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Clinical markers in heart failure: a narrative review

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Abstract

Heart failure is a complex clinical syndrome that is one of the causes of high mortality worldwide. Additionally, healthcare systems around the world are also being burdened by the aging population and subsequently, increasing estimates of patients with heart failure. As a result, it is crucial to determine novel ways to reduce the healthcare costs, rate of hospitalizations and mortality. In this regard, clinical biomarkers play a very important role in stratifying risk, determining prognosis or diagnosis and monitoring patient responses to therapy. This narrative review discusses the wide spectrum of clinical biomarkers, novel inventions of new techniques, their advantages and limitations as well as applications. As heart failure rates increase, cost-effective diagnostic tools such as B-type natriuretic peptide and N-terminal pro b-type natriuretic peptide are crucial, with emerging markers like neprilysin and cardiac imaging showing promise, though larger studies are needed to confirm their effectiveness compared with traditional markers.

Keywords

Heart failure, biomarkers, diagnosis, prognosis, treatment, healthcare cost, monitoring

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Introduction

Heart failure (HF), a complex syndrome with cardinal features and impacted by various comorbidities, is becoming a major problem worldwide impacting approximately 1% to 2% of adults.[1–3] A study from 2019 estimated the global prevalence of HF to be approximately 56.19 million.[4] HF caused 5.05 million years of healthy life lost due to disability globally.[4]

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Approximately 5.8 million adults in the US are impacted by HF.[5] With increasing age and changing demographic dynamics, the mean expenditure on HF increased from $26,864 in 2009–2010 to $32,955 in 2017–2018, which represented a 23% increase in patients with HF.[6] This increase in expenditure comprised of the following: inpatient expenditure (7.3%), medication expenditure (21.2%), office-based expenditure (38.4%), outpatient expenditure (9.9%), emergency department (22.2%) and home health expenditure (65.6%).[6] Furthermore, estimates reveal that the total cost of HF is expected to increase from $30.7 billion to $69.8 billion in 2030.[7] Biomarkers are one of the potential solutions to the issue, given their non-invasive and less costly nature.[8] These markers can also help in differentiating HF from other causes that present with the same cohort of symptoms, for example in chronic obstructive pulmonary disease.[9–11] A biomarker-based strategy for HF management has been beneficial. For example, soluble isoform of suppression of tumorigenicity 2 (ST2) and galectin-3 have been correlated with mortality risk and used in serially-guided medical therapy. A few markers have been independently used to determine re-occurrence rates of HF. Natriuretic peptides have emerged as key players of point-of-care medicine and the diagnostic indices are further improved by use of troponin. However, these markers also have some limitations, including variation in bioavailability based on clearance, lack of sex-specific data and effects and limited data about pharmacokinetics. With the advent of newer markers, the increased costs associated with the markers might also emerge as a potential issue.[12] This narrative review was conducted in accordance with the principles outlined in SANRA.[13] The main parameters used to outline the narrative review included justification of the article's topic for readership, formulation of review question, description of literature search, referencing, scientific reasoning and data presentation. The aim of this narrative review was to discuss the biomarkers available for clinical use in patients with HF and the evidence for their use. For the purposes of this review, PubMed®, CINAHL and Google Scholar were used for the retrieval of articles with the following MESH terms: ("ambulatory care facilities"[MeSH Terms] OR ("ambulatory"[All Fields] AND "care"[All Fields] AND "facilities"[All Fields]) OR "ambulatory care facilities"[All Fields] OR "clinic"[All Fields] OR "clinics"[All Fields] OR "clinical"[All Fields] OR "clinically"[All Fields] OR "clinicals"[All Fields] OR "clinics"[All Fields]) AND ("biomarkers"[All Fields] OR "biomarkers"[MeSH Terms] OR "biomarkers"[All Fields] OR "biomarker"[All Fields]) AND ("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields]).

Classification of biomarkers

The mechanism of cardiac biomarkers is explained in Table 1.

Natriuretic peptides

BNP and NT-proBNP

Myocardial stretch leads to stimulation of B-type natriuretic peptide (BNP) receptors in the ventricles, which increases natriuresis to antagonize the effects of the neurohormonal system.[14] One form of this type of marker, N-terminal pro b-type natriuretic peptide (NT-proBNP), has a half-life of 70 min and approximately 50% is excreted through the kidneys.[15] Circulatory concentrations of the markers are relatively lower in healthy adults; however, women tend to have higher concentrations.[16] In one study, patients with acute decompensated HF had higher BNP levels that significantly correlated with the severity of the HF.[17] Reference limits for age were first

Table 1. The mechanism of cardiac biomarkers in heart failure.

