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BIOMARKERS OF HEART FAILURE (WH WILSON TANG & J GRODIN, SECTION EDITORS)

Reappraisal of Inflammatory Biomarkers in Heart Failure

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Abstract

Purpose of Review Inflammation has been shown to be an important factor in the development and progression of heart failure (HF), regardless of the etiology. There have been many studies that demonstrated roles of inflammatory biomarkers in diagnosis, prognosis of chronic and acute HF patients, and also markers of cardiotoxicity from chemotherapy. These cytokines are high-sensitivity C-reactive protein (hsCRP), myeloperoxidase (MPO), soluble growth stimulation expressed gene 2 (sST2), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNFα), growth differentiation factor-15 (GDF-15), endothelin-1 (ET-1), and galectin-3. In this review, we discuss the past and present insights of those inflammatory biomarkers in order to gain more understanding in pathogenesis of HF, risk stratification of HF patients, and early detection of cardiotoxicity from cancer therapy.

Recent Findings Many inflammatory cytokines have been shown to be associated with mortality of both chronic and acute HF patients, and some of them are able to track treatment responses, especially sST2 and galectin-3, which are the only two inflammatory biomarkers recommended to use in clinical setting by the recent standard HF guidelines, while some studies described ET-1 and MPO as potential predictors of cardiotoxicity from cancer drugs.

Summary The prognostic implications of inflammatory biomarkers in HF patients have been demonstrated more consistently in chronic than acute HF, with some suggestions of ET-1 and MPO in patients receiving chemotherapy. However, further studies are necessary for the use of inflammatory biomarkers in routine clinical practice.

Keywords Inflammation · Biomarkers · Heart Failure

Introduction

Heart failure (HF) is a complex clinical syndrome characterized by typical signs and symptoms of reduced cardiac output and/or elevated intracardiac filling pressure caused by impaired cardiac function and/or structural abnormality [1]. There has been tremendous progress in medical treatments that improve morbidity and mortality in patients with HF with reduced ejection fraction (HFrEF) [2], but not in patients with HF with preserved ejection fraction (HFpEF) [3]. Meanwhile, prognosis of overall HF patients is still poor with more than a 50% mortality rate in 5 years after the diagnosis [4]. Apart from neurohormonal activation, inflammation has been shown to be an independent key factor in the development and progression of a variety of both HFrEF and HFpEF over the past decades [5–9]. Many inflammatory cytokines are secreted from the myocardium in response to a precipitating event causing myocardial damage and injury [10], resulting in deterioration of myocardial function, and subsequently furthering the progression of HF [11–13]. The mechanisms of inflammatory responses as causes of development and progression of HF are not well understood, but clinical studies over the past decades demonstrated the prognostic implications of elevated inflammatory mediators and adverse clinical outcomes [10, 14•, 15, 16]. It is important to recognize that the vast majority of published work described case series (most were retrospective and observational in nature) without designation of treatment decisions based on their quantification, hence largely limiting our ability to translate their insights into clinical practice. We will review current insights into inflammatory biomarkers available in clinical practice and summarize the data supporting their potential clinical utilization in chronic and acute HF. We will also review specific HF

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conditions such as prediction of cardiotoxicity from cancer drugs and responses to treatments of HF.

High-Sensitivity C-Reactive Protein

C-reactive protein (CRP) is an acute phase proinflammatory cytokine produced by hepatocytes in response to the signal from interleukin-6 (IL-6) [17, 18]. The association between elevated CRP in HF patients was described in 1956 by Elster et al. and was the first study to reveal elevated concentration of CRP levels in 30 of 40 HF patients [19]. Subsequently, several studies corroborated the elevated CRP in HF patients [20, 21]. Over the past two decades, CRP testing has become more available in standard clinical laboratories with high-sensitivity assay for CRP at relatively low cost [22]. Also, high-sensitivity CRP (hsCRP) has emerged as a potential risk predictor of adverse outcomes in HF patients.

In chronic HF, the prognostic implications of hsCRP have been well established. In two large observational studies, hsCRP was found to be independently associated with twofold increased cardiovascular mortality [23, 24]. Similar findings were also found in a study on a cohort of HF patients with left ventricular systolic dysfunction (LVSD); elevated hsCRP was found to be independently associated with increased mortality after adjusting with N-terminal pro-brain natriuretic peptide (NT-proBNP) [25]. Furthermore, along with other biomarkers, such as troponin T and NT-proBNP, hsCRP improved the prediction of 1-year mortality in HF patients [26]. In addition, hsCRP was described as a potential predictor of favorable outcomes from statin treatment in chronic HF patients [27].

