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REVIEW

Emerging biomarkers informed diagnosis and prognosis of heart failure

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ABSTRACT

Heart failure (HF) poses a significant burden on healthcare systems due to its cost of treatment, morbidity, and mortality. HF can arise from various cardiac dysfunctions or comorbidities such as hypertension, obesity, diabetes, kidney disease, and dyslipidemia. Biomarkers, especially natriuretic peptides (NP), play a crucial role in HF diagnosis and prognosis. Emerging biomarkers like galectin-3 and sST2 show promise, particularly for HFpEF and HFmrEF. Investigating cellular signatures at the single-cell level and somatic mutations in hematopoietic cells has revealed their links to HF progression and outcomes. Metabolomics profiling distinguishes between HFpEF and HFrEF, with distinct metabolite profiles indicating variations in pathophysiological mechanisms. This review article provides a concise overview of emerging biomarkers for diagnosis and prognosis of HF. It is apparent that the future of HF diagnosis and treatment should focus on comprehensive single-cell multi-omics panels, combining transcriptomics, metabolomics, and proteomics. This approach will aid in identifying more precise biomarkers and risk factors related to the HF phenotype, allowing for improved diagnostics and targeted therapies.

KEYWORDS

Heart failure biomarkers; Cardiovascular risk factors; Diagnostic biomarkers; Prognostic biomarkers

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Introduction

Heart failure (HF) remains challenging to clinicians, scientists, and healthcare systems, resulting in a significant cost, morbidity, and mortality burden. Ideally, HF is a composite clinical syndrome attributable to multiple etiologies and a progressive condition where the heart ceases to supply blood to the peripheral organs required to meet the body's metabolic requirements. According to the canonical definition of HF, "HF is a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide (NP) levels and/or objective evidence of pulmonary or systemic congestion" [1]. Nevertheless, any dysfunction of cardiac activity could originate in the heart itself or may be because of comorbidities occurring as cardiovascular risk factors like hypertension, obesity, diabetes mellitus, kidney disease, and dyslipidemia. Over recent years, knowledge has expanded after extensive investigations and a thorough understanding of the pathophysiological mechanisms underlying HF.

HF phenotypes are classified based on left ventricular ejection fraction (LVEF). HF with diminished LVEF is also known as systolic heart failure, a condition in which heart muscles fail to contract effectively, resulting in reduced levels of oxygen-rich blood pumped out to the body. When LVEF is about 50-70% termed normal, it is normal to perform regular activities by the body. A borderline LVEF (41-49%), also termed as mid-range LVEF (HFmrEF), means oxygenated blood is not adequately pumped out of the chamber, and symptoms become noticeable during activity. A reduced EF (HFrEF) means the heart is pumping ≤40 % of blood from the chamber, not enough for maintaining regular activities, and symptoms become noticeable even during rest. Heart failure with preserved ejection fraction (HFpEF), a type of diastolic heart failure, is characterized by ventricles unable to relax as required for normal ventricular filling (or when the ventricles rest) despite the regular and proper contraction of the heart muscle.

Predicting the onset of HF is a complex challenge because it can develop gradually over time and is often preceded by other cardiovascular risk factors and conditions. However, healthcare professionals use several risk factors, signs, and tools to assess an individual's risk of developing HF. These can aid in identifying individuals at a higher risk of developing HF in the future. These include hypertension, coronary artery disease, diabetes, obesity, smoking, family history and lifestyle factors. It is evident that biological biomarker measurement along with clinical signs and symptoms risk scoring such as Framingham Heart Failure Risk Score [2] or the American College of Cardiology/American Heart Association (ACC/AHA) risk calculator [3], proved to be useful to estimate an individual's risk of developing HF based on various factors. While these methods can help assess the risk of developing HF, predicting its onset with absolute certainty is challenging. Early detection, prevention, and management of underlying risk factors and conditions are crucial in reducing the likelihood of HF and its associated complications.