Mechanism	Biomarkers
Myocardial stretch	BNP, NT-proBNP, MR-proANP
Myocyte injury	High-sensitivity troponin, troponin I, myosin light-chain I, heart-type fatty-acid protein, CK-MB
Oxidative stress	Myeloperoxidase, uric acid, oxidized low-density lipoproteins, urinary biopyrrins, urinary and plasma isoprostanes, plasma malondialdehyde
Neurohormonal activation	Norepinephrine, adrenomedullin, arginine vasopressin, copeptin, renin, angiotensin II, aldosterone, chromogranin A, MR-proADM, endothelin-1
Myocardial fibrosis	ST-2, galectin-3
Extracellular matrix remodeling structures	Matrix metalloproteinases, tissue inhibitors of metalloproteinases, microRNA
Apoptosis	Growth differentiation factor-15, insulin-like growth factor binding protein-7
Endothelial dysfunction	CD146, neutrophil gelatinase-associated lipocalin
Inflammation	C-reactive protein, TNF-α, soluble TNF receptors, Fas, interleukins (I, 6 and 18), osteoprotegerin, adiponectin
Renal biomarkers	Creatinine, BUN, eGFR, cystatin C, β-trace protein
Hepatic biomarkers	Liver function test
Hematological biomarkers	Hemoglobin, RDW, iron, ferritin, transferrin saturation

BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro b-type natriuretic peptide; MR-proANP, mid-regional pro-atrial natriuretic peptide; CK-MB, creatine kinase-MB; MR-proADM, mid-regional proadrenomedullin; ST-2, soluble isoform of suppression of tumorigenicity 2; CD146, cluster of differentiation 146; TNF, tumor necrosis factor; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; RDW, red cell distribution width.

investigated in the 'International Collaborative on NT-proBNP' study.[16] The 'B-type natriuretic peptide for Acute Shortness of breath EvaLuation', 'Improved Management of Patients With Congestive Heart Failure' and 'NT-proBNP for EValuation of dyspnoeic patients in the Emergency Room and hospital' studies all demonstrated either biomarker to be cost-effective.[18–20] BNP and NT-proBNP have prognostic value as well. Higher values on admission correlated with in-hospital admissions and mortality across all groups with HF.[21] In one study, NT-proBNP values > 986 pg/ml predicted death at 1 year ($P < 0.001$; 79% sensitivity and 68% specificity).[21] These values also demonstrated prognosis at 4 months post-discharge, implying that serial assessment of BNP or NT-proBNP can also identify patients at risk for remodelling.[22] The GUIDE-IT trial did not find NT-proBNP-guided therapy to be more effective than usual care in improving outcomes, including the primary end-point of HF hospitalization or cardiovascular mortality among patients with chronic HF with reduced ejection fraction (HFrEF).[23] NT-proBNP levels are correlated with the increased incidence of major cardiovascular events, severity of HF and determining prognosis after discharge.[23] However, the markers have not been shown to predict all-cause or cardiovascular-specific mortality unless cut-off values have been mentioned; these cut-off values are yet to be established. BNP-based point-of-care HF management reduced rates of left ventricular (LV) systolic dysfunction, diastolic dysfunction and HF.[24]

There are a few limitations to BNP testing. Patients with chronic kidney disease

tend to have higher BNP and NT-proBNP concentrations because of peptide accumulation or chronic volume overload.[25] Lower BNP and NT-proBNP values are observed in overweight and obese patients.[26] Additionally, proBNP-based studies have contradictory findings in elderly patients with HFpEF.[24]

ANP and mid-regional pro-atrial natriuretic peptide

Atrial stretch also causes increased atrial natriuretic peptide (ANP). The precursor protein, proANP, which is stable and has a longer half-life, has been observed to diagnose acute decompensated HF as well as BNP or NT-proBNP.[15] Furthermore, the GISSI-HF study demonstrated that proANP had prognostic accuracy for 4-year mortality among several novel and established biomarkers (area under the curve = 0.74; 95% confidence interval, 0.70, 0.76).[27] ANP has a potential therapeutic role as well by use of vasodilation and diuresis.[28] While the economic costs of developing proANP have not been specifically highlighted, the main limitation is a gradual increase in concentrations with age, which is difficult to interpret in the setting of HF.

