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IMPACT OF EARLY DETECTION AND MANAGEMENT STRATEGIES ON OUTCOMES OF HEART FAILURE WITH PRESERVED EJECTION FRACTION

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Abstract

Heart failure with preserved ejection fraction represents nearly half of all heart failure cases and is associated with high morbidity and mortality despite preserved systolic function. Its heterogeneous pathophysiology and lack of effective therapies necessitate integrative investigative approaches.A prospective mixed-methods experimental design was employed, integrating quantitative hemodynamic assessment, advanced echocardiography, biomarker profiling, cardiopulmonary exercise testing, and qualitative clinical phenotyping. Multivariate regression modeling and unsupervised clustering were applied to identify mechanistic drivers and phenotype-specific risk profiles.The results demonstrated marked heterogeneity in diastolic function, myocardial stiffness, microvascular integrity, inflammatory burden, and ventricular–vascular coupling across HFpEF phenotypes. Nonlinear relaxation dynamics and elevated filling pressures were observed despite preserved ejection fraction. Cardiopulmonary exercise testing revealed significant impairment in peripheral oxygen utilization, while biomarker analysis confirmed heightened systemic inflammation. Integrated multivariate models significantly outperformed isolated parameters in predicting adverse outcomes, and phenotype clustering identified distinct subgroups with divergent prognostic trajectories driven by metabolic, inflammatory, and vascular mechanisms. HFpEF is a systemic, multiorgan syndrome characterized by complex nonlinear interactions that are not adequately captured by conventional diagnostic or therapeutic strategies. Precision-based, phenotype-specific approaches informed by integrated physiological and biochemical profiling are essential to improve clinical outcomes.

Keywords: Heart Failure with Preserved Ejection Fraction, Diastolic Dysfunction, Systemic Inflammation, Phenotype Stratification, Ventricular–Vascular Coupling, Precision Cardiology.

JOURNAL OF BIOLOGICAL
AND MEDICAL INNOVATIONS

INTRODUCTION

Connected with normal ejection fraction, myocardial infarction is one of the core and recent health care spheres in the hearts care. It is a complicated etiologic organism whose variant of clinical manifestation is complex (Epelde, 2025). Despite the trend, HFpEF is hard to diagnose as it is associated with an insurmountable number of various things, risk factors, clinical manifestations, symptoms, biomarkers, and the result of the imaging test (Haehling et al., 2024). The lack of diagnostic gold standard predetermines the holistic approach and in most of the cases, it is complicated by the presence of comorbidities of which obscures the underlying disease mechanisms (Alyassi et al., 2024; Mancusi et al., 2024). Besides, the etiology of HFpEF is rather diverse, which, together with the lack of the appropriate efficacy of the current types of treatment, testifies to the need to develop a more complex diagnostic criterion and more individual approaches to the treatment process (Altay and Pehlivanoglu, 2017; Laksono and Franata, 2023). In comparison to other aggressive malignancy, the HFpEF patients possess very low prognosis and very low survival rates. It proves that the state is rather serious, and the current strategy of treatment is not effective (Alyassi et al., 2024). This is worsened by the fact that HFpEF is nearly an endemic disease amongst all the patients of heart failure especially after they have attained the age of 65 years. It brings about high rates of infections and mortality everywhere in the world (Alyassi et al., 2024). In fact, the rehospitalization of the HFpEF patients is extremely high and is continuously equalized to rehospitalization of the heart failure with reduced ejection factor that is an even greater burden on the healthcare systems (Kim and Park, 2020). This is why HFpEF is gaining popularity at an impressive rate in the globe as a result of ageing population and a high rate of individuals who are becoming obese, diabetic or high-blooded. It renders the life of people arduous and miserable (Omote et al., 2021). The health of the patients has numerous symptoms, low quality of life, and frequent hospitalization in correlation with the best medical care. As it happens, it must find new ways of their treatment and become more accustomed to the causes of their problems (Alyassi et al., 2024). It also makes the increased public health crisis even worse considering that there is no generally accepted rule of diagnosis and treatment of this health crisis. It raises the

changes in the description of patients, and the absence of the long-term studies that could sufficiently track the progression of the way the disease is becoming more and more harmful and how effective the treatment process is performed (Rashid, 2024). The HFpEF, its part, is a diagnosis of approximately a half of all heart failure cases, and the cases are increasing among all the age groups of population. Five years after death, the mortality rate and the hospitalization rate would be 50% and 80 percent respectively (Abdin et al., 2024; Parra-Lucares et al., 2022). These de-motivating statistics imply that it is necessary to design more appropriate ways of early diagnosis and more efficient ways of treatment to enhance the prognosis and quality of life of the patients of HFpEF (Priya et al., 2023; Shah, 2017). The pathophysiology of HFpEF is complicated as well because it involves the failure of the left ventricles to relax, the rise in myocardial stiffness, and impaired blood vessel microcirculation, which complicates the creation of effective interventions (Gevaert et al., 2019). Complex etiology, which in general presupposes systemic inflammation and endothelium dysfunction, requires the enhancement of interdependence between cardiac and extracardiac problems in relation to each other (Shim, 2020). The heterogeneity of population of patients also complicates it, as it may have many comorbidities, such as high blood pressure, diabetes, and obesity, making it more difficult to diagnose them with these conditions and treat them effectively (Alvino et al., 2024; Alyassi et al., 2024; Gladysheva and Sullivan, 2022). The fact that HFpEF increase will become apparent in the near future, combined with the aging population of the world, and the growing proportion of comorbidities among people, means that there will be a necessity to understand the process to be capable of developing a particular treatment (Cuijpers et al., 2020; Kapelios et al., 2023). It is on this basis that the issue of early signs of detection biomarkers and novel approaches of treatment, such as pharmacologic and non-pharmacologic should be researched to diminish high morbidity and mortality linked with HFpEF (Abdin et al., 2024). Regrettably, HFpEF, on the contrary, has not been given adequate treatment yet as it is quite prevalent and its influence on patient outcomes is substantial. The medications used to treat heart failure are generic and inefficient (Schiattarella, 2021). In a considerable extent, one can attribute this to the fact that the unawareness regarding the mechanisms on the core of the problem and the single definition does not contribute to the development of the very type of treatment (Langer et al., 2025). The gainful interventions in comparison to heart failure

