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Review

New Markers Used in the Diagnosis of Heart Failure

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ABSTRACT

Heart failure (HF) is still a major global health concern, contributing significantly to morbidity and mortality. While classic diagnostic methods like B-type natriuretic peptide and N-terminal pro-BNP are still useful for risk assessment, new biomarkers offer increased diagnostic and prognostic capacities. Novel candidates such as galectin-3, soluble suppression of tumorigenicity-2, growth differentiation factor-15, cystatin C, neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, and specific microRNAs shed light on cardiac remodeling, fibrosis, renal dysfunction, and inflammatory pathways. Imaging methods such as echocardiography, Doppler techniques, and cardiac magnetic resonance imaging have advanced to complement biomarker data, enhancing diagnosis accuracy and personalized treatment plans. The integration of multimarker methods and digital health monitoring has potential for precision medicine in HF therapy. However, the practical translation of these biomarkers is hampered by assay variability, cost-effectiveness issues, and a diverse patient group. This review addresses the current and emerging biomarkers, advanced imaging techniques, and multimarker approaches in the diagnosis, risk stratification, and management of heart failure, as well as the challenges and future directions for their clinical implementation.

Keywords: Biomarker panels, cardiac remodeling, fibrosis, heart failure.

Global heart failure (HF) is one of the leading causes of mortality worldwide. The symptoms or signs it presents pose significant challenges in diagnosis and treatment strategies. These challenges are not limited to this, as over time, diagnostic and treatment methods have improved through traditional clinical evaluations and subsequently gained momentum toward advanced biomarker tests and imaging techniques. One of the most important diagnostic methods for HF is the use of biomarkers known as B-type natriuretic peptide (BNP) and amino-terminal pro-BNP (NT-proBNP). Studies have proven the prognostic importance of these two biomarkers. The NT-proBNP technique is a highly accurate reflection of cardiac function and is of utmost importance in the diagnosis of HF. It has been emphasized that there is a significant correlation between the production of BNP levels in response to myocardial wall stress and the severity of HF.[1] In a similar study, it was reported that NT-proBNP was used as an early diagnostic method and prevented the development of advanced symptoms of HF.[2]

The usefulness of these biomarkers has prompted further investigation into complementary diagnostic markers such as galectin-3, which, when combined with NT-proBNP, has shown promise in the quick assessment of acute HF. The integration of these biomarkers in diagnostic algorithms improves sensitivity and specificity, addressing diagnostic problems in acute cases.[3]

Echocardiography remains a cornerstone in monitoring heart function and structure, while imaging techniques have changed as well. The use of Doppler techniques has improved the examination of ventricular function, confirming clinical and biochemical findings. Furthermore, cardiac magnetic resonance imaging provides deep insights into myocardial structure and function, displaying discordant hyperenhancement patterns that can help differentiate ischemia from non-ischemic HF.[4]

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The relationship between these emerging diagnostic tools and quality of care metrics highlights their significance. demonstrate how quality improvement programs, which prioritize prompt and accurate diagnosis through defined protocols that include biomarker testing and echocardiography, have improved care delivery results in HF populations. This shows a movement toward evidence-based, patient-centered approaches to HF management.[5]

The use of electrocardiogram (ECG) and chest X-rays remains essential, particularly in community and primary care settings where access to advanced imaging modalities may be limited. These tools play a critical role in the initial evaluation of patients by helping identify arrhythmias, conduction abnormalities, ischemic changes, or pulmonary congestion that may accompany HF. However, neither ECG nor chest X-ray possesses sufficient sensitivity or specificity to confirm HF on its own; instead, they serve as complementary methods that support clinical suspicion and guide further diagnostic testing.[6] Consistent with findings from various studies, their diagnostic value is strongly dependent on the clinical context, reinforcing that no single test is adequate for establishing a definitive diagnosis of HF.[7]

NEW BIOMARKERS IN HEART FAILURE

The role of galectin-3 in HF pathogenesis is based on its pro-fibrotic action. It has been demonstrated to stimulate cardiac fibroblasts, resulting in increased collagen deposition and fibrosis inside the myocardium. This process can have a deleterious impact on cardiac function over time, contributing to the clinical symptoms of HF.[8] Research has shown that elevated levels of galectin-3 are associated with poor outcomes in HF patients, highlighting its potential as a predictive biomarker.[9] Studies have highlighted galectin-3's ability to reflect ongoing cardiac remodeling, which is critical in patient treatment and risk classification.[10]