Troponins

Myocardial necrosis is detected more specifically by high-sensitivity troponin (hsTn) compared with conventional assays. In one study in patients with acute decompensated HF (ADHF), hsTnT predicted the risk of death and therefore had a prognostic role.[29] In another study in patients with LV systolic dysfunction, elevated concentrations of hsTnI at baseline were associated with a significantly shorter time-to-first event.[30] The rate of progressive remodeling was also correlated with higher troponin levels.[31] The limitation to using hsTn assays is the relatively unspecific nature of elevated levels in patients with concomitant conditions such as ventricular enlargement, arrhythmias, thyroid diseases, stroke, pulmonary embolism, sepsis and shock.[32] The cost of using the assay is dependent upon the frequency of monitoring and has not been associated with increased efficiency.[33]

Heart fatty acid binding protein

Heart fatty acid-binding protein (H-FABP) is also released because of myocyte injury. It has been observed in cases of myocardial infarction with negative troponin and is associated with worse outcomes in myocardial infarction and HF.[34] The main benefit of using H-FABP is in acute emergency department settings where the pharmacokinetics of troponin assays can lead to prolonged length and cost of hospitalizations.[34] However, the values of the assay might also be altered in other non-myocardial cases such as pulmonary embolism.[34]

Soluble ST2

Soluble ST2, a protein member of the interleukin-1 receptor family, is released under conditions of myocardial and vascular strain. The role of ST2 has been primarily investigated as a prognostic marker in both acute and chronic HF.[35] The elevations of ST2 concentrations were significantly associated with higher rates of mortality at 1 year.[36] In a multimodal approach, the use of both ST2 and NT-proBNP accurately identified high-risk patients more often.[36] The main advantage of ST2 is that the concentrations are not influenced by factors such as obesity, age, atrial fibrillation or renal function. However, the use of mineralocorticoid receptor antagonists, β-blockers, angiotensin receptor blockers and angiotensin receptor–neprilysin inhibitors can all reduce concentrations of ST2 and limit their utility.[37] Additionally, data about the economic cost of ST2 are limited.

Galectin-3

Galectin-3 is a macrophage lectin product that plays a role in tissue fibrosis. In one study, increased galectin-3 concentrations were strongly associated with high rates of 60-day mortality (odds ratio, 10.3; $P < 0.01$) and recurrent HF within the same time frame.[38] However, the prognostic ability of galectin-3 in chronic HF is more variable.[39] The cost of using galectin-3 is expected to be high, given that the estimated price of a kit is approximately $300.[40]

Growth differentiation factor

Growth differentiation factor (GDF)-15 is another inflammation marker that is observed to be high in HF and myocardial infarction. Elevated levels of GDF-15 were associated with increased symptomatic severity and higher mortality.[41] The limitation of the marker is that high levels are also observed in certain malignancies and pregnancies.[42] The cost of the assay is much higher compared with that of conventional assays.[40]

Adrenomedullin and mid-regional precursor peptide

Adrenomedullin, a vasodilator, was observed to be elevated in patients with chronic HF due to diastolic LV dysfunction.[43] In one study, it was observed that mid-regional propeptide was higher in patients with ADHF and had the greatest accuracy for predicting death during the first year.[43] Additionally, it was an independent marker for prognostication and risk analysis in a 4-year time frame.[43]

Endothelin

In one study, high concentrations of endothelin were associated with poor diastolic performance and worse clinical outcomes, specifically in patients with HFrEF.[44] In the 'Catheter Sampled Blood Archive in Cardiovascular Diseases' trial, endothelin was observed to predict HF in patients undergoing coronary angiography.[44]

Insulin-like growth factor-binding protein 7

High levels of insulin-like growth factor-binding protein 7 (IGFBP7) have been associated with poor HF prognosis, especially in HF with preserved ejection fraction (HFpEF); and a higher baseline IGFBP7 was significantly correlated with worse diastolic function, higher E velocity ($\rho = 0.40$), E/E′ ($\rho = 0.40$), left atrial volume index ($\rho = 0.39$) and estimated right ventricular systolic pressure ($\rho = 0.41$; all $P < 0.001$) and weakly correlated with transmitral E/A ($\rho = 0.26$; $P = 0.006$).[45] Concentrations of IGFBP7 were also independently prognostic of death in patients with HFpEF.[45]

Parathyroid hormone

In one study, parathyroid hormone was correlated with natriuretic peptide levels in acute HF patients and accurately diagnosed HFpEF and severe HFrEF.[46] This might present a cost-effective alternative to many assays. However, the marker is non-specific and is also used in a large range of calcium- and bone-related diseases.