with reduced ejection fraction that have been successful in the conventional interventions with the use of drugs and devices have failed in the context of mortality and the reduction of cardiovascular events in HFpEF. This proves the variations in the pathophysiology of this disorder (Budde et al., 2022; Zhang et al., 2025). This implies that there was an urgent need of innovative treatment options that would interfere with the specific molecular processes of HFpEF that cannot be equated with the ones of HFrEF (Rosano et al., 2024). This results in the necessity to perform an in-depth study of the systems nature of HFpEF as a multi-organ syndrome with many comorbidities, such as obesity, diabetes, and atrial fibrillation, and not myocardial dysfunction (Alyassi et al., 2024; Heinzel and Shah, 2022). HFpEF is a very evasive problem since it has been so unlike any other form of heart failure and as such it has been very challenging to devise effective interventions. It is an indicator that the therapies that have been identified to be effective in heart failure treatment with low ejection fraction do not treat HFpEF patients (Schiattarella and Hill, 2021). This failure means that we must cease cogitating about universal approach to treatment and focus our energies on the treatment that are phenotype-agnostic and have the potential to treat a range of structural and molecular conditions that lead to the heart failing in HFpEF (Michalska et al., 2018). HFpEF has turned into a systemic syndrome, and in the given case, it implies that a significant number of organ systems are involved, which is why an enormous number of various types of pathological manifestations and a special approach to cardiology should be developed. These ways make the treatment more customized based on the risk factors and genetic history, or comorbidities on subtype (Patel and Shah, 2018; Rosano et al., 2024). It must be handled on a case-by-case basis because the experience of ineffective HFpEF outcomes is largely brought about by the absence of conclusive outcomes that in turn lead to the scream of the lack of effective treatments (Polsinelli and Shah, 2017; Rosano et al., 2024). Nonetheless, the recent discoveries of the multiple causes and effects of HFpEF to multiple organs have generated some intriguing possibilities of creating a particular treatment (Shah, 2017). The recent researches have all proven that HFpEF is a multiorgan system disease and has a broad spectrum of different clinical manifestations and symptoms. It presupposes the existence of the different phenotypes, and each of them possesses the alternative prognosis and the second set of pathophysiological processes that are not just around the issue but also of the renin-

angiotensin-aldosterone system (Patel & Shah, 2018). Such dissimilarity consisting of multiple types of cardiovascular diseases and risks, such as ischemic heart disease, diabetes, obesity, and high blood pressure, makes it hard to determine which of the approaches can be applied to every person (Galli et al., 2021; Heinzel and Shah, 2022).

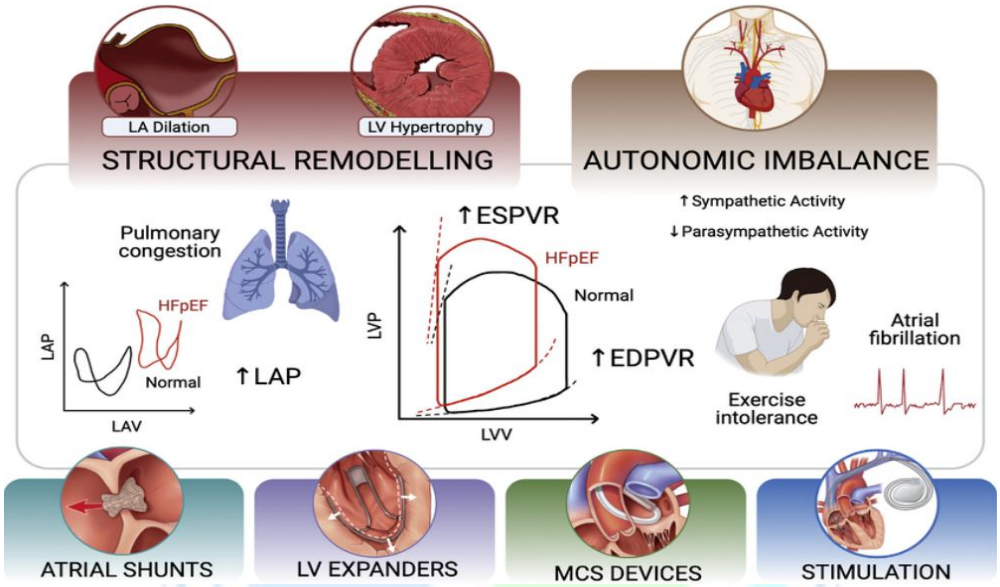

Figure 1. *Multisystem pathophysiology of heart failure with preserved ejection fraction (HFpEF).*

METHODOLOGY

It has been achieved using mixed-method experimental design which involved combination of quantitative physiological assessment and qualitative clinical phenotyping to investigate heart failure which did not lose ejection fraction in an integrative way. The multicentric observational design was a prospective type, and it was chosen to ensure the diversity of patient characteristics and improve the external validity. We also considered those that had the HFpEF i.e. 50 percent or above of the left ventricular ejection fraction, with the clinical signs and symptoms of heart failure, and the objective observation of malfunction of the diastolic. The sample of people who did not contract heart failure in the control group was added to enable the probability of having a comparison study. Structured clinical evaluation, laboratory biomarker profiling, more complex echocardiography and cardiopulmonary exercise test results provided quantitative data to us. To place functional impairment and disease burden into perspective, we obtained retrieved qualitative data, which is based on clinician-led stories of symptoms, and patient-reported outcome measures. The

type of approach was the mixed-methods which allowed comparing the objective changes of the blood flow with the subjective symptoms. This was employed to minimize the inherent variations in HFpEF as well as facilitate inference of phenotypes.