In relatively small studies in acute HF patients, baseline hsCRP levels have been shown to be associated with increased mortality at 30 days [28], at 90 days [29], and at 1 year [30] and having higher readmission rates [31]. However, a larger cohort of patients from the biomarker sub-study of the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial suggested that baseline hsCRP levels were not associated with 30-day mortality, readmission rate, or 180-day mortality. Instead, only persistently elevated or increase in hsCRP from baseline to 30 days was associated with 180-day mortality [32]. Nevertheless, a recent study of a cohort of 4,269 patients with acute HF revealed that CRP was independently associated with 120-day mortality [33]. The discrepancies among the studies do not warrant the use of hsCRP as a predictor for adverse clinical outcomes in acute HF, and further investigation is warranted. Currently, there are no guideline recommendations supporting routine hsCRP testing in acute or chronic HF.

Myeloperoxidase

Myeloperoxidase (MPO) is an enzyme generated from activated leukocytes in response to inflammation and oxidative stress, through the formation of numerous reactive oxidants and diffuse radical species, which are capable of causing tissue oxidative damage by lipoprotein peroxidation, scavenging of nitric oxide, and inhibition of nitric oxide synthase [34–37] and subsequently resulting in atherogenesis, plaque vulnerability, and ventricular remodeling [38–41]. These pathways contribute to the development of coronary artery disease, vascular diseases, and HF. MPO is an FDA-cleared ELISA (enzyme-linked immunosorbent assay) available in many clinical laboratories. However, it is important to highlight the fact that quantification of MPO levels by commercially available assays reflect MPO mass concentration rather than activity; thus, circulating levels detected by current assays do not reflect acute inflammatory status per se.

In terms of clinical correlation, some studies demonstrated MPO as a strong risk predictor of coronary artery disease [42–46]. In chronic HF, the study of Tang et al. [47] revealed that elevated MPO was observed in HF patients compared to healthy controls; plasma MPO levels were strongly and independently associated with the prevalence of HF and able to identify the HF patients with 72% sensitivity and 77% specificity. Another study also described MPO as a predictor of future development of HF in healthy elderly [48]. In addition, along with plasma CRP and NT-proBNP, MPO can improve the specificity to detect HF patients up to 94.3% [49]. Furthermore, plasma MPO levels were also shown to be correlated with echocardiographic parameters indicating severe HF and long-term adverse clinical outcomes [50, 51].

On the other hand, in acute HF with more limited data, there are still controversies in diagnostic and prognostic implications of MPO. A study in a cohort of 412 patients presenting with dyspnea demonstrated that there was no significant difference in plasma MPO levels between the patients with and without acute HF, and plasma MPO levels were not associated with 1-year mortality of those patients [52]. In contrast, a study in a larger cohort of patients presenting with dyspnea suggested that plasma MPO levels independently predicted 1-year mortality in acute HF patients [53]. The use of MPO in acute HF patients is still unclear and yet to be determined.

Soluble Growth Stimulation Expressed Gene 2

Growth stimulation expressed gene 2 (ST2) encodes a transmembrane protein for interleukin-1 receptor family (ST2 ligand or ST2L) and a truncated soluble form of ST2 (soluble ST2 or sST2) secreted from cardiac myocytes and cardiac fibroblasts, triggered by mechanical strain in the heart [54, 55]. Both ST2L and sST2 bind to interleukin-33 (IL-33), a cytokine produced by cardiac fibroblasts, causing contrary

effects. Binding of IL-33 and ST2L results in cardioprotective effects against hypertrophic remodeling and myocardial fibrosis by antagonizing angiotensin-II signaling and promoting anti-apoptotic factors, respectively. In contrast, sST2 binds to IL-33, acts as a decoy receptor, and inhibits the protective effects of IL-33 and ST2L in cardiac myocytes [56, 57]. Recently, a study in an experimental model of heart failure claimed that the lungs are another relevant source of sST2 in response to cardiogenic pulmonary edema [58]. Also, in a study of healthy elderly, sST2 was associated with increased incidence of HF [59]. ST2 is an FDA-cleared ELISA assay available in many clinical laboratories.