Myeloperoxidase

Myeloperoxidase (MPO) released by leukocytes has also been investigated in HF. Elevated levels of MPO in patients with acute HF have been associated with increased 1-year mortality and have been found to be more feasible for predicting HF in the 65–75-year-old population.[47]

Extracellular matrix modelling

An altered balance between matrix metalloproteinases (MMPs) and tissue inhibitors

Table 2. Summary of clinical biomarkers and their uses in heart failure.

Biomarker	Disease	Purpose	Cost	Advantages	Disadvantages
BNP and NT-proBNP	ADHF (HFrEF/HFpEF)	• Severity of disease • In-hospital admission rate and mortality • Point-of-care utility • Prognosis post-discharge	$	• Cost-effective • Widely available	• Need sex-adjusted values • Need specific cut-off values • Limited use in therapy response
ANP and MR-proANP	ADHF (HFrEF/HFpEF)	• Diagnosis • Prognosis • Used as therapy	NA	• Therapeutic role	• Need age-adjusted values • Cost not analyzed
Troponins	ADHF (HFrEF/HFpEF)	• Prognosis • Time-to-adverse event estimation	$	• Cost-effective • Widely available	• Unreliable with conditions causing demand ischemia
H-FABP	MI-AHF	• Diagnosis when initial troponins are negative	$$	• Use in emergency settings	• Unreliable with conditions causing demand ischemia
Soluble ST2	ACHF, CCHF	• Risk stratification • Prediction of mortality	NA	• Independent biomarker	• Cost not analyzed • Limited in case of mineralocorticoid antagonist use
Galectin-3	ACHF	• 60-day mortality • Recurrent HF prediction	$$$	• Prediction of recurrent HF	• Limited in CHF • Expensive
Growth differentiation factor	MI-AHF	• Mortality • Severity	$$$	• When clinical suspicion is high	• Expensive • Also in pregnancies/ malignancies
Adrenomedullin and MRPP	ADHF, CHF	• 1-year mortality risk prediction • Prognostication at 4 years	NA	• Independent of other confounders	• Cost not analyzed
Endothelin	CHF with reduced EF	• Recurrence in HF patients undergoing procedures	$$	• Possible use in a very specific cohort	• Not cost-effective
IGFBP-7	CHF with preserved EF	• Prognosis • Mortality	NA	• Diastolic remodeling • Independent markers	• Cost not analyzed

(continued)

Table 2. Continued.

Biomarker	Disease	Purpose	Cost	Advantages	Disadvantages
MPO	AHF	• 1-year mortality	$$	• For use in elderly	• Elevated in inflammatory conditions
Extracellular matrix modelling	CHF with reduced EF	• All-cause mortality • Monitoring response to therapy	NA	• Response to therapy	• Elevated in inflammatory conditions

BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro b-type natriuretic peptide; ADHF, acute decompensated heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; ANP, atrial natriuretic peptide; MR-proANP, mid-regional pro-atrial natriuretic peptide; NA, not applicable; H-FABP, heart fatty acid-binding protein; MI-AHF, myocardial infarction associated heart failure; ST-2, soluble isoform of suppression of tumorigenicity 2; ACHF, acute compensated heart failure; CCHF, chronic compensated heart failure; HF, heart failure; CHF, chronic heart failure; MRPP, mid-regional pro-adrenomedullin; EF, ejection fraction; IGFBP-7, insulin-like growth factor-binding protein 7; MPO, myeloperoxidase; AHF, acute heart failure.

of metalloproteinases can result in ventricular remodeling. MMP-2 was observed to be a predictor of cardiac mortality in HF patients.[48] MMP-3 and MMP-9 were found to predict all-cause mortality in patients with HFrEF.[49] In one trial, the response to spironolactone therapy was monitored using procollagen type III amino-terminal peptide and the impact of spironolactone therapy was significant in patients with elevated levels of the markers at baseline.[50] A summary of all the biomarkers and their uses is outlined in Table 2.

