COMORBIDITY-DRIVEN PHENOTYPING AND FIBROSIS BIOMARKERS IN HEART FAILURE WITH PRESERVED EJECTION FRACTION: TOWARD PRECISION RISK STRATIFICATION

Nuriddinov Umed Zayniddin ugli
Asia International University Department of Preclinical Sciences
DOI:https://doi.org/10.5281/zenodo.23170272

ABSTRACT. Heart failure with preserved ejection fraction (HFpEF) is a clinically and biologically heterogeneous syndrome in which patients with similar left ventricular ejection fraction may demonstrate substantially different comorbidity profiles, patterns of myocardial remodeling, inflammatory activity, and prognosis. Arterial hypertension, obesity, type 2 diabetes mellitus, atrial fibrillation, chronic kidney disease, and ischemic heart disease frequently coexist with HFpEF and may contribute differently to diastolic dysfunction, myocardial stress, systemic inflammation, and interstitial fibrosis.

Objective. To evaluate the scientific rationale for integrating comorbidity-based phenotyping with echocardiographic parameters and fibrosis-associated biomarkers, particularly galectin-3 and soluble suppression of tumorigenicity-2 (sST2), in order to improve biological characterization and prognostic stratification of patients with HFpEF.

Materials and Methods. A prospective observational cohort design is proposed for adult patients with clinically confirmed HFpEF. Diagnosis should be based on symptoms and/or signs of heart failure, left ventricular ejection fraction of at least 50%, and objective evidence of structural or functional abnormalities associated with elevated cardiac filling pressures. Clinical assessment should include age, sex, NYHA functional class, arterial blood pressure, body mass index, previous hospitalizations for heart failure, pharmacological treatment, and major comorbidities. Echocardiographic evaluation should include left ventricular ejection fraction, chamber geometry, left atrial parameters, indices of diastolic function, E/e′ ratio, and, when available, estimated pulmonary artery pressure. Serum galectin-3 and sST2 should be measured using validated laboratory assays. Unsupervised clustering may be applied to identify reproducible comorbidity-driven HFpEF phenotypes.

Expected Results and Discussion. The proposed approach is expected to identify clinically distinct HFpEF phenotypes characterized by different combinations of cardiometabolic, renal, rhythm-related, and ischemic comorbidities. These clusters may differ not only in symptom burden and echocardiographic characteristics but also in the activity of myocardial remodeling and fibrotic pathways. Galectin-3 is associated with macrophage activation, inflammation, extracellular matrix remodeling, and profibrotic signaling. Elevated concentrations may therefore reflect a biological environment characterized by persistent tissue remodeling and fibrosis. sST2 represents a complementary biomarker related to myocardial stress, inflammation, and remodeling. Unlike ejection fraction, which predominantly reflects global systolic performance, these biomarkers may provide additional information about the biological processes underlying HFpEF progression.

The combined interpretation of biomarker profiles and echocardiographic indices may therefore identify subgroups with different degrees of myocardial remodeling. For example, patients with obesity, diabetes, and hypertension may demonstrate a predominantly cardiometabolic-inflammatory phenotype,

© Ushbu material Creative Commons Attribution 4.0 International (CC BY 4.0) litsenziyasi asosida tarqatiladi.

whereas patients with atrial fibrillation and marked left atrial remodeling may represent a distinct hemodynamic-rhythm phenotype. A subgroup characterized by chronic kidney disease may have a different biomarker profile because renal dysfunction can influence systemic inflammation, volume status, and circulating biomarker concentrations. Such heterogeneity is clinically important because HFpEF cannot be sufficiently characterized by left ventricular ejection fraction alone. An ejection fraction of ≥50% does not exclude substantial abnormalities in diastolic relaxation, filling pressures, atrial remodeling, pulmonary circulation, or myocardial extracellular matrix composition. Therefore, a multidimensional phenotype incorporating comorbidity burden, imaging parameters, and circulating biomarkers may provide more clinically meaningful information than a single cardiac measurement.

Statistical evaluation should compare galectin-3 and sST2 concentrations, echocardiographic variables, and predefined clinical outcomes across identified phenotypes. Correlation analysis may be used to assess relationships between biomarkers and structural-functional cardiac parameters. Multivariable regression models may determine whether biomarker concentrations and comorbidity patterns independently predict adverse clinical outcomes. Where appropriate, receiver operating characteristic analysis and area under the curve may be applied to assess the incremental prognostic value of biomarker-based models. Particular attention should be given to recurrent decompensation and hospitalization for heart failure. If specific combinations of comorbidities are consistently associated with elevated galectin-3 or sST2 concentrations and more pronounced echocardiographic remodeling, these patterns may identify patients at increased risk of progressive disease. However, galectin-3 and sST2 should not be interpreted as isolated diagnostic markers for HFpEF. Their principal value lies in complementing clinical and instrumental assessment. The biological meaning of biomarker elevation must also be considered in the context of age, renal function, inflammatory burden, obesity, and associated cardiovascular disease.

CONCLUSION

HFpEF represents a heterogeneous syndrome in which comorbidities contribute substantially to differences in myocardial remodeling, diastolic dysfunction, inflammation, and clinical progression. A precision-phenotyping strategy combining comorbidity clustering, echocardiographic characteristics, and fibrosis-associated biomarkers may provide a more comprehensive representation of disease biology than classification based solely on preserved ejection fraction. Galectin-3 and sST2 are promising complementary biomarkers for characterizing myocardial stress, remodeling, inflammation, and fibrotic activity. Their integration with clinical and echocardiographic data may help identify HFpEF subgroups with different risks of recurrent decompensation, hospitalization, and disease progression. Prospective follow-up is required to determine whether reproducible biomarker profiles correspond to specific comorbidity-driven phenotypes and whether these integrated models provide independent prognostic value in patients with HFpEF.

Keywords: HFpEF, preserved ejection fraction, comorbidity phenotypes, galectin-3, sST2, myocardial fibrosis, cardiac remodeling, echocardiography, precision phenotyping, risk stratification.

© Ushbu material Creative Commons Attribution 4.0 International (CC BY 4.0) litsenziyasi asosida tarqatiladi.