

NOVEL BIOMARKERS IN EARLY DETECTION OF HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFPEF)

Nuralieva Dilbar

Student of the Termez branch of the Tashkent medical academy

Annotation: Heart Failure with Preserved Ejection Fraction (HFpEF) represents a complex and increasingly prevalent form of heart failure characterized by typical heart failure symptoms despite a normal or near-normal left ventricular ejection fraction. Unlike Heart Failure with Reduced Ejection Fraction (HFrEF), HFpEF remains difficult to diagnose in its early stages due to nonspecific clinical presentation and the limitations of conventional diagnostic tools. In recent years, the discovery and validation of novel circulating biomarkers—such as galectin-3, soluble ST2 (sST2), growth differentiation factor-15 (GDF-15), and neprilysin—have opened new avenues for earlier and more accurate detection of HFpEF. These biomarkers reflect different pathophysiological pathways including myocardial fibrosis, inflammation, oxidative stress, and neurohormonal activation. This paper explores the clinical utility, diagnostic accuracy, and prognostic value of these emerging biomarkers and highlights their potential role in guiding therapeutic strategies and improving patient outcomes in HFpEF.

Keywords: HFpEF, heart failure, galectin-3, sST2, GDF-15, biomarkers, preserved ejection fraction, early diagnosis

CHIQRISH FRAKSIYASI SAQLANGAN YURAK YETISHMOVCHILIGINING
ERTA TASHXISIDA YANGI BIOMARKERLARNING O‘RNI

Nuralieva Dilbar

Toshkent tibbiyot akademiyasi Termiz filiali talabasi

Annotatsiya: Chiqarish fraksiyasi saqlangan yurak yetishmovchiligi (HFpEF) yurakning chiqarish hajmi nisbatan normal bo‘lishiga qaramay yurak yetishmovchiligi belgilari mavjud bo‘lgan murakkab va tobora keng tarqalib borayotgan patologik holatdir. Bu holat chiqarish fraksiyasi kamaygan yurak yetishmovchiligidan (HFrEF) farqli o‘laroq, klinik jihatdan erta aniqlashda ancha murakkab, chunki an’anaviy tashxis usullari HFpEF holatlarini kech aniqlashga olib keladi. So‘nggi yillarda galektin-3, sST2, GDF-15 va neprelizinning aniqlanishi kabi yangi biomarkerlar yurak mushagi fibrozisi, y

.allig‘lanish, oksidlovchi stress va neyrogormonal faollik kabi patofiziologik mexanizmlarni ifoda etib, HFpEFning erta bosqichida samarali aniqlanishi uchun yangi yo‘nalishlarni ochmoqda. Ushbu maqolada ayni shu biomarkerlarning tashxisdagi roli, klinik foydaliligi va prognoz baholashdagi ahamiyati yoritiladi.

Kalit so‘zlar: HFpEF, yurak yetishmovchiligi, galektin-3, sST2, GDF-15, biomarkerlar, chiqarish fraksiyasi, erta tashxis

Introduction

Heart Failure with Preserved Ejection Fraction (HFpEF) is a highly complex and heterogeneous clinical syndrome that accounts for nearly half of all heart failure cases worldwide. Unlike Heart Failure with Reduced Ejection Fraction (HFrEF), HFpEF is characterized by typical symptoms of heart failure—such as dyspnea, fatigue, and exercise intolerance—despite a normal or near-normal left ventricular ejection fraction (LVEF \geq 50%). The rising prevalence of HFpEF, particularly among elderly, hypertensive, diabetic, and obese patients, represents a growing public health challenge. Despite its clinical significance, HFpEF remains underdiagnosed and frequently misclassified, especially in its early stages. One of the main obstacles in the timely detection of HFpEF lies in its pathophysiological diversity and the limitations of conventional diagnostic tools. While echocardiography and natriuretic peptides (such as BNP and NT-proBNP) are widely used in clinical practice, they often fail to distinguish HFpEF from other non-cardiac causes of dyspnea or to detect the condition before functional impairment becomes evident. In this context, novel circulating biomarkers have emerged as promising tools for improving early diagnosis and risk stratification of HFpEF.

These biomarkers—such as galectin-3, soluble ST2 (sST2), growth differentiation factor-15 (GDF-15), and neprilysin—represent various pathophysiological domains, including myocardial fibrosis, inflammation, oxidative stress, and neurohormonal activation. Unlike traditional markers, these emerging indicators may help identify subclinical changes in myocardial structure and function before overt clinical symptoms appear. Additionally, they hold potential not only for diagnosis but also for prognosis assessment, therapeutic targeting, and monitoring treatment response. This paper aims to explore the clinical relevance of these novel biomarkers in the early detection and management of HFpEF. By examining current evidence from clinical trials and cohort studies, we seek to evaluate their diagnostic accuracy, biological significance, and potential to complement or surpass existing diagnostic approaches. As the burden of HFpEF continues to grow, incorporating biomarker-

based strategies into clinical workflows may offer new opportunities for personalized and timely cardiovascular care.