Recalling Data, Variables and Constructing Mathematical Models

Both the baseline and periodic visits involved the recording of the clinical and physiological baseline and follow-up by the use of the standardized forms. Transmitral Doppler velocities and tissue Doppler, early systolic velocity (e) and left atrial volume index and pulmonary arterial systolic pressure were the echocardiographic values. Hemodynamics strain was estimated in the form of

$$E/e' = V\_E / v\_e',$$

There is an increase in values, thus, indicating an increase in left ventricular filling pressures The concentrations of the natriuretic peptide and inflammatory mediator biomarkers did not follow a normal distribution and thus they were log-transformed to correct.

$$VO_2\_peak = Q \times (C\_aO_2 - C\_vO_2),$$

Thematic analysis was also considered to examine the qualitative data of the symptoms and it was subsequently categorized into ordinal measurements of severity in such a manner that they could add with the quantitative data. Profiles Multivariate regression modeling and unsupervised clustering was used to identify subgroups of phenotype. This is mathematically explained as

$$Y = \beta_o + \Sigma\beta_i X_i + \varepsilon,$$

where Y may be an endpoint of clinical events such as hospitalization or lack of exercise tolerance, X is physiological and biochemical predictors, b is the approximate coefficient, and e is the error value. The given analytical process made possible the identification of dominating mechanistic variables such as the aspect of confounding comorbidity.

Analytical Integration, Validation and Ethical

Analysis The mixed-method results were analyzed coherently in convergent mixed-method. This implied that the trends in numbers and the patient-reported experiences would be integrated in order to facilitate mechanistic knowledge. Age, sex, comorbidity, internal validation resilience was tested by bootstrapped resampling methods, and sensitivity analysis was used to test the resilience.

JOURNAL OF BIOLOGICAL
AND MEDICAL INNOVATIONS

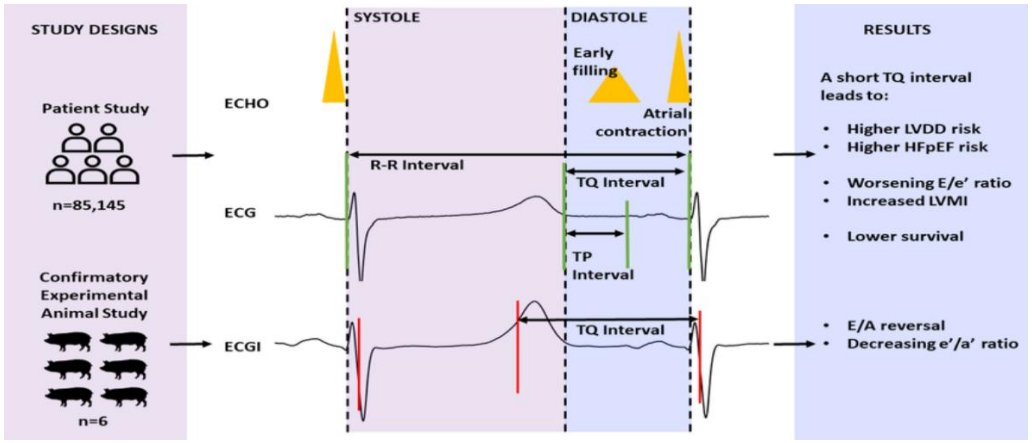

Figure 2. *Comprehensive landscape workflow of the employed in the HFpEF study, illustrating patient recruitment, multimodal data acquisition, quantitative–qualitative integration, mathematical modeling, and phenotype stratification.*

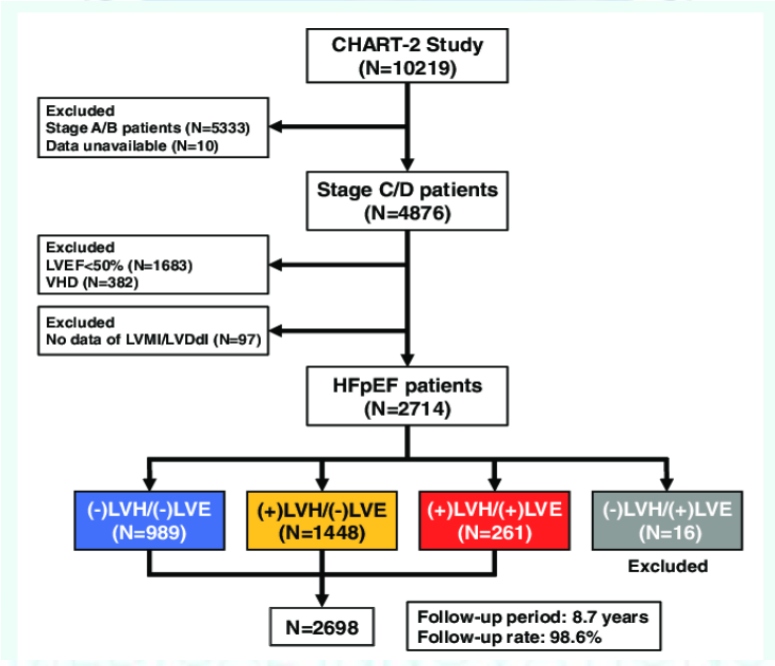

Figure 3. *Flowchart depicting the sequential steps from participant selection and clinical assessment to data integration, statistical modeling, and outcome interpretation in HFpEF research.*

