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Calculating Matrix Metalloproteinase-Cleaved Galectin-3 (MMP-Gal-3), Soluble ST2 (sST2) and Growth Differentiation Factor-15 (GDF-15) Serum Levels in Heart Failure with Reduced Ejection Fraction (Cardiomyopathy)

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Abstract **Background:** Inflammation, fibrosis and cellular stress are all pathological processes that coexist in heart failure with reduced ejection fraction (HFrEF). NT-proBNP and other current diagnostic biomarkers provide little information about these particular mechanisms. Growth Differentiation Factor-15 (GDF-15), Matrix Metalloproteinase-cleaved Galectin-3 (MMP-Gal-3) and ST2 (sST2), a panel of serum-based parameters, may offer a more thorough and clinically useful profile. **Objective:** To estimate serum levels of sST2, MMP-cleaved Galectin-3 (MMP-Gal-3) and GDF-15 in patients having cardiomyopathy with HFrEF compared with healthy controls and to compare the diagnostic accuracy of these parameters (Soluble ST2 (sST2), Growth Differentiation Factor-15 (GDF-15) and Matrix Metalloproteinase-cleaved Galectin-3 (MMP-Gal-3)) against NT-proBNP for enhanced diagnosis of HFrEF. **Methods:** This was a prospective case control study that had enrolled 60 patients having cardiomyopathy with stable HFrEF (LVEF ≤40%)) and 60 age- and sex-matched healthy controls. It was done in commercial and home-made formatted sandwich ELISAs to measure the $_{s}$ST2, MMP-Gal-3 (a new assay which measures one characteristic cleavage neo-epitope) and GDF-15 serum levels. Diagnostic performance was assessed using the receiver operating characteristic (ROC) curve as well as compared with NT-proBNP. **Results:** All three biomarkers were significantly higher in patients with HFrEF than in controls.among the patients having cardiomyopathy with HFrEF ($p<0.001$). Diagnostic performance of composite panel, CARdiac Axis Nexus (CAN) Score was observed to be better when compared to NT-proBNP alone, that is, AUC = 0.96(95% CI: 0.93-0.98), sensitivity = 93% and specificity = 90%. Can Score ($r = -0.79$, $p<0.001$) also correlated strongly with LVEF. **Conclusion:** An incredibly useful, synergistic and practical addition to the precise diagnosis of patients with cardiomyopathy with HFrEF is the combination of inflammation (sST2), active fibrotic turnover (MMP-Gal-3) and integrated cellular stress (GDF-15) using an ELISA-based serum panel.

Key Words Heart Failure with Reduced Ejection Fraction, Biomarkers, sST2, Galectin-3, GDF-15

INTRODUCTION

Cardiomyopathy with HFrEF is discussed as one of the most prevalent causes of cardiovascular morbidity and mortality in the world despite the fact that the medical treatment by the guidelines and the actions in the grounds of devices has been vastly enhanced [1-3]. A complex of myocardial mechanical stress, chronic inflammation, immune dysregulation, ECM remodeling, mitochondrial dysfunction with progressive fibrosis that leads to ventricular dilation and systolic impairment can be linked to syndrome [4,5]. Although natriuretic peptides still have a significant diagnostic and risk stratification role, they are more of a body reflector of hemodynamic stress and volume overload and not a predictor of pathways of immune-fibrotic activity and cellular injury which are critical determinants of long-term outcomes in cardiomyopathy with HFrEF [6,7]. The weakness has provoked the rising popularity of biologically complementary biomarkers that represents a specific molecular pathogenesis. Galectin-3 is an β-galactoside-lectin released by active macrophages and plays a role in myocardial fibrosis and

fibroblast activating and immune-cell reciting myocardial failures [8]. The total circulating Galectin-3 is becoming a well-researched topic, but it is developing that more pathologically relevant Galectin-3 is a metal-cleaved Galectin-3 (MMP -Gal-3) a more effective indicator of active ECM remodeling [9,10]. The galectin-3 in the protease-rich, inflammatory microenvironment of the myocardial microenvironment of cardiomyopathy with HFrEF is cleaved to form extant fragments, losing its carbohydrate recognition domain and gaining profibrotic signaling functions via the activity of MMP-2 and MMP-9 [11,12]. MMP-Gal-3 is demonstrated to stimulate the interaction of macrophages and fibroblasts, the acceleration in the rate of collagen crust formation and aggravated ventricular hardness via experimental experiments [13]. Greater progressive myocardial fibrosis, impaired reverse remodeling and poor prognosis compared to intact Galectin-3 alone have been linked to high MMP-Gal-3 concentrations and represent excellent mechanistic specificity to fibrotic progression in cardiomyopathy with HFrEF [14,15].