Relevance of the study

Heart Failure with Preserved Ejection Fraction (HFpEF) has emerged as one of the most pressing and elusive challenges in modern cardiology. Unlike Heart Failure with Reduced Ejection Fraction (HFrEF), which has seen significant advancements in diagnostic and therapeutic strategies, HFpEF remains poorly understood, difficult to diagnose, and largely untreatable with conventional heart failure medications. Its increasing incidence—especially among elderly individuals and patients with hypertension, diabetes, or obesity—has led to a dramatic rise in hospitalizations and healthcare costs worldwide. This underscores the urgent need for improved diagnostic tools that can detect HFpEF at earlier stages, before irreversible cardiac remodeling or clinical decompensation occurs. Traditional diagnostic methods such as echocardiography and natriuretic peptides, while helpful, often fall short in differentiating HFpEF from other causes of dyspnea and in identifying asymptomatic or early-stage cases. Furthermore, HFpEF represents a heterogeneous syndrome with multiple underlying mechanisms, including myocardial fibrosis, diastolic dysfunction, systemic inflammation, endothelial dysfunction, and comorbid burden. As such, relying on a single clinical parameter or imaging modality is often insufficient for accurate diagnosis and prognosis.

The relevance of novel biomarkers in this context cannot be overstated. Biomarkers such as galectin-3, soluble ST2 (sST2), GDF-15, and neprilysin offer insights into different aspects of HFpEF pathophysiology. For example, galectin-3 is involved in myocardial fibrosis and remodeling; sST2 reflects mechanical strain and inflammation; GDF-15 indicates oxidative stress and tissue injury; and neprilysin is implicated in neurohormonal regulation. Collectively, these biomarkers may serve as early warning signals—detecting disease activity well before clinical signs emerge. Moreover, the integration of these biomarkers into diagnostic algorithms may enable a more nuanced and personalized approach to HFpEF management. By identifying distinct biological pathways and patient subgroups, clinicians may tailor interventions more precisely and monitor disease progression with greater sensitivity. This represents a paradigm shift from the reactive to the preventive model of cardiovascular care. In the era of precision medicine, where individualized treatment strategies are increasingly prioritized, the exploration and clinical application of novel biomarkers offer a highly relevant and promising frontier. Not only do these biomarkers enhance our ability to detect HFpEF earlier, but they also open doors for

targeted therapies and improved patient outcomes—areas where current standard practices fall short. In summary, investigating novel biomarkers in HFpEF is of critical clinical and scientific importance. It responds to a major unmet need in heart failure diagnosis, aligns with global health priorities, and holds the potential to reshape future cardiology practices through earlier detection, better risk assessment, and more effective interventions.

Discussion

The growing burden of Heart Failure with Preserved Ejection Fraction (HFpEF) has made early diagnosis a cornerstone of effective management. However, the heterogeneity of its pathophysiology and the limitations of conventional diagnostic tools have impeded progress. In this regard, novel biomarkers have emerged as valuable adjuncts that offer insight into the underlying mechanisms of HFpEF and hold promise for improving both diagnosis and prognosis. Each biomarker examined in this paper reflects a distinct biological process implicated in HFpEF:

Galectin-3 plays a central role in myocardial fibrosis and remodeling. Elevated levels have been consistently associated with adverse outcomes in HFpEF patients.

Soluble ST2 (sST2) is a marker of cardiac stress and inflammation, providing prognostic information beyond natriuretic peptides.

Growth Differentiation Factor-15 (GDF-15) reflects oxidative stress and tissue injury, and has shown utility in risk stratification.

Nepriylsin, an enzyme involved in natriuretic peptide degradation, offers both diagnostic and therapeutic implications, especially in light of neprilysin inhibitor therapies (e.g., sacubitril/valsartan).

Unlike natriuretic peptides alone, these novel biomarkers provide a multi-dimensional view of HFpEF, capturing both structural and functional aspects of the disease. Moreover, studies have shown that combining multiple biomarkers increases diagnostic accuracy and helps identify distinct HFpEF phenotypes, which could guide individualized treatment approaches. Despite these advances, several challenges remain. Many biomarker studies are limited by small sample sizes, lack of standardization, and variability in reference ranges. Additionally, the clinical adoption of biomarker-guided strategies requires further validation through large-scale prospective trials. There are also economic considerations, as routine testing for multiple biomarkers may not yet be feasible in all healthcare settings.

Nonetheless, the potential of these biomarkers to facilitate earlier and more precise detection of HFpEF cannot be overlooked. They could serve as an essential component of risk prediction models, help identify subclinical disease, and monitor responses to therapy—thus enabling a more proactive and personalized form of cardiovascular care.

Conclusion

In conclusion, novel biomarkers offer a promising new dimension in the early detection and management of Heart Failure with Preserved Ejection Fraction. By targeting key pathophysiological mechanisms—such as fibrosis, inflammation, oxidative stress, and neurohormonal imbalance—biomarkers like galectin-3, sST2, GDF-15, and neprilysin provide valuable clinical information that traditional diagnostics may miss. As our understanding of HFpEF continues to evolve, integrating these biomarkers into diagnostic algorithms could significantly improve patient outcomes through earlier intervention, better risk stratification, and personalized therapy. Future research should focus on standardizing biomarker measurement, validating their predictive value across diverse populations, and assessing cost-effectiveness to support widespread clinical use. Ultimately, biomarker-based diagnostics represent a step toward precision cardiology, offering hope for one of the most complex and underdiagnosed forms of heart failure.

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