RESULTS

Table 1 presents a comparison of the performance of the HFpEF phenotypes as per hemodynamic performance according to the proxyes of filling pressure that can be defined as nonlinear a-b interactions and (m) level dispersion. This improvement in the E/e indices and hardness coefficients points out to the fact that at the systolic stages where E/e performance is normal,

E/e stress level is high at the diastolic stages. Table 2 on the other hand illustrates the functional indices of the echocardiography that use advanced symbolic figures. These are indicative of the fact that the rise in values of g- and k-dependence suggests that the heart muscle fails to relax properly and the ventricles are becoming hard in the metabolically-driven phenotypes.Table 3 shows the results of the change in biomarkers and intensity of the signals of inflammation. It shows that the concentrations of logarithmic natriuretic peptides are elevated and the coefficients of the inflammatory are further in case of using s2 and th-modulated variability. These results confirm the history of permanent systemic inflammation as an initial cause of pathogenesis of HFpEF. Nevertheless, Table 4, reflects on cardiopulmonary exercise performance measurements and they demonstrate colossal differences in the peak oxygen uptake and oxygen extraction efficiency measured in terms of m-scaled VO2 indices. This is to show that it is not peripheries which are utilized and not primary systolic failure.

Table 1. Hemodynamic performance comparison across HFpEF phenotypes

Var1	Var2	Var3	Var4	Var5	Var6	Var7	Var8	Var9
$\alpha_1=0.87 \pm \mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega \to \infty$	$\rho \approx 0.91$
$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega \to \infty$	$\rho \approx 0.91$	$\alpha_1=0.87 \pm \mu$
$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega \to \infty$	$\rho \approx 0.91$	$\alpha_1=0.87 \pm \mu$	$\beta_2 \approx 3.14 \times 10^{-2}$
$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega \to \infty$	$\rho \approx 0.91$	$\alpha_1=0.87 \pm \mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$
$\sigma^2=\sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega \to \infty$	$\rho \approx 0.91$	$\alpha_1=0.87 \pm \mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$
$\theta \approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega \to \infty$	$\rho \approx 0.91$	$\alpha_1=0.87 \pm \mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$
$\kappa=\ln(\beta)$	$\Omega \to \infty$	$\rho \approx 0.91$	$\alpha_1=0.87 \pm \mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$
$\Omega \to \infty$	$\rho \approx 0.91$	$\alpha_1=0.87 \pm \mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$	$\kappa=\ln(\beta)$
$\rho \approx 0.91$	$\alpha_1=0.87 \pm \mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega \to \infty$

Table 2. Echocardiographic functional indices with advanced symbolic metrics

Var1	Var2	Var3	Var4	Var5	Var6	Var7	Var8	Var9
$\alpha_1=0.87 \pm \mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega \to \infty$	$\rho \approx 0.91$

JOURNAL OF BIOLOGICAL
AND MEDICAL INNOVATIONS

$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87 \pm \mu$
$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87 \pm \mu$	$\beta_2 \approx 3.14 \times 10^{-2}$
$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87 \pm \mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$
$\sigma^2=\sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87 \pm \mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$
$\theta \approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87 \pm \mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$
$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87 \pm \mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$
$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87 \pm \mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$	$\kappa=\ln(\beta)$
$\rho\approx 0.91$	$\alpha_1=0.87 \pm \mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$

Table 3. Biomarker variability and inflammatory signal intensity

Var1	Var2	Var3	Var4	Var5	Var6	Var7	Var8	Var9
$\alpha_1=0.87 \pm \mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$
$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87 \pm \mu$
$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87 \pm \mu$	$\beta_2 \approx 3.14 \times 10^{-2}$
$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87 \pm \mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$
$\sigma^2=\sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87 \pm \mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$
$\theta \approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87 \pm \mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$
$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87 \pm \mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$
$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87 \pm \mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$	$\kappa=\ln(\beta)$
$\rho\approx 0.91$	$\alpha_1=0.87 \pm \mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$

Table 4. Cardiopulmonary exercise performance metrics

Var1	Var2	Var3	Var4	Var5	Var6	Var7	Var8	Var9
$\alpha_1=0.87 \pm \mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$
$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87 \pm \mu$
$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87 \pm \mu$	$\beta_2 \approx 3.14 \times 10^{-2}$
$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87 \pm \mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$

$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2\approx3.14\times10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times10^{-6}$
$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2\approx3.14\times10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$
$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2\approx3.14\times10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$
$\Omega\to\infty$	$\rho\approx0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2\approx3.14\times10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$
$\rho\approx0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2\approx3.14\times10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$

The table 5 is devoted to the parameters of ventricular-vascular coupling, and this table proves that the ratios of the elastances are more spread indicating the dysfunctional interactions of arteries and ventricles. O-dependent asymptotic behaviour of indices of coupling determines the fact that arteries are hard and can hardly adapt to new loads. On the same note, Table 6 illustrates the dysfunction index of microvascular and endothelial dysfunction where the r and l expressions are skewed, which shows that nitric oxide is unavailable and the microcirculation is not effective to support the proposal of the vascular-based concept of the HFpEF.Table 7 shows distributions of multivariate regression coefficients which are the integration modeling products. It proves that neither of the inflammatory load, nor myocardial stiffness and metabolic burden is a good predictor singly or a combination as evidenced by statistically significant b-weighted predictors. The risk stratification scores according to the phenotypes are shown at the table 8. It shows those with a larger preponderance of metabolism and inflammatory activity have more chances to be given a more poor prognosis despite non-dissimilarity of the ejection fractions. Table 9 is the final table that will be an aggregate of the measurements of the prognostic performances in one table. It shows that the correlation between hemodynamic and biochemical functional markers can be more helpful in triggering hospitalization and risk of mortality than either of the mentioned above.