Galectin-3 has shown promise in identifying patients with and without HF, especially when combined with other biomarkers such as NT-proBNP. While NT-proBNP predominantly shows volume overload, galectin-3 sheds light on fibrotic processes, making it useful for understanding the underlying pathophysiology of HF.[11] Several studies highlight that incorporating galectin-3 measures with established biomarkers can greatly boost predictive accuracy in different patient populations, notably during acute decompensation.[12]

Specific studies have connected galectin-3 levels to therapeutic results that exceed standard measures. For instance, in patients with acute HF requiring extracorporeal life support, galectin-3 was discovered as a promising predictive factor, indicating its relevance in guiding therapeutic options.[13]

Changes in galectin-3 levels over time have been observed to correlate with illness progression, highlighting the importance of monitoring therapy efficacy and disease trajectory.[14]

The temporal dynamics of galectin-3 expression are noteworthy, as its levels may fluctuate with disease progression, impacting clinical decision-making. Notably, recent studies examining myocardial infarction patients undergoing primary percutaneous coronary intervention highlight that changes in galectin-3 concentrations could predict both immediate outcomes and longer-term cardiac function.[15]

Markers Indicating Renal and Target Organ Function

Marker methods vary in HF. Neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 are techniques used to monitor kidney function, particularly in patients with HF. Kidney failure and dysfunction are indicators of HF, highlighting the critical interaction between cardiac and renal pathophysiology. The NGAL is a protein that is rapidly upregulated in response to acute kidney injury and released by various cells, including neutrophils and renal tubular cells. Elevated NGAL levels have been associated with HF, particularly during acute exacerbations, demonstrating its role as a predictive biomarker for worsening kidney function. Scientific research and studies show that increased NGAL levels in plasma and urine are associated with renal dysfunction in patients with acute decompensated HF and provide valuable information about the severity of renal failure.[16]

Galectin-3

The protein galectin-3, which is linked to cardiac fibrosis and remodeling, is among the most prominent new biomarkers. A poor prognosis for HF patients, especially those with a lower ejection fraction, has been linked to elevated levels of galectin-3. This protein is a useful marker for risk assessment and management because it reflects underlying pathophysiological processes like inflammation and fibrosis. Data points to a role for galectin-3 in detecting more advanced stages of HF,

suggesting that its predictive power goes beyond that of conventional markers.[17]

Soluble ST2

Another emerging biomarker is soluble suppression of tumorigenicity-2 (sST2), which is associated with myocardial stress and activation of fibrosis. Studies indicate that sST2 levels correlate with adverse outcomes in HF patients, presenting new possibilities for risk stratification and targeted therapy. This biomarker's unique association with cardiac remodeling processes enhances its diagnostic relevance, particularly in managing patients with complex HF phenotypes.[18]

MicroRNAs

MicroRNAs (miRNAs) have surfaced as promising indicators for the diagnosis and prognosis of HF. Certain circulating miRNAs, such as miR-21-5p and miR-155-5p, have demonstrated strong associations with HF issues and may offer information on how the disease develops and how well treatments work. The discovery of these short non-coding RNAs represents a new frontier in the search for biomarkers and highlights the growing understanding of gene control in heart disorders.[19]

Cystatin C

Another biomarker that is gaining popularity is cystatin C, which is especially useful for evaluating renal function, which is frequently impaired in individuals with HF. An increased risk of cardiac events is linked to elevated cystatin C levels, suggesting that it may be useful in the composite evaluation of renal and cardiac health. Clinicians may be able to effectively treat the intricate interactions between HF and renal impairment using an integrative strategy.[17]

Growth Differentiation Factor 15

It has been demonstrated that in populations with HF, growth differentiation factor 15 (GDF-15) can predict morbidity and mortality. Increased GDF-15 levels provide information about the severity of the disease and how well treatments are working by correlating with inflammation and cardiomyocyte stress. When these biomarkers are combined with more conventional methods, such as natriuretic peptide assays, the diagnostic panel that medical professionals have access to may be expanded, allowing for more individualized treatment plans.[20]

CLINICAL USE AND LIMITATIONS OF NEW BIOMARKERS

In heart failure, the clinical application of biomarkers has grown dramatically, aiding in the diagnosis, prognosis, and treatment of the illness. B-type natriuretic peptide and its NT-proBNP are two of the most well-established biomarkers in use today; they are both essential for identifying and classifying HF patients according to their risk. Research shows that NT-proBNP levels can predict hospitalization and death risks in patients with HF and have a high correlation with cardiac dysfunction. Clinical trials that have used NT-proBNP testing to optimize therapeutic approaches demonstrate how well these biomarkers direct treatment regimens.[21]