Future directions

There are a number of novel markers being studied including neutrophil gelatinase-associated lipocalin, soluble cluster of differentiation 146, pentraxin 3, neprilysin, resistin and microRNAs.[51] Cardiac imaging is also being evaluated as a marker in a few pilot studies. However, it is important to note that these newer markers have not been investigated in terms of risk-stratification, therapy and prognosis for HF management. In addition, point-of-care testing involving newer markers is one of the potential areas of development. A suggested point-of-care testing regimen using both conventional and novel biomarkers is shown in Figure 1. Further interventions should focus on screening, diagnosis, risk stratification and medical therapy in the form of compensated and decompensated HF by use of novel biomarkers. Interventions should also focus on discussing the same principles with respect to acute or chronic HF by use of novel biomarkers. There are certain limitations to the use of these novel biomarkers for point-of-care therapy in HF, which include marketing and large-scale development of the markers, regulated approval by authorities and clinical testing of their efficacy and safety.

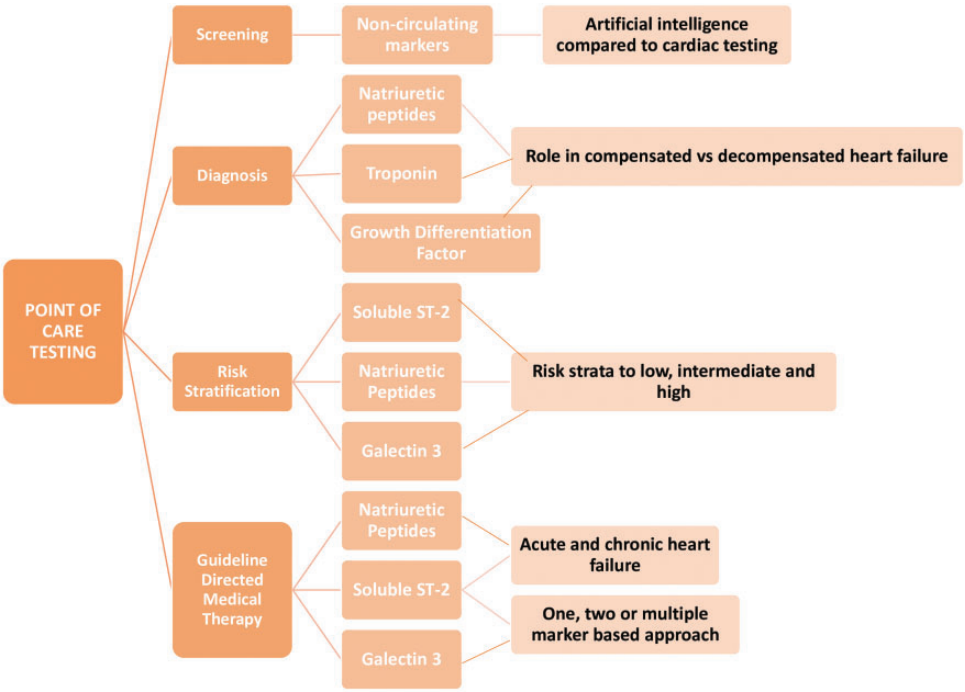

Figure 1. A suggested point-of-care testing regimen using both conventional and novel biomarkers for the management of heart failure. ST-2, soluble isoform of suppression of tumorigenicity 2. The color version of this figure is available at: http://imr.sagepub.com.

Conclusion

With the increasing prevalence of HF and the associated healthcare costs, it is important to employ tools that are cost-effective and specific for the pathology to optimize resources. BNP and NT-proBNP are used widely in patients with HF. However, new markers are also emerging, for example, neprilysin that might be an important landmark in this investigation. In addition, the use of markers with cardiac imaging might play a prominent role given the benefit of simultaneously using markers with concomitant imaging. As discussed earlier, certain biomarkers have been studied in specific cohorts and their evaluation should be extended to further groups of HF patients. These markers can be studied with respect to the widely available point-of-care HF model in order to improve outpatient outcomes. Further large-scale studies are needed to determine the impact of newer markers as compared with conventional markers.

Author contributions

Conceptualization: T.V.; data curation: N.J., M.F.; formal analysis: N.J.; investigation: M.F., N.J.; methodology: N.J.; project administration: T.V.; resources: T.V.; supervision: T.V.; validation: T.V.; visualization: N.J.; writing – original draft: N.J., M.F.; writing – review & editing: N.J., M.F., T.V.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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