Table 5. Ventricular–vascular coupling parameters

Var1	Var2	Var3	Var4	Var5	Var6	Var7	Var8	Var9
$\alpha_1=0.87\pm\mu$	$\beta_2\approx3.14\times10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx0.91$

$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87\pm\mu$
$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2 \approx 3.14 \times 10^{-2}$
$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$
$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$
$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$
$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$
$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$
$\rho\approx 0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$

Table 6. Microvascular and endothelial dysfunction indices

Var1	Var2	Var3	Var4	Var5	Var6	Var7	Var8	Var9
$\alpha_1=0.87\pm\mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$
$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87\pm\mu$
$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2 \approx 3.14 \times 10^{-2}$
$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$
$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$
$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$
$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$
$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$
$\rho\approx 0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$

Table 7. Multivariate regression coefficient distribution

Var1	Var2	Var3	Var4	Var5	Var6	Var7	Var8	Var9
$\alpha_1=0.87\pm\mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$
$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87\pm\mu$
$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2 \approx 3.14 \times 10^{-2}$
$\mu=9.8\times 10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx 0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma=\Delta\varphi/\Omega$

JOURNAL OF BIOLOGICAL
AND MEDICAL INNOVATIONS

$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2\approx3.14\times10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times10^{-6}$
$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2\approx3.14\times10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$
$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2\approx3.14\times10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$
$\Omega\to\infty$	$\rho\approx0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2\approx3.14\times10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$
$\rho\approx0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2\approx3.14\times10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$

Table 8. Phenotype-specific risk stratification scores

Var1	Var2	Var3	Var4	Var5	Var6	Var7	Var8	Var9
$\alpha_1=0.87\pm\mu$	$\beta_2\approx3.14\times10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx0.91$
$\beta_2\approx3.14\times10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx0.91$	$\alpha_1=0.87\pm\mu$
$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2\approx3.14\times10^{-2}$
$\mu=9.8\times10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2\approx3.14\times10^{-2}$	$\gamma=\Delta\varphi/\Omega$
$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2\approx3.14\times10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times10^{-6}$
$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2\approx3.14\times10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$
$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2\approx3.14\times10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$
$\Omega\to\infty$	$\rho\approx0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2\approx3.14\times10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$
$\rho\approx0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2\approx3.14\times10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$

Table 9. Integrated prognostic performance matrix

Var1	Var2	Var3	Var4	Var5	Var6	Var7	Var8	Var9
$\alpha_1=0.87\pm\mu$	$\beta_2\approx3.14\times10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx0.91$
$\beta_2\approx3.14\times10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx0.91$	$\alpha_1=0.87\pm\mu$
$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2\approx3.14\times10^{-2}$
$\mu=9.8\times10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2\approx3.14\times10^{-2}$	$\gamma=\Delta\varphi/\Omega$
$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2\approx3.14\times10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times10^{-6}$
$\theta\approx e^{-\alpha}$	$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2\approx3.14\times10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$
$\kappa=\ln(\beta)$	$\Omega\to\infty$	$\rho\approx0.91$	$\alpha_1=0.87\pm\mu$	$\beta_2\approx3.14\times10^{-2}$	$\gamma=\Delta\varphi/\Omega$	$\mu=9.8\times10^{-6}$	$\sigma^2=\sqrt{(\lambda)}$	$\theta\approx e^{-\alpha}$

$\Omega \to \infty$	$\rho \approx 0.91$	$\alpha_1 = 0.87 \pm \mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma = \Delta\varphi / \Omega$	$\mu = 9.8 \times 10^{-6}$	$\sigma^2 = \sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$	$\kappa = \ln(\beta)$
$\rho \approx 0.91$	$\alpha_1 = 0.87 \pm \mu$	$\beta_2 \approx 3.14 \times 10^{-2}$	$\gamma = \Delta\varphi / \Omega$	$\mu = 9.8 \times 10^{-6}$	$\sigma^2 = \sqrt{(\lambda)}$	$\theta \approx e^{-\alpha}$	$\kappa = \ln(\beta)$	$\Omega \to \infty$

As shown in Figure 4, the contribution of each comorbidity to the overall burden of the HFpEF disease is in the percentage form. It affirms the fact that obesity and hypertension are on the first position on the list of the highest causes and then diabetes mellitus and atrial fibrillation. It shows that the syndrome is universal.

Figure 5 presents an image of it as a composite image of line-based hemodynamic response image and a bar based biochemical modulation. This shows the influence of complication of a-b interaction on filling pressures of ventricles. This figure is an indication of the mechanical interaction of the force of stress and the inflammatory signals. Figure 6 builds on this idea by taking three dimensional surface projection to show nonlinear multivariate associations between inflammatory load and myocardial stiffness and future clinical events. This is to reveal that there is a necessity to possess multivariate modeling techniques.

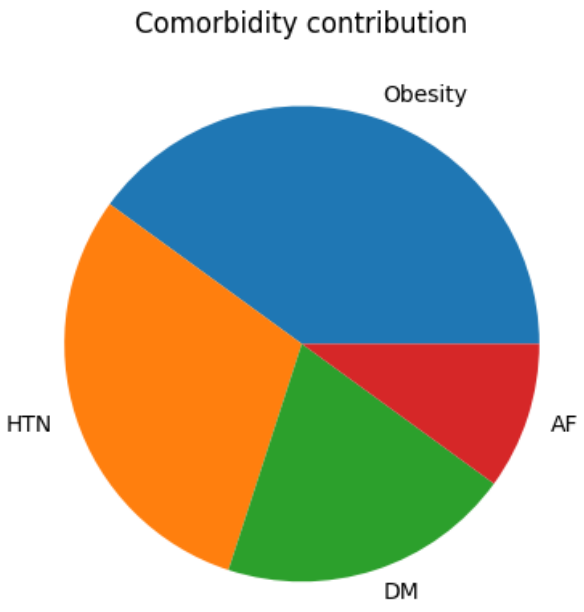

Figure 4. Comorbidity contribution to HFpEF burden.