A biomarker-based approach would be more effective to target since it gives precise information about HF, determines its severity risk assessment for future events, and guides therapeutic regimens. Several biomarkers are relevant to

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diagnosis prognosis, and even biomarker-guided therapy for preventing and treating HF has been implicated. In addition to the top clinical diagnosis, the most useful circulating biomarker for HF, NP, can vary in its prognostic power based on the HF phenotype and profile of comorbidities. Alternative biomarkers, including galectin-3 and sST2, appear to improve the predictive value of NPs, particularly in individuals with increased HF risk [4]. An increasing prevalence of HFpEF and HFmrEF has been noticed in developing and developed countries recently compared to stabilized treatment options of HFrEF phenotype [5]. While we could understand in more depth the causes and treatment of HPrEF, there is a scarcity of knowledge behind the causes of HFpEF, triggering factors for the transformation of HFpEF to HFrEF phenotype, and inter-relationship between HF and various CV risk factors make it challenging to tackle with multifactorial etiologies to consider rather than a disease which has known targets. The vast majority of HF remains asymptomatic in young adults, although it can develop symptomatic in later years. Therefore, we aim to highlight a few emerging evidence-based biomarker strategies in HF with specific attention to its different phenotypes established appropriately compatible with the current definition of HF for its diagnosis and prognosis.

Inflammation and HF

Inflammation in cardiomyocytes in the context of HF has been studied in recently published investigations. A mechanism proposed by Mao et al. identified the role of bile acid intermediates as a mediator of inflammation by triggering mitochondrial damage and mtDNA release, which, in turn, triggers type I interferon responses and AIM2 inflammasome activation, thereby contributing to HF progression and chronic myocardial inflammation [6-8]. Metabolic derangement caused by CRAT suppression in a failing heart led to an increase in intracellular cholesterol catabolism through the bile acid pathway, which further links elevated levels of bile acid synthesis and activation of the inflammatory cascade. It is yet unclear if circulating levels of bile acid intermediates could be used as a diagnostic for HF assessment.

A recent study by Girerd et al. identified plasma multiprotein biomarkers which improved incident HF prediction in 3 large cohorts of the elderly (HOMAGE cohort [Heart Omics and Ageing], ARIC study [Atherosclerosis Risk in Communities], and FHS [Framingham Heart Study] when added to NP and clinical risk factors. Proteins identified to be linked with incident HF in all cohorts were BNP (brain natriuretic peptide), eukaryotic translation initiation factor 4E-BP1 (4E-binding protein 1), Gal-9 (galectin-9), hepatocyte growth factor (HGF), NT-proBNP (N-terminal pro-B-type natriuretic peptide), THBS2 (thrombospondin-2), TGF-alpha (transforming growth factor alpha), and U-PAR (urokinase plasminogen activator surface receptor) [9]. Moreover, these proteins were found to be related to inflammatory (e.g., TNF and interleukins) and remodeling (e.g., extracellular matrix and apoptosis) pathways, indicating the pivotal role of inflammation in HF pathogenesis.

The Cardiovascular Heart Study (CHS) by Niezen S et al. and group reported elevated plasma levels of ketone bodies (3-hydroxybutyrate, acetoacetate, and acetone) at baseline were found to be associated with incident HF and all-cause mortality in older adults, independent of metabolic and cardiovascular covariates [10]. Failing heart senses a shortage of energy due to reduction in mitochondrial oxidative capability. Altered energy metabolism from glucose to ketone bodies in the setting of ageing could be a triggering factor in progressively failing heart, which warranted the role of ketone body production and consumption to be further evaluated in the context of HF. Importantly, ketone body levels were able to predict HFrEF significantly but not HFpEF. Moreover, there is a report that BNP induced a rise in ketone body production in the liver for its use as an alternative fuel in failing heart [11].

Cellular signatures in HF

A more advanced view of cellular signatures in HF phenotype can be achieved by intracellular gene expression at a single cell level determined with spatially resolved information using single-cell RNA-seq (scRNA-seq) with spatially resolved transcriptomics (ST) [12]. These are the most powerful technologies for unraveling the molecular and cellular complexities of HF phenotypes. It enables researchers to examine the heterogeneity of cell populations, identify disease-specific markers, and gain a deeper understanding of the underlying mechanisms. This information can ultimately lead to improved diagnostics and targeted therapies for HF patients.

A study by Dorsheimer et al. demonstrated that clonal hematopoiesis of indeterminate potential (CHIP), attributable to somatic mutations, is more common as people age and is linked to inflammation and atherosclerosis. Their findings imply that somatic mutations in hematopoietic cells, particularly those in the two most frequently altered CHIP driver genes, Tet methylcytosine dioxygenase 2 (TET2) and DNA methyltransferase 3 alpha (DNMT3A), may be strongly linked to the development and poor prognosis of chronic HF [13]. Pascual-Figal et al. discovered in another study that HFrEF patients frequently have somatic mutations that induce clonal hematopoiesis and that these mutations are linked to faster HF progression independent of ischemia or non-ischemic cause. In individuals with mutations in either DNMT3A or TET2, HF progression accelerated significantly in terms of death (hazard ratio [HR]: 2.79), death or hospitalization for HF (HR: 3.84), and HF-related death or HF hospitalization (HR: 4.41) [14]. In an observational study, circulating monocyte cells of patients with DNMT3A CH driver mutations and cardiovascular disease demonstrated an elevated expression of inflammatory genes at the single-cell level [15]. The gene expression profiles of NK cells, monocytes, and CD4+ T cells with DNMT3A mutations were shown to be changed, according to a recent study by Abplanalp et al. In monocytes, there was a greater elevation of phagocytosis and inflammation-related genes, while in NK and T cells, there was a greater emphasis on effector function and activation markers. In addition, the mutant monocytes and T cells had enhanced paracrine signaling pathways compared to wild-type monocytes and T cells. According to the results, HF individuals have poor prognoses because of cell-intrinsic effects associated with DNMT3A mutations in circulating immune cells [16].

Conserved metabolomics profiling in HF

More recently, a metabolomic study targeted the knowledge gap on whether myocardial fuel flexibility is compromised in case HFpEF, HFrEF in the settings of marked obesity and diabetes [17]. HFpEF metabolite profile exhibited lower fatty

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acid metabolites compared to HFrEF, suggesting decreased fatty acid use as a source of energy. Alternative fuel use has also been compromised, as evident by lower levels of ketones and metabolites of TCA and BCAA in HFpEF. This shows that HFpEF patients with obesity and diabetes could be discriminated from HFrEF using distinct conserved metabolic profiling at the tissue level.

Another metabolomics study of patients with new onset HFpEF seems to be having a varied metabolite profile when compared to patients with new onset HFrEF in the setting of comorbidities such as diabetes and kidney dysfunction [18]. This in turn suggests the involvement of different pathophysiological mechanisms attributed related to the phenotype. Key metabolites in this exploratory study were found to be elevated in HFpEF reflecting fibrosis (hydroxyproline), oxidative stress (symmetrical dimethylarginine), and increased state of inflammation (alanine, cystine, and kynurenine). Moreover, impaired cell signalling, mitochondrial dysfunction, and impaired lipid metabolism were also evident due to lowered levels of cGMP and cAMP, L-carnitine, and lysoPC (18:2), respectively, in patients with HFpEF when compared to HFrEF. Endothelial dysfunction was also evident due to lower levels of serine and arginine in HFpEF.

Conclusions

The future of HF diagnosis, prognosis, and treatment methods needs to be developed based on a single-cell multi-omics panel that combines single-cell transcriptomics with spatial resolution, metabolomics, and proteomics. This will provide a more detailed picture and knowledge of heart disease processes at the microscopic level. To address this, a more complete identification of biomarkers informed perspective of cardiovascular risk factors and non-cardiovascular risk variables linked with the HF phenotype is required.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

1. Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, et al. Universal definition and classification of heart failure: a report of the heart failure society of America, heart failure association of the European society of cardiology, Japanese heart failure society and writing committee of the universal definition of heart failure. J Card Fail. 2021;27(4):387-413.
2. D'Agostino Sr RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008;117(6):743-753.
3. Goff Jr DC, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(25_suppl_2):S49-S73.
4. Berezin AE, Berezin AA. Biomarkers in heart failure: from research to clinical practice. Ann Lab Med. 2023;43(3):225-236.
5. Vasan RS, Xanthakis V, Lyass A, Andersson C, Tsao C, Cheng S, et al. Epidemiology of left ventricular systolic dysfunction and heart failure in the Framingham study: an echocardiographic study over 3 decades. JACC Cardiovasc Imaging. 2018;11(1):1-11.
6. Mao H, Angelini A, Li S, Wang G, Li L, Patterson C, et al. CRAT links cholesterol metabolism to innate immune responses in the heart. Nat Metab. 2023;5:1382-1394.
7. Lim GB. Cholesterol catabolism and bile acid synthesis in cardiomyocytes promote inflammation and heart failure. Nat Rev Cardiol. 2023;20:647.
8. Tong D, Hill JA. Bile acid binds heart failure and inflammation. Nat Metab. 2023;5:1260-1261.
9. Girerd N, Levy D, Duarte K, Ferreira JP, Ballantyne C, Collier T, et al. Protein biomarkers of new-onset heart failure: insights from the heart omics and ageing cohort, the atherosclerosis risk in communities study, and the Framingham heart study. Circ Heart Fail. 2023;16(5):e009694.
10. Niezen S, Connelly MA, Hirsch C, Kizer RJ, Benitez ME, Minchenberg S, et al. Elevated plasma levels of ketone bodies are associated with all-cause mortality and incidence of heart failure in older adults: the CHS. J Am Heart Assoc. 2023;12(17):e029960.
11. Manolis AS, Manolis TA, Manolis AA. Ketone bodies and cardiovascular disease: an alternate fuel source to the rescue. Int J Mol Sci. 2023;24(4):3534.
12. Long X, Yuan X, Du J. Single-cell and spatial transcriptomics: advances in heart development and disease applications. Comput Struct Biotechnol J. 2023;21:2717-2731.
13. Dorsheimer L, Assmus B, Rasper T, Ortmann CA, Ecke A, Abou-El-Ardat K, et al. Association of mutations contributing to clonal hematopoiesis with prognosis in chronic ischemic heart failure. JAMA Cardiol. 2019; 4(1):25-33.
14. Pascual-Figal DA, Bayes-Genis A, Díez-Díez M, Hernández-Vicente Á, Vázquez-Andrés D, de la Barrera J, et al. Clonal hematopoiesis and risk of progression of heart failure with reduced left ventricular ejection fraction. J Am Coll Cardiol. 2021;77(14):1747-1759.
15. Abplanalp WT, Mas-Peiro S, Cremer S, John D, Dimmeler S, Zeiher AM. Association of clonal hematopoiesis of indeterminate potential with inflammatory gene expression in patients with severe degenerative aortic valve stenosis or chronic postischemic heart failure. JAMA Cardiol. 2020;5(10):1170-1175.
16. Abplanalp WT, Schuhmacher B, Cremer S, Merten M, Shumliakivska M, Macinkovic I, et al. Cell-intrinsic effects of clonal hematopoiesis in heart failure. Nat Cardiovasc Res. 2023;2:819-834.
17. Hahn VS, Petucci C, Kim MS, Bedi Jr KC, Wang H, Mishra S, et al. Myocardial metabolomics of human heart failure with preserved ejection fraction. Circulation. 2023;147(15):11471161.
18. Hage C, Löfgren L, Michopoulos F, Nilsson R, Davidsson P, Kumar C, et al. Metabolomic profile in HFpEF vs HFrEF patients. J Card Fail. 2020;26(12):1050-1059.

https://doi.org/10.61577/ijcri.2023.100003