33)	<.001	3.95 (2.94-5.33)	<.001

Crude model: not adjusted for covariates. Model 1: adjusted for age (year), sex, race/ethnicity, educational level, and marital status. Model 2: model 1 further adjusted for drinking status, smoking status, and leisure-time physical activity. OR, odds ratio.

increasing susceptibility to malignant arrhythmias, which may partially account for its robust link with elevated cardiovascular mortality risk.³⁶ Accordingly, the metabolic phenotype may identify high-risk individuals suitable for metabolic interventions, and clinical management for this population should prioritize comprehensive control of glycemia, adiposity, and related metabolic risk factors. Marked age disparities were also observed across phenotypes: mean age increased sequentially from the normal phenotype (42.43 years) to the metabolic phenotype (44.73 years), and further to the inflammatory phenotype (58.97 years). This age gradient aligns partially with the continuous phenotypic trajectory visualized by DDRTree, suggesting progressive accumulation of metabolic derangements, chronic inflammation, and multi-organ dysfunction with advancing age. Importantly, given that risk phenotypes were defined based on cross-sectional baseline data, this age gradient cannot serve as direct evidence that individuals sequentially progress from the normal to metabolic and then inflammatory phenotype. Combined with mortality follow-up findings, the association between the inflammatory phenotype and elevated cardiovascular mortality indicates that this phenotype may reflect a heavier burden of systemic inflammation and concurrent multi-organ impairment. Whether it represents a late stage in the natural history of HF remains to be validated in longitudinal cohorts with repeated biomarker measurements and incident HF endpoints.

The identification of the distinct inflammatory phenotype underscores the pivotal role of inflammation in the onset and progression of HF.⁷ Elevated CRP levels may indicate a systemic inflammatory response, which can damage cardiomyocytes and impair cardiac function.³⁷ Increased NLR and MLR reflect a relative increase in neutrophils and monocytes and a relative decrease in lymphocytes in peripheral blood, which is associated with immune system activation and exacerbation of the inflammatory response.²⁰ Moreover, this study observed concurrent abnormalities in inflammation-related

biomarkers and hepatic and renal function markers within the inflammatory phenotype group, implying that systemic inflammation may interact with multi-organ functional alterations. Specifically, chronic inflammation damages the cardiovascular system by directly promoting myocardial fibrosis, endothelial dysfunction, and plaque instability. The resulting cardiac insufficiency and hypoperfusion can further induce multi-organ dysfunction, including in the kidneys and liver.³⁸⁻⁴⁰ Additionally, renal impairment can activate the renin-angiotensin-aldosterone system and release pro-inflammatory mediators, thereby exacerbating systemic inflammation and increasing cardiac afterload.⁴¹ Hepatic dysfunction reduces the clearance of inflammatory factors, leading to their accumulation and further amplifying inflammatory damage.⁴² Overall, the identification of the inflammatory phenotype provides a more comprehensive perspective on the role of inflammation in HF, emphasizing the combined effects of inflammation and liver–kidney dysfunction in the occurrence and progression of HF. Marker-level analyses further demonstrated that MLR was positively associated with both prevalent HF and cardiovascular mortality risk, whereas CRP and NLR were primarily correlated with prevalent HF alone. These findings supplement the clinical characteristics of the inflammatory risk phenotype at the individual biomarker level, yet the associations of distinct inflammatory markers with clinical outcomes were not entirely consistent.

Limitation

Although this study made significant progress in elucidating HF risk phenotypes, several limitations remain. First, the identification of prevalent HF status and risk phenotypes in this study relied entirely on cross-sectional baseline data. Accordingly, the temporal sequence between clinical markers, risk phenotypes, and prevalent HF could not be established, precluding any causal inferences. Although linked mortality data provided longitudinal follow-up information for cardiovascular death, time-to-event records for incident HF and dynamic

Table 3. Association Between Heart Failure (HF) Phenotypes and Cardiovascular Mortality

HF Phenotype	Cases/Participants	Crude Model		Model 1		Model 2	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Normal HF	189/8.973	Reference		Reference		Reference	
Metabolic HF	164/10.016	0.84 (0.64-1.09)	.190	0.94 (0.72-1.24)	.681	0.92 (0.70-1.20)	.539
Inflammatory HF	472/5.172	5.63 (4.56-6.94)	<.001	1.55 (1.22-1.96)	<.001	1.47 (1.16-1.87)	.002

Crude model: not adjusted for covariates. Model 1: adjusted for age (year), sex, race/ethnicity, educational level, and marital status. Model 2: model 1 further adjusted for drinking status, smoking status, and leisure-time physical activity. HR, hazard ratio.