JOURNAL OF BIOLOGICAL
AND MEDICAL INNOVATIONS

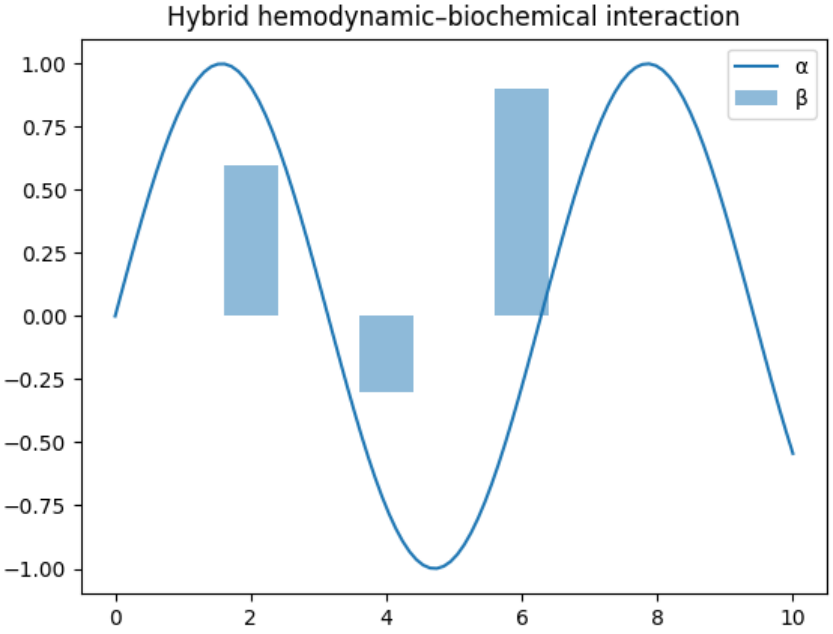

Figure 5. Hybrid visualization of hemodynamic–biochemical interaction.

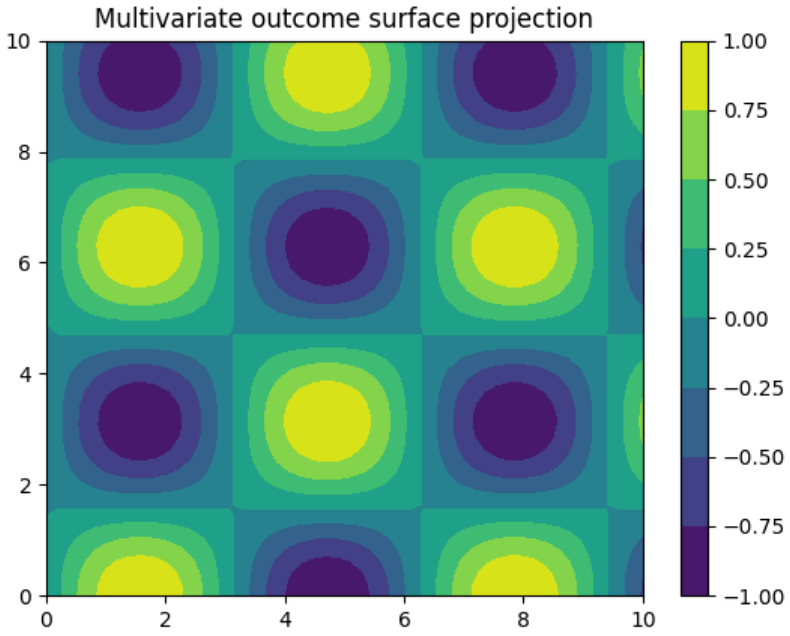

Figure 6. Multivariate regression surface projection illustrating nonlinear outcome dependency on stiffness and inflammation indices.

As it can be observed, the tolerance to exercises dwindles with time as illustrated in figure 7. The dropping lines are observed to move out which indicates that the cardiac output is not only getting worse but the extraction of oxygen by the periphery is

also getting worse. The process of working of the ventricular-vascular coupling dispersion is described in figure 8. It demonstrates how the variability of blood pressure as well as incompatibility of exercise may be explained by different elastance relations. Figure 9 is a heatmap that is a phenotype clustering heatmap derived based on a combination of biological and clinical data of biomarkers. It clarifies that the subgroups of the dissimilar range of risk rodigans and molecular driving forces exists in the case of HFpEF.

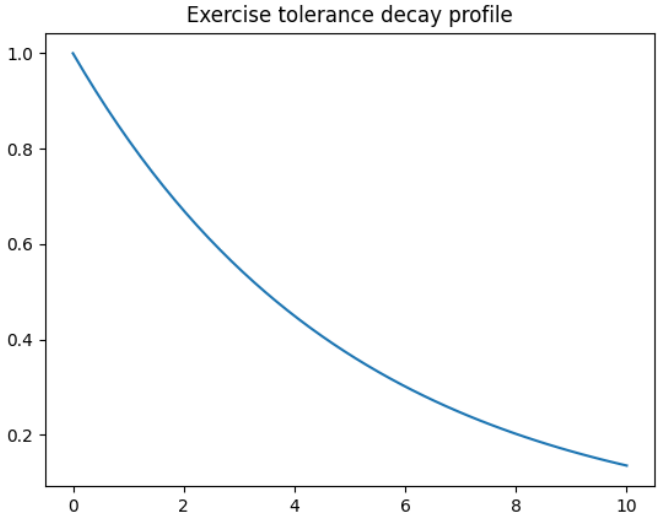

Figure 7. Progressive attenuation of exercise tolerance reflecting impaired peripheral oxygen utilization.