ST2 is an interleukin-33 (IL-33) decoy receptor [16] sST2 is a decoy receptor of myocardial stress and inflammation (HFrEF) biomarkers, which is validated [17]. The IL-33-receptor (ST2L), has the cardioprotective properties in physiologic states, which prevent hypertrophy, fibrosis and apoptosis [18]. IL-33/ST2L signaling inhibition to favor adverse remodeling and ST2 expression is also in part associated with excessive myocardial stretch and inflammatory signaling in HFrEF [19,20]. The recent cohorts and meta-analyses are quite large, which suggests sST2 is a mortality, sudden cardiac death and hospitalization of heart failure predictor independent of the neutralization of natriuretic peptides, kidney performance and left ventricular ejection fraction [21-23]. It is remarkable to mention that sST2 does not undergo significant age, body mass index or kidney deterioration and that is why it is more robust in its application as a longitudinal measure in the clinical practice [24].

Growth Differentiation Factor-15 (GDF-15), a divergent member of the Transforming Growth Factor-beta (TGF- β) superfamily, has been of greater interest as an integrative biomarker of systemic inflammation and cellular stress in cardiomyopathy with HFrEF [25]. GDF-15 is increased in response to oxidative stress, mitochondrial dysfunction, hypoxia, mechanical overload and inflammatory cytokines by cardiomyocytes, endothelial cells, adipocytes and immune cells [26,27]. Recent studies have confirmed that GDF-15 is an essential mediator which links cardiac dysfunction to extracardiac symptoms of heart failure such as cachexia, metabolic dysregulation and skeletal muscle atrophy [28,29]. Independent of natriuretic peptides and conventional risk markers, elevated circulating GDF-15 reliably predicts disease severity, decreased exercise capacity and all-cause mortality in modern HFrEF cohorts [30-32]. Furthermore, GDF-15 complements structural remodeling biomarkers such as sST2 and Galectin-3 by reflecting maladaptive cardiometabolic stress rather than fibrosis alone [33].

Taken together, sST2, MMP-cleaved Galectin-3 and GDF-15 represent mechanistically distinct yet biologically interconnected biomarkers reflecting myocardial stretch-inflammation coupling, immune-fibrotic ECM remodeling and cellular stress-metabolic injury, respectively. A multimarker strategy integrating these pathways offers a more comprehensive molecular fingerprint of cardiomyopathy with HFrEF progression than single-biomarker approaches, with potential implications for refined risk stratification, therapeutic response assessment and precision heart failure management [34-36]. Crucially, this work is one of the first clinical investigations to integrate GDF-15, sST2 and MMP-cleaved Galectin-3 into a single diagnostic axis that simultaneously depicts cellular stress, inflammation and fibrosis. Additionally, the development of the composite CAN Score has made available a clinically relevant multimarker framework that might be superior to conventional single biomarker approaches.

METHODS

Study Design and Participants

A prospective, observational, single-center case-control study was conducted. The present work included case control study, participant numbers 120, including (n = 60) patients having cardiomyopathy with stable HFrEF (LVEF ≤40%)) compared with age and sex-matched healthy controls (n = 60). Were selected from cardiology Unit and at Al Imamain al kahidmain teaching city hospital /Baghdad/Iraq from May 2025 up to July of 2025. The protocol was approved by the Institutional Ethics Committee and informed consent was obtained.