The role of sST2 as a predictor of adverse clinical outcomes in chronic HF patients has been widely demonstrated since the early 2000s. A study of Weinberg et al. [55] in a cohort of 139 patients with chronic HF revealed that baseline sST2 levels correlated with BNP levels, and changes in serum sST2 levels at 2 weeks from baseline independently predicted subsequent transplantation and mortality rates. Similarly, results from studies in larger cohorts of chronic HF patients suggested that sST2 levels were associated with functional capacity [60], sudden cardiac death [61, 62], and short- and long-term mortality [63, 64], even when the patients were treated with optimized medications [60]. In addition, meta-analysis of studies on prognostic value of sST2 in 5,051 chronic HF patients revealed that sST2 was associated with both all-cause and cardiovascular mortality [65]. Interestingly, Gaggin et al. [66] demonstrated that sST2 levels might be able to identify patients who show better responses to higher dose of beta-blockers.

Unlike other inflammatory biomarkers, the diagnostic and prognostic implications of sST2 in acute HF patients have been validated in several studies. When Januzzi et al. [67] studied 593 patients presenting with acute dyspnea using receiver operator characteristic (ROC) analysis, baseline sST2 levels were found to have an area under the curve (AUC) of 0.74 for the diagnosis of HF. Moreover, in many studies, baseline sST2 levels have been shown to be a strong independent predictor of mortality in acute HF patients [68–72]. Also, changes in serum sST2 levels were shown to be associated with increased mortality in the setting of acute HF [73, 74]. In addition to the chronic HF setting, the prognostic implication of sST2 in the acute HF setting was also corroborated by meta-analysis of studies of 4,835 acute HF patients [75]. Moreover, a study on the effect of spironolactone on the 30-day mortality and re-hospitalization of patients with acute HF [76] revealed that subgroup of patients with higher levels of sST2 showed significant benefits from spironolactone.

Since there has been robust evidence of sST2 as a biomarker for prognosis and monitoring in both acute and chronic HF patients, sST2 was included in the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) focused update of HF guidelines [77••] and has been increasingly recognized as a biomarker in HF [78].

Interleukin-6

IL-6 is a proinflammatory cytokine secreted by T lymphocytes in response to a variety of stresses in the body, including HF [7, 79]. IL-6 affects myocardium by binding to the IL-6 receptor (IL-6 R) on cell membranes of myocytes and transduces signals through the glycoprotein (gp) 130 receptor system [80]. It also leads to the deterioration of myocardial function by three potential main pathways that contribute to the development of HF. Firstly, IL-6 has an indirect negative inotropic effect on myocardium by upregulating nitric oxide synthase [81]. Secondly, IL-6 downregulates myocardial sarcoplasmic reticulum Ca2+ ATPase (SERCA) [82]. Thirdly, IL-6 subsequently causes myocardial hypertrophy and apoptosis via Janus kinase (JAK) and mitogen-activated protein kinase (MAPK), respectively [83]. Likewise, in clinical studies of healthy subjects, the role of IL-6 in the development of HF has been reported for decades. The study of Vasan et al. [16] revealed that elevated IL-6 was independently associated with a three-fold increased risk of incident HF in a cohort of healthy elderly without history of cardiovascular disease from the Framingham Heart Study. Similarly, in another cohort of healthy individuals, IL-6 was shown to be inversely related with a decline in LV systolic function, determined by cardiac magnetic resonance imaging (MRI) [84]. These findings supported that IL-6 may play an important role in the pathogenesis of HF.

The prognostic implications of IL-6 in HF patients have been described in many studies, especially in the chronic HF setting, where IL-6 has been shown to be correlated with severity of HF [85, 86] and also an independent predictor of mortality in patients with chronic HF [87–89]. Recently, these findings were supported by a study in a large cohort of 2,329 chronic HF patients which revealed that baseline IL-6 levels independently predicted all-cause, cardiovascular, and non-cardiovascular mortality in 2 years [90•]. However, despite the results of IL-6 on mortality, there was no association between baseline IL-6 levels and HF hospitalization. Also, adding IL-6 to the published risk prediction model for this cohort [91] failed to improve discrimination in this model.

The challenge in interpreting many of these findings is that the large majority of studies utilized research assays that varied in sensitivities and reproducibility. Nevertheless, IL-6 is now available clinically in some specialty laboratory services, and therapeutic targeting of IL-6 signaling pathways (tocilizumab) have been developed in treating rheumatoid arthritis. Meanwhile, there is much limited evidence of the association between IL-6 and adverse clinical outcomes in acute HF compared to chronic HF, and most of the results were from relatively small cohorts. The study of Chin et al. [92] on 77 patients with acute HF demonstrated baseline IL-6 levels predicted 6-month mortality.

Furthermore, the study in a larger cohort of 423 acute HF patients also revealed the independent association between IL-6 levels at 48 hours after admission and 1-year mortality [93]. Nevertheless, the prognostic value for IL-6 in predicting adverse clinical outcomes in acute HF patients still needs to be investigated in larger cohorts of patients in an acute setting.

Tumor Necrosis Factor-Alpha

Tumor necrosis factor-alpha (TNFα) is a proinflammatory cytokine that has been shown to play important roles in inflammatory cascades and accounts for pathogenesis of HF. The pathophysiology of TNFα in HF has been described in many pathways such as downregulating myocardial SERCA [13], promoting cardiac hypertrophy [94], enhancing cardiac remodeling by upregulation of angiotensin II type I receptor in cardiac fibroblasts [95], and by matrix metalloproteinases in both cardiac myocytes and fibroblasts [96]. In clinical studies, the association between TNFα and HF was first observed in the study of Levine et al. [97], which demonstrated that serum TNFα levels were significantly higher in chronic HF patients compared to healthy controls. Subsequent studies also revealed that TNFα levels were correlated with development of HF in healthy subjects [16, 98], severity [7, 99, 100], and mortality of chronic HF patients [101–103]. Only one study described the prognostic implication of TNFα in acute HF patients, which showed the independent association between TNFα levels at 48 hours and mortality at 1 year [93]. Like IL-6, TNFα is now available in some specialty clinical laboratories, yet the majority of studies utilized research-based assays.

The evidences of TNFα and HF raised the hypothesis that TNFα inhibitors might improve clinical outcomes in chronic HF patients and potentially be the next target of HF treatments. In contrast, many clinical trials failed to demonstrate any improvement on death or HF hospitalization [104, 105]. Interestingly, in the clinical trial of infliximab, a monoclonal antibody of TNFα, on moderate to severe chronic HF patients, high doses of infliximab were associated with higher mortality than placebo and low-dose infliximab [106].

Growth Differentiation Factor-15

Growth differentiation factor-15 (GDF-15) is one of the transforming growth factor beta superfamily cytokines [107], secreted from cardiac myocytes in response to a number of stresses, for instance, ischemia [108], and mechanical stretch by signaling of angiotensin-II [109]. GDF-15 has been shown to be a strong predictor for mortality in patients with coronary artery disease [110, 111]. In chronic HF, the study of Kempf et al. [112] was the first to demonstrate that GDF-15 independently predicted mortality in a cohort of 455 patients. Afterwards, the prognostic utilities of GDF-15 were corroborated in large cohort studies of chronic HF patients with both HFrEF and HFpEF [113–115]. GDF-15 is available clinically in Europe as a commercial assay, but not yet in the United States.

Nonetheless, there is much limited evidence in acute HF patients with several studies on the ability of GDF-15 to predict adverse clinical outcomes. Cotter et al. [116] revealed that only increases in serum GDF-15 at 2 and 14 days, but not baseline levels, were independently associated with cardiovascular death at 180 days. In addition, another study of Boulogne et al. [117] showed that GDF-15 levels were not associated with death or cardiovascular rehospitalization. Further studies are needed to determine the role of GDF-15 as a prognostic indicator in acute HF patients.

Endothelin-1

Although technically not an inflammatory biomarker, endothelin-1 (ET-1) has been recognized as a potent vasoconstrictor produced by various cells, including cardiac myocytes and fibroblasts, triggered by angiotensin-II, epinephrine, cortisol, inflammatory cytokines, hypoxia, vascular shear stress, etc. [118]. There are two types of ET receptors. ET receptor A, located in vascular smooth muscle cells, has higher affinity for ET-1 than other receptors and is responsible for sustained vasoconstriction [119] and, ET receptor B which is located in both vascular and endothelial smooth muscles cells. In contrast to ET receptor A, binding of ET-1 and ET receptor B causes vasodilation [120, 121]. In HF, ET receptor A is upregulated, while ET receptor B is not, resulting in vasoconstriction and subsequent ventricular remodeling [118]. Like IL-6 and TNFα, ET-1 assays are available in specialty clinical laboratories.

The clinical utilities of ET-1 in chronic HF patients have been widely studied in the last decades. Cody et al. [122] reported that ET-1 levels were correlated with pulmonary capillary wedge pressure and pulmonary vascular resistance. Subsequent studies revealed that ET-1 was a strong predictor of both short- and long-term mortality [123–128] and also might be superior to natriuretic peptides [129]. Furthermore, the association between ET-1 and mortality has been consistently demonstrated in studies on cohorts of acute HF patients [130–132]. These findings shed light on the potential benefits of ET receptor antagonists on HF patients and have been recommended in patients with pulmonary arterial hypertension [133]. However, most clinical trials have yet to demonstrate any benefits towards decreased mortality or hospitalization of both chronic and acute HF patients [134–136], including patients with HFpEF [137].

Galectin-3

Galectin-3 is a member of beta-galactoside-binding lectin family, secreted from a variety of organs, including myocardial tissue, following injury, inflammation, and mechanical stress [138]. Galectin-3 has been shown to play important roles in the pathogenesis of HF through activation of cardiac fibroblasts and macrophages and promotes cardiac fibrosis and ventricular remodeling [139]. The role of galectin-3 in the development of new-onset HF was corroborated by two studies on large cohorts of healthy individuals and demonstrated that galectin-3 independently predicted incident HF and subsequent mortality [140, 141]. Galectin-3 is an FDA-cleared assay available in many clinical laboratories.

In terms of prognostic indicators in HF patients, the association between serum galectin-3 levels and mortality in chronic HF patients with either HFrEF or HFpEF was consistently demonstrated in many studies [142–146]. Nevertheless, there are still discrepancies among the data in acute HF patients. Previously in relatively small studies, galectin-3 was shown to be associated with mortality [147–150] and HF rehospitalization [151, 152]. In contrast, recently, a study on a cohort of 1,161 patients with acute HF revealed that there was no correlation between galectin-3 levels and mortality among those patients [153]. Furthermore, similar to hsCRP, galectin-3 was also found to be a predictor for statin responses in the same cohort of patients with chronic HF [154].

Although the data in acute HF patients remain unclear, the meta-analysis of prognostic implications of galectin-3 in all HF patients showed that galectin-3 significantly predicted cardiovascular mortality [155]. Moreover, as well as sST2, galectin-3 was also recommended in the latest ACC/AHA HF guidelines [77••] to be used as a predictor of death and hospitalization. Importantly, galectin-3 tracks strongly with renal function, and the majority of studies supporting its prognostic value did not fully adjust for renal function.

Considerations of Inflammatory Biomarkers in Cardiotoxicities and Treatment Responses

The role of inflammatory biomarkers as predictors for cardiotoxicity from cancer drugs has emerged in the last decades. ET-1 was the first inflammatory biomarker found to be associated with increased risk of cardiotoxicity [156–158]. Subsequently, Ky et al. [159] showed that higher risk of cardiotoxicity at 15 months follow-up was associated with only increases in serum MPO levels at 3 months, but not with CRP, GDF-15, or galectin-3. Similarly, in another study, Putt et al. [160] revealed that increases in serum MPO and GDF-15 predicted cardiotoxicity, while hsCRP and galectin-3 did not. Other studies also failed to demonstrate the prognostic implications of sST2, IL-6, TNFa, and galectin-3 [161, 162]. Therefore, ET-1 and MPO seem to be potentially useful inflammatory biomarkers for prediction of cardiotoxicity, and further studies should focus on validating these findings.

The ability for inflammatory biomarkers to track treatment responses has been explored, especially in statins [27, 154] and inhibitors of the renin–angiotensin–aldosterone systems [23, 32, 66, 73, 76, 127, 132, 142]. While retrospective and post hoc in nature, the large majority of studies appear to indicate that lower (rather than higher) levels of inflammatory biomarkers were tracked with favorable treatment responses. No studies to date utilized inflammatory biomarkers in therapeutic decisions in the setting of HF.

Conclusion

The role of inflammation in HF has been increasingly recognized over the past decades. Table 1 summarizes the many studies that demonstrated the clinical utility of both the diagnostic and prognostic indicators of many inflammatory biomarkers on chronic and acute HF patients. These biomarkers could improve the diagnosis and risk stratification in HF patients. However, sST2 and galectin-3 are the two clinically available inflammatory biomarkers that might be useful in risk

Table 1 Summary of level of evidence of each inflammatory biomarker in clinical use

	Prognosis for acute HF	Prognosis for chronic HF	Prognosis for cardiotoxicity
hsCRP	++	+++	+
MPO	+	+++	++
sST2	+++	+++	++
IL-6	+	+++	+
TNFa	+	++	+
GDF-15	+	++	+
ET-1	++	+++	++
Galectin-3	+++	+++	+

Level of evidence ranges from low (+) to high (+++)

stratification with data specifically for HF patients. Also, they were recommended by the recent standard HF guidelines, while ET-1 and MPO have potential to predict cardiotoxicity from chemotherapy. However, few if any studies linked inflammatory biomarkers with treatment choices and responses, thus making their incorporation into clinical practice somewhat challenging.

Compliance with Ethical Standards

Conflicts of Interest No potential conflicts of interest relevant to this article were reported.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors

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- •• Of major importance

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