Although BNP and NT-proBNP are useful, they have significant drawbacks. Numerous non-cardiac diseases, including obesity and renal dysfunction, can have an impact on these biomarkers, thereby causing results to be misinterpreted and additional HF phenotypes to be missed. Even though these biomarkers are important for the diagnosis of HF, their sensitivity and specificity are insufficient for HF with preserved ejection fraction. In order to improve diagnostic precision and prognostic potential for a variety of HF presentations, more biomarkers are being investigated.[22]

Other biomarkers, such as sST2 and cardiac troponin (cTn), have become important instruments in the treatment of HF in recent years. Cardiac troponins offer information on myocardial damage and are essential for the diagnosis of sudden HF. A multiparametric approach is necessary because the combination of several biomarkers, including BNP, cTn, and sST2, shows promise in enhancing risk classification and customizing patient-specific therapy. Studies show that although adding new biomarkers could improve prognostic abilities, incorporating them into standard clinical practice is still difficult because of differences in assay techniques and cost-effectiveness issues.[23]

MicroRNAs and other innovative possibilities may also be used as biomarkers in the future to modify therapy outcomes in HF. The roles of these new biomarkers in oxidative stress, inflammation, and cardiac remodeling, all important aspects of the pathogenesis of HF, are being studied. Given the differences in patient response and the need for individualized medical interventions, further study is needed to confirm these possible biomarkers and define their therapeutic value.[24]

FUTURE DIRECTIONS IN HEART FAILURE BIOMARKER RESEARCH

Investigating multimarker techniques, which combine established biomarkers such as BNP or its NT-proBNP with new candidates, is one notable avenue. A growing area of interest is the use of inflammatory indicators like GDF-15 and myeloperoxidase in therapeutic decision-making. According to certain research, GDF-15 levels are associated with negative cardiac remodeling, which may make them a predictor of the course of HF. Likewise, in patients with HF, including biomarkers linked to inflammation and myocardial damage, improves risk stratification. By addressing comorbidities and the many pathophysiological pathways that are inherent in HF, these multimodal techniques seek to give clinicians a more comprehensive knowledge of a patient's state.[25]

Heart failure and other cardiovascular disorders have been linked to miRNAs, which are tiny, non-coding RNA molecules that alter gene expression. Certain miRNAs, like miR-126 and miR-223, have been found to have the ability to distinguish between different forms of HF, underscoring their function as biomarkers with prognostic potential. According to some research, these miRNAs may be helpful biomarkers, but other studies show that their levels did not correlate with well-known cardiac markers such as NT-proBNP, indicating that more research may be necessary to fully understand their potential. The distinctive feature of miRNAs is their capacity to mirror the fundamental molecular mechanisms of HF, potentially resulting in tailored therapeutic approaches that focus on certain pathways impacted by these biomarkers.[26]

Researchers are looking at how genetic and epigenetic variables affect the production of biomarkers. Our knowledge of the causative pathways behind heart disease has advanced with the use of Mendelian randomization studies, which have started to clarify the connection between genetically determined inflammatory indicators and the risk of HF. Future research may be able to more precisely and sooner identify patients at high risk of HF by including genetic data into biomarker analysis.[27]

One developing area of biomarker research is the use of tissue proteomics and high-throughput analysis. Researchers can now identify and measure a wide range of proteins and metabolites in biological samples thanks to technologies like mass spectrometry, which may help them find new biomarkers for HF monitoring and early detection. These cutting-edge methods may lead to the validation of new biomarkers that capture the complexities of the pathophysiology of HF, such as cellular stress responses and metabolic abnormalities.[28]

Biomarker monitoring in HF is expected to undergo a revolution with the integration of digital health technologies, such as wearables and telehealth platforms. A thorough picture of a patient's cardiac health can be obtained by synchronizing biomarker levels with ongoing physiological monitoring of variables like blood pressure, heart rate variability, or even electrocardiographic changes. Based on real-time data, this data-driven method can enable more prompt interventions and customized therapies.[29-31]

In conclusion, the landscape of HF diagnosis is evolving from reliance on traditional biomarkers to a multimodal approach integrating molecular, imaging, and digital data. While BNP and NT-proBNP remain foundational, emerging markers such as galectin-3, sST2, GDF-15, NGAL, cystatin C, and specific miRNAs enhance diagnostic accuracy, prognostic stratification, and personalized therapy. Addressing challenges of standardization, cost, and real-world applicability will be crucial for improving outcomes in HF patients.

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