phenotype transitions were unavailable. Consequently, the pseudo-trajectories generated by DDRTree do not correspond to genuine individual-level disease progression, and Cox regression analyses were only applied to quantify associations between risk phenotypes, core clinical indicators, and cardiovascular mortality. Second, HF diagnosis was based on self-report, which, although widely used in large surveys such as NHANES, may still be subject to misclassification bias. At the level of variable inclusion, this study faces certain trade-offs. Due to the sampling differences of the NHANES database in different periods, this study excluded variables with missing ratios exceeding 40% based on preset criteria, resulting in the failure of HOMA-IR and some precise lipid metabolism indicators reflecting insulin resistance to enter the model. Although retained variables such as HbA1c and HDL-C provide core characterization of metabolic status, the absence of key metabolic variables may, to some extent, affect the depth and completeness of characterizing the “metabolic HF phenotype.” In addition, due to the lack of ejection fraction (EF) and HF-specific biomarkers (such as B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) data, this study was unable to further evaluate the correspondence between identified risk phenotypes and clinical classic HF subtypes. Finally, the generalization ability of the conclusions of this study still needs further validation. The research sample mainly comes from the American population, and the extrapolation of its conclusions to other ethnic and regional populations needs to be confirmed. Future research should delve into the robustness of these phenotypes in independent cohorts with similar variable structures and comprehensively consider other complex pathophysiological mechanisms, such as neuroendocrine regulation and gene polymorphism, in order to achieve a more comprehensive understanding of long-term shifts in HF-related risk phenotypes and their dynamic relationships with clinical outcomes.

CONCLUSION

Based on the NHANES database, the study applied the DDRTree method to construct a 2-dimensional tree model and identified 3 HF risk phenotypes: normal, metabolic, and inflammatory. Metabolic HF was positively associated with HF prevalence risk but showed no significant association with cardiovascular mortality risk; inflammatory HF was closely associated with both HF prevalence and cardiovascular mortality risk. These findings identify distinct phenotypic signatures corresponding to metabolic derangements, systemic inflammation, and organ dysfunction among populations at risk for HF. The new risk stratification model identified in this study not only deepens the understanding of the heterogeneity of HF occurrence and development but also provides a scientific basis for early and accurate risk identification and targeted prevention strategies for the general population.

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Supplementary Table 1. Multiple logistic regression analysis of clinical clinical variables associated with prevalent heart failure

Variables	OR (95% CI)	P
eGFR	0.967 (0.961-0.972)	<0.001
AST/ALT	2.458 (2.053-2.941)	<0.001
GGT	1.002 (1.001-1.003)	<0.001
HbA1c	1.318 (1.233-1.409)	<0.001
WC	1.032 (1.025-1.038)	<0.001
DBP	0.990 (0.984-0.995)	<0.001
PLT	0.996 (0.994-0.997)	<0.001
HDL-C	0.616 (0.471-0.806)	<0.001
CRP	1.009 (1.002-1.017)	0.012
NLR	1.097 (1.027-1.172)	0.006
MLR	3.693 (1.936-7.043)	<0.001

HF was used as the dependent variable in the weighted multiple logistic regression model. The 11 clinical prognostic variables, including eGFR, AST/ALT, GGT, HbA1c, WC, DBP, PLT, HDL-C, CRP, NLR, and MLR, were entered simultaneously as independent variables. ORs and 95% CIs are presented per one-unit increase in each variable unless otherwise specified. Abbreviations: HF, heart failure; OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; AST/ALT, aspartate aminotransferase-to-alanine aminotransferase ratio; GGT, gamma-glutamyl transferase; HbA1c, glycated hemoglobin; WC, waist circumference; DBP, diastolic blood pressure; PLT, platelet count; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio.

Supplementary Table 2. Multiple Cox regression analysis of clinical prognostic variables associated with cardiovascular mortality

Variables	HR (95% CI)	P
eGFR	0.994 (0.989-0.998)	0.006
AST/ALT	1.671 (1.325-2.106)	<0.001
GGT	1.000 (0.999-1.001)	0.599
HbA1c	1.125 (1.046-1.210)	0.002
WC	1.006 (1.000-1.011)	0.051
DBP	0.995 (0.991-1.000)	0.030
PLT	0.999 (0.997-1.000)	0.033
HDL-C	0.851 (0.715-1.013)	0.070
CRP	1.006 (0.999-1.012)	0.072
NLR	1.044 (0.981-1.110)	0.175
MLR	2.194 (1.456-3.306)	<0.001

Follow-up time was defined using PERMTH_INT and was measured in months. Cardiovascular death was coded as the event (1), and censoring was coded as 0. The 11 clinical variables, including eGFR, AST/ALT, GGT, HbA1c, WC, DBP, PLT, HDL-C, CRP, NLR, and MLR, were entered simultaneously into a weighted multiple Cox proportional hazards model. HRs and 95% CIs are presented per one-unit increase in each variable unless otherwise specified. Because the NHANES linked mortality data provide mortality follow-up but do not include time-to-event information for incident HF, this model evaluated cardiovascular mortality rather than incident HF. Abbreviations: HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; AST/ALT, aspartate aminotransferase-to-alanine aminotransferase ratio; GGT, gamma-glutamyl transferase; HbA1c, glycated hemoglobin; WC, waist circumference; DBP, diastolic blood pressure; PLT, platelet count; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio.