Aging Pathobiology and Therapeutics 2025; 7(2): 129-131 ***129***
DOI: 10.31491/APT.2025.06.176

Biomarkers for prognostic stratification in chronic heart failure in older patients

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This article belongs to the Special Issue: Oxidative Stress and Mitochondrial Dysfunction in aging

Abstract

Chronic heart failure (CHF) is a common complication of cardiovascular diseases in older adults. It has complex pathogenesis and different biomarkers to assess this process. Only natriuretic peptides are recommended in current guidelines to diagnose CHF. The role of other markers remains unclear. Some studies showed prognostic value of such markers as sST2, galectin-3, troponins. We need further investigations to find markers for assessing prognosis in older adults with CHF to choose the optimal treatment strategy for them and prolong their lives.

Keywords: Chronic heart failure, NT-proBNP, sST2, galectin-3, troponins, older patients

Chronic heart failure (CHF) is a clinical syndrome consisting of symptoms (*e.g.* breathlessness, ankle swelling, and fatigue) and signs (*e.g.* elevated jugular venous pressure, pulmonary crackles, peripheral edema) resulting from functional and/or structural disorders, that lead to decreased cardiac output and/or increased filling pressure of the heart at rest or on exertion and/or increased level of natriuretic peptides [1, 2]. CHF is a common complication of cardiovascular diseases, which remain a leading cause of death worldwide. The risk of developing it increases with age [3]. Due to the increase in life expectancy, an increase in the number of patients with CHF is awaited. In the coming decades, the prevalence of heart failure is projected to increase by 34% [4]. Survival rates worsen as the age increases at the time of diagnosis [5]. Recent study showed a rise in the mortality rate from heart failure among adults over the age of 75 in the United States since 2012 [3].

The pathogenesis of heart failure is complex and diverse. The pathological processes that lead to its development continue to be studied. Arterial hypertension, obesity, and cardiomyocyte damage of any origin cause inflammation, which, in combination with mechanical stretch and neurohumoral mechanisms, leads to the development of oxidative stress [6]. This can lead to remodeling, fibrosis and further myocardial damage. Furthermore, heart failure itself can cause oxidative stress [6]. A vicious circle can be seen in the pathogenesis of heart failure. At the same time, depending on the CHF phenotype, certain peculiarities of pathogenesis can be identified. In patients with systolic dysfunction, changes to the myocardium following injury lead to pathological ventricular remodeling and dilatation, as well as changes in geometry and impaired contractility. Further changes may be associated with new myocardial damage or increased activity of the pressor systems in response to decreased left ventricular systolic function [2]. Diastolic dysfunction is the basis of CHF with a preserved ejection fraction. It develops due to chronic inflammation causing endothelial dysfunction, resulting in impaired relaxation and rigidity of the left ventricle [2]. These are usually patients with hypertension, diabetes, and obesity [2, 7].

Biomarkers that may reflect different pathological processes in CHF have been identified [6, 8]:

- natriuretic peptides (B-type natriuretic peptide (BNP), N-terminal pro–B-type natriuretic peptide (NT-proBNP), atrial natriuretic peptide (ANP), mid-regional pro-atrial natriuretic peptide (MR proANP));
- micro RNAs;

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Received: 23 June 2025 / Accepted: 26 June 2025
Published: 27 June 2025

- markers of myocardial injury (high-sensitivity troponin I/T (hs-TnT/I), creatine kinase MB (CK-MB), myosin light chain 1, heart-type fatty acid binding protein (hFABP));
- markers of cardiac remodeling (soluble suppression of tumorigenesis-2 (sST2), galectin-3, growth differentiation factor 15 (GDF15), matrix metalloproteinase (MMP) 2, 3, 4, 8, 9, tissue inhibitor of metalloproteinase (TIMP) 1, 4), collagen propeptides (procollagen peptide type III-N-terminal (PIIINP), collagen C-telopeptide type I (ICTP));
- markers of inflammation (C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), interleukin (1, 2, 6, 8, 10, 18), cancer antigen 125 (CA-125), procalcitonin, lipoprotein-associated phospholipase A2 (LP-PLA2), tumor necrosis factor-like weak inducer of apoptosis (TWEAK), fas /apoptosis 1 antigen (Fas/APO-1), osteoprotegerin);
- markers of oxidative stress (myeloperoxidase (MPO), quiescin Q6, oxidized LDL, urinary biopyrrins).