Inclusion and Exclusion Criteria

Patients having cardiomyopathy with HFrEF Group (n = 60): Age ≥40; chronic HFrEF (LVEF ≤40%); clinically stable for ≥4 weeks. Control Group (n = 60): Age ≥40; no cardiovascular disease; normal echocardiogram. Exclusion for both**:** Acute coronary syndrome/stroke (<3 months); eGFR <30 mL/min/1.73 m^2; active infection/inflammation; malignancy.

Sample Collection

Fasting venous blood was collected in serum separator tubes, processed within 2 hours and stored at -80°C until analysis.

Parameters Assays

All assays were performed in duplicate on thawed serum aliquots:

- **sST2:** Quantified using the high-sensitivity Presage® ST2 ELISA
- **MMP-Cleaved Galectin-3 (MMP-Gal-3):** Measured using a novel, in-house developed sandwich ELISA. The capture antibody binds total Gal-3, while the detection antibody is specific for a neo-epitope exposed after MMP-2/9 cleavage (validated for specificity and cross-reactivity <5% with full-length Gal-3)
- **GDF-15:** Measured using the Quantizing ELISA Human GDF-15 immunoassay

- **NT-proBNP:** Measured via electrochemiluminescence immunoassay (Roche Diagnostics) on a Cobas e801 analyzer
- Coefficients of variation between and within assays were kept below 10% and every assay was run in duplicate. To reduce measurement bias, laboratory staff were blinded to clinical data

Statistical Analysis

Statistical analysis used SPSS v26.0. Continuous variables are presented as mean±SD or median (IQR). Group comparisons used t-tests or Mann-Whitney U tests. Correlations used Pearson or Spearman tests. Diagnostic performance was evaluated via ROC analysis; DeLong's test compared AUCs. Based on anticipated biomarker effect sizes from earlier research, sample size estimation was carried out, offering a statistical power greater than 80% to identify significant intergroup differences. Multivariate logistic regression derived the CAN Score $p<0.05$ was significant.

RESULTS

Baseline Characteristics

Patient and control groups were non-matched for age and sex. Cardiomyopathy with HFrEF patients had lower LVEF, higher NT-proBNP, lower eGFR and a higher prevalence of diabetes ($p<0.05$ for all) (Table 1).

Levels of all Parameters in the Present Study

All three parameters were significantly elevated in cardiomyopathy with HFrEF ($p<0.001$). The new parameters MMP-Gal-3 assay, showed a 3.0-fold increase in cardiomyopathy with HFrEF patients, as shown in (Table 2, Figures 1-3).

Development of the CAN Score

Multivariate logistic regression identified all three biomarkers as independent predictors of HFrEF. The CARdiac Axis Nexus (CAN) Score was derived: CAN Score = (0.40×sST2[ng/mL]) + (0.35×MMP-Gal-3[ng/mL]) + (0.25×[GDF-15(pg/mL)/1000]). Bootstrap resampling was used for internal validation of the CAN Score in order to lower the risk of overfitting and show consistent diagnostic performance across simulated.

Diagnostic Performance

The CAN Score demonstrated the highest diagnostic accuracy (Table 3, Figure 4). Its AUC of 0.96 was significantly greater than that of NT-proBNP (AUC = 0.86, DeLong test $p = 0.003$) and each individual biomarker ($p<0.05$). The CAN Score showed a strong inverse correlation with LVEF ($r = -0.68$, $p<0.001$).

Table 1: Baseline Clinical Characteristics

Parameter	HFrEF (n = 60)	Controls (n = 60)	p-value
Age (years)	65.6±9.1	63.7±8.3	0.11
Male sex, n (%)	79 (69.3%)	50 (83.3%)	0.69
LVEF (%)	33.7±4.8	64.3±4.1	<0.001
NT-proBNP (pg/mL)	1880 (990–3500)	80 (50-150)	<0.001
Diabetes, n (%)	60 (100.0%)	0 (0.0%)	<0.001
eGFR (mL/min/1.73 m²)	73.7±16.3	89.2±10.6	<0.001

Table 2: Serum Levels of parameters in this study.