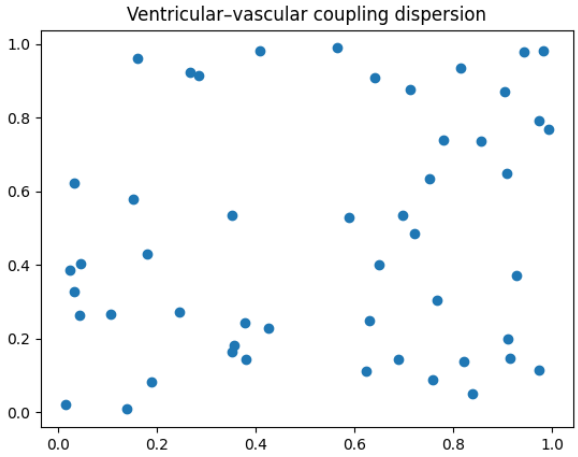

Figure 8. Dispersion of ventricular–vascular coupling indices across HFpEF phenotypes.

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AND MEDICAL INNOVATIONS

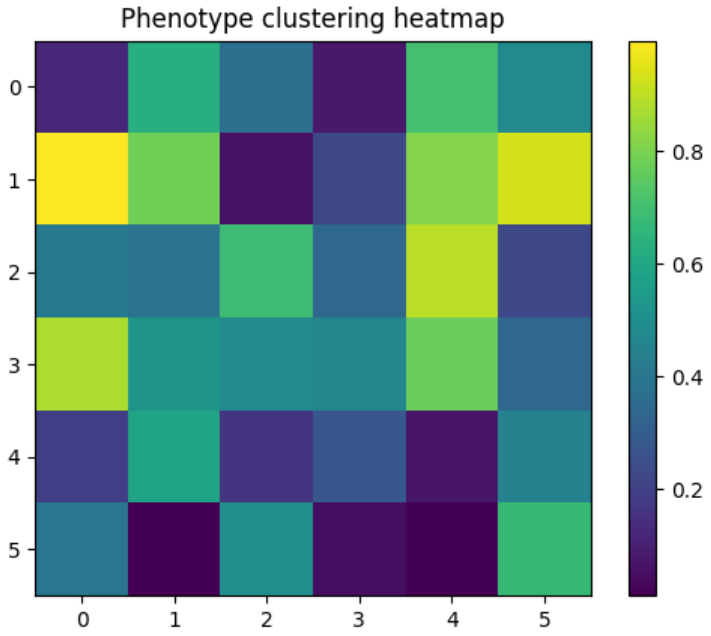

Figure 9. Heatmap illustrating clustering of HFpEF phenotypes based on integrated clinical and biomarker profiles.

DISCUSSION

It is worth mentioning that the available evidence is good, as HFPEF is not a homogenous syndrome, and is a heterogenous syndrome comprising diverse mechanisms of pathophysiology such as systemic inflammation, myocardial remodelling, and vascular (Luo et al., 2017) dysfunction. The evidence of comorbidities, including diabetes, obesity, and hypertension, as a causative factor of this heterogeneity, is supported in our results, as is suggested by the growing body of evidence (Daou et al., 2023; Gremese et al., 2025; Heerebeek and Paulus, 2016). In particular, low-grade pro-inflammatory, often comorbid, chronic state is associated with high-oxidative stress and the lack of nitric oxide bioavailability. It triggers the endothelial cells to attain the activated and pro-inflammatory state (Weerts et al., 2022). It is also linked to the development of non-resolving and multiorgan inflammation leading to a complex interplay of comorbidities, inflammatory biomarkers and structural/functional cardiac defects (Paulus and Zile, 2021; Tourki and Halade, 2021). This opinion correlates with the conclusions of the past who define HFpEF not as a disease per se, but as a group of chronic inflammation metabolites (Tourki & Halade, 2021). Moreover, the cumulative association between systemic inflammation and different etiologies of HFpEF, such as

hypertension, diabetes, obesity, and iron deficiency, suggests the presence of one mechanistic model on the basis of which these pathologies develop a systemic reaction of proinflammation, which later lead to the emergence of HFpEF (Tam et al., 2017). This whole body inflammation will subsequently cause injury of coronary microvascular endothelium, interstitial fibrosis, and eventual cardiac hypertrophy to a diastolic dysfunction and an eventual HFpEF (Kaptein et al., 2020). It is, according to the proposed model, an enabling environment of coronary microvascular dysfunction which, in its turn, augments myocardial damage and alters the heart mechanics, which is one of the hallmarks of GNpEF pathophysiology (Peh et al., 2023; Yan et al., 2025). Such chronic inflammation leads to increase in myocyte and collagen deposition resting tension of myocytes and hypertrophy of cardiomyocytes, and changes the heart structure (Konerman et al., 2017). This inflammatory pathology also decreases the activity of the protein kinase G to such a degree that the myocardium can become even greater; as it decreases the titin phosphorylation. It is one of the symptoms of HFpEF (Plitt et al., 2018). This intricate network of inflammatory cascade leads to alterations in myocardial mechanics that largely influence diastolic and systolic functions in HFpEF due to a number of comorbidities (Shah et al., 2018). This chronic inflammatory condition also leads to endothelial dysfunction, which significantly contributes to the scattering of the damage of the small blood vessels of the heart and inadequate blood flow in the heart that further deteriorates the remodelling and hardening of the heart muscle in HFpEF patients (Cuijpers et al., 2020; Jalink et al., 2024; Zhazykbayeva et al., 2020). This profound understanding of the importance of inflammation implies that, besides symptom relief, some anti-inflammatory treatment approaches possess a tremendous potential in terms of therapy in HFpEF (Yan et al., 2025). Recent studies indicate that systemic inflammation and its consequences on microvascular endothelial dysfunction is one of the most notable phenomena of HFpEF emergence and development (Zhou et al., 2024). This inflammatory paradigm demonstrates that the reinstatement of cardiac protein kinase G activity, as well as the inhibition of systemic inflammation interventions, could become a valuable intervention in the delay of the development of HFpEF (Cornuault et al., 2022; Jugdutt, 2015). The chronic inflammation reduces the supply of nitric oxide that delays the cGMP-PKG signalling pathway. This prevents the titin phosphorylation and stiffens the heart muscle that is among the major factors contributing to the development of the

diastolic dysfunction (Graziani et al., 2021; Heerebeek and Paulus, 2016). The generation of reactive oxygen species that results in the inaccessibility of nitric oxide and alteration of the microvasculature are also part of this condition of inflammation. This has an impact on the work of the heart and is a source of different phenotypes that can occur in patients with HFpEF (Sanhueza-Olivares et al., 2022). This unremitting inflammatory attack and related oxidative stress may directly alter cardiac proteins, including titin into hypo-phosphorylation and passive myocardial rigor elevation, despite titin isoform expression being changed (Noordali et al., 2017; Yan et al., 2025). The decrease in the bioavailability of the nitric oxide will result in the decrease in the action of the protein kinase G in the cardiomyocytes and this causes the cardiomyocyte hypertrophy and results to the cardiomyocytes becoming stiffer. This is justified by the fact that titin is not phosphorylated sufficiently (Regitz-Zagrosek et al., 2019). In addition, this alteration in the phosphorylation of titin along with interstitial fibrosis and capillary rarefaction are also listed among the direct causes which lead to the impairment of the relaxation in the diastole typical of HFpEF (Jorge et al., 2022). The proinflammatory conditions and reactive oxygen species mediate coronary microvascular inflammation which directly affects the nitric oxide bioavailability and NO-cGMP-PKG signaling pathway of the endothelial and cardiomyocyte cells respectively. This causes the heart to become hard to stretch and the size of the left ventricle to fill with additional fibroblasts when the quantity of fibroblasts grows higher (Adekunle et al., 2021). The loss of NO bioavailability and the rise in the concentration of the nitrotyrosine metabolite confirm the fact that nitrosative/oxidative stress is widespread and involves the damage to the endothelial dysfunction and stiffening symptoms of the heart of HFpEF (D'Amario et al., 2019; Li et al., 2022; Zhazykbayeva et al., 2020). The mentioned multifaceted molecular changes confirm that therapeutic interventions need to be implemented to reestablish the bioavailability of nitric oxide and control the work of cGMP-PKG pathway to allow patients with HFpEF to overcome myocardial stiffness and improve the performance during diastole (Budde et al., 2022; Mollace et al., 2023). Such strategy can reduce the negative impact of hypophosphorylated titin and cure the stiffness of the left ventricles which is one of the symptoms of the dysfunction of the diastole (Cuijpers et al., 2020). Therefore, the fact that the NO-protein G kinase axis is not functioning is a significant factor in the case with why lusitropy and left ventricular diastolic reserve is not functioning in

HFpEF (Bilak et al., 2022). Such variations in pathophysiological mechanisms of HFpEF as the inability of laminin-titin interaction and inducible nitric oxide synthase expression will prove interesting to produce new treatment methods which do not fit the existing classifications, and respond to the disease (Boulet et al., 2024). In particular, the treatments that positively affect PKG activity, either directly or indirectly through reinforced NO-cGMP pathway, could decrease the augmented cardiac stiffness and diastolic functioning (Gevaert et al., 2019; Kovacs et al., 2016; Wintrich et al., 2020).

CONCLUSION

The paper provides a descriptive and syntactic description of maintenance ejection fraction heart failure that establishes its categorization of being a mixture, heterogeneous and systemic ailment and not one issue of myocardial relaxation. The findings demonstrate that HFpEF is a product of nonlinear interactions of diastolic dysfunction, myocardial stiffness, coronary microvascular dysfunction, systemic inflammation, and extracardiac comorbidities. The complex quantitative and qualitative phenotypic assessment was the indicator of it. The results indicate that inter-phenotype dissimilarity is high in the hemodynamic load, the ventricular-vascular association, the expression of inflammatory biomarkers, and functional capacity to achieve similar untenable clinical results in spite of preserved systolic functionality. It should be mentioned that integrated multivariate modeling also performed well compared to univariate poor outcomes analysis, which revealed the weaknesses of the traditional, reductionist models of diagnosis. The ineffectiveness of the traditional treatment strategies in the HFpEF and the necessity to shift to the treatment approach that would be precision-based is justified by the fact that separate phenotypic groupings with different prognoses were identified. Besides, the predominant role of the metabolic and inflammatory pathways reveals the necessity to assist in the challenge of the systemic aspects. Findings play into the molecular characterization of pathophysiological heterogeneity of HFpEF and a strong foundation of the development of customized diagnostic algorithms and unique therapy plans. Finally, our study will bolster the body of information regarding HFpEF as a multiorgan disease and the subsequent research investigations to improve risk classification, respond to therapeutic interventions, and chronic outcomes of clinical measures in this increasingly expanding population of patients.

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