To date the natriuretic peptides BNP and NT-proBNP are the closest to ideal laboratory markers for diagnosing CHF, and are the only ones recommended for this purpose according to current clinical guidelines [1, 2, 8]. Most current guidelines do not include biomarkers for risk assessment in cardiovascular diseases due to the lack of a convincing evidence base. Nevertheless, according to ACC/AHA guidelines from 2017, sST2, galectin-3 and hs-TnI/T can be used for prognostic stratification in addition to NT-proBNP, and combining these biomarkers provides more information than assessing them individually [6, 8, 9]. These biomarkers reflect different processes of CHF pathogenesis.

Hs-TnT/I are produced only in heart. Their elevation in CHF is associated with cardiomyocyte damage, apoptosis or necrosis due to different causes: transient elevations of left ventricular end-diastolic pressure, with reversible stretch-induced stunning in the absence of ischaemia, inflammation, neurohormonal activation, increased wall tension, supply-demand mismatch, *etc*. [10].

Soluble ST2 is primarily produced outside the heart in response to hemodynamic overload, inflammation, and stimulation of fibrosis, which is characteristic of CHF [8]. sST2 acts as a decoy receptor that binds to interleukin-33, thereby preventing its interaction with the membrane-bound ST2 isoform [11, 12]. Consequently, elevated sST2 levels can negate the beneficial effects of the IL-33/ST2L system, promoting cardiac hypertrophy, myocardial fibrosis and ventricular dysfunction [11].

BNP/NT-proBNP are produced only by cardiac tissue, resulting in end-diastolic wall stress in the ventricular and atrial myocardium. Therefore, an increase in NP levels is generally caused by volume expansion and/or pressure overload. By binding to multiple NP receptors, NPs lead to natriuresis, diuresis, vasodilation, improved myocardial relaxation and reduced myocardial fibrosis [13].

Cardiac macrophages secrete galectin-3, which promotes fibroblast proliferation and collagen deposition and leads to adverse cardiac remodeling and fibrosis [14]. A more detailed study of the role of galectin-3 in cardiac remodeling revealed that it was localized to the sites of fibrosis, co-localizing with fibroblasts and macrophages, but not with cardiomyocytes [15]. Galectin-3 may also increase inflammation by activating macrophages and attracting monocytes [14]. Researchers have also identified galectin-3 as a potentially important mediator of removal of advanced glycosylation end-products [15].

It seems promising to use these markers in isolation or as part of multi-marker models to determine the prognosis of patients with CHF [16, 17]. This can help in choosing the optimal treatment strategy for patients, especially older adults, and prolonging their lives.

Conclusions

Thus, the four recommended biomarkers (BNP/NT-proBNP, sST2, galectin-3, and hs-TnI/T) reflect different processes of CHF pathogenesis and complement each other successfully. Further study of the interrelationships between processes occurring in the heart and other organs in CHF in older adults is necessary. This could help to identify biomarkers or create a multi-marker prognostic model that could be used to evaluate risk in CHF in older patients.

Declarations

Authors' contributions: Conceptualization: Kiselev AR; Original draft, Dorogoykina KD; Review & editing, References curation, Kiselev AR.

Availability of data and materials: Not applicable.

Financial support and sponsorship: None.

Conflicts of interest: All authors declared that there are no conflicts of interest.

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

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Cite this article as: Dorogoykina KD, & Kiselev AR. Biomarkers for prognostic stratification in chronic heart failure in older patients. *Aging Pathobiol Ther*, 2025, 7(2): 129-131. doi: 10.31491/APT.2025.06.176