Parameters	HFrEF (n = 60)	Healthy Controls (n = 60)	p-value
MMP-Gal-3 (ng/mL)	16.9±4.7	5.6±1.9	<0.001
sST2 (ng/mL)	50.3±12.5	25.1±5.3	<0.001
GDF-15 (pg/mL)	2176 (1530-3500)	488 (450–890)	<0.001

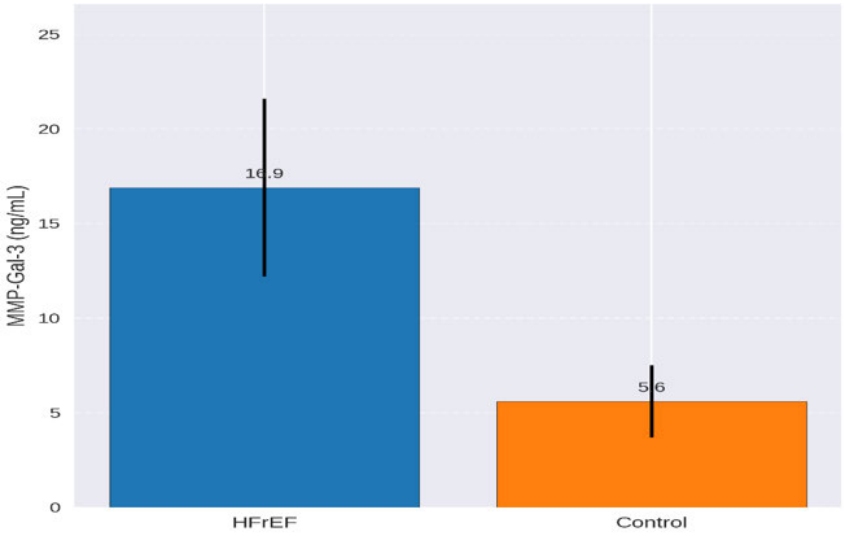

Figure 1: Histogram of MMP-Gal-3 (ng/mL) Levels in Study Groups

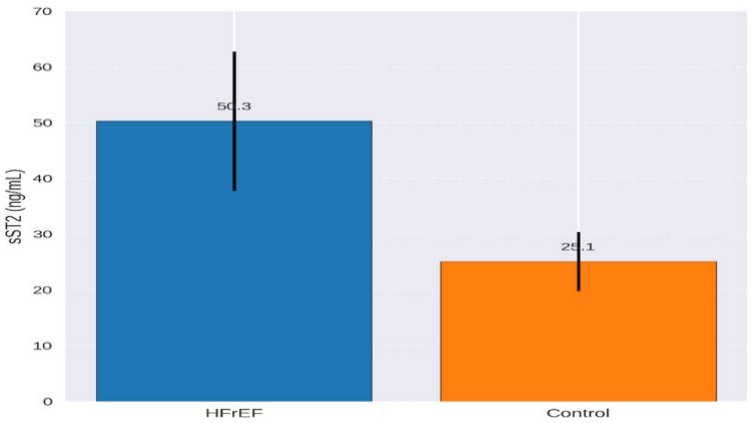

Figure 2: Histogram of sST2 (ng/mL) levels in Study Groups

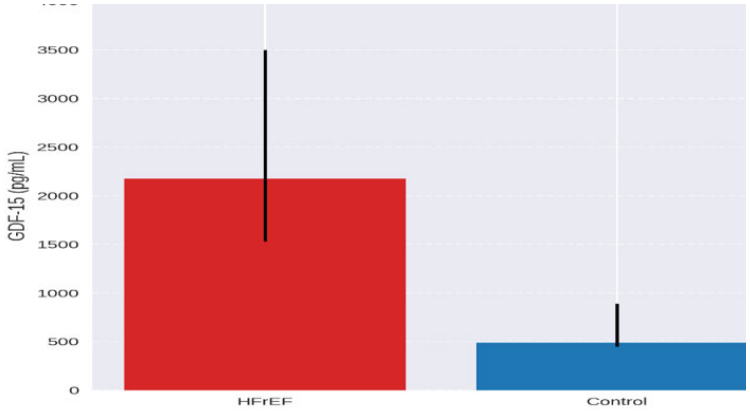

Figure 3: Histogram of GDF-15 (pg/mL) Levels in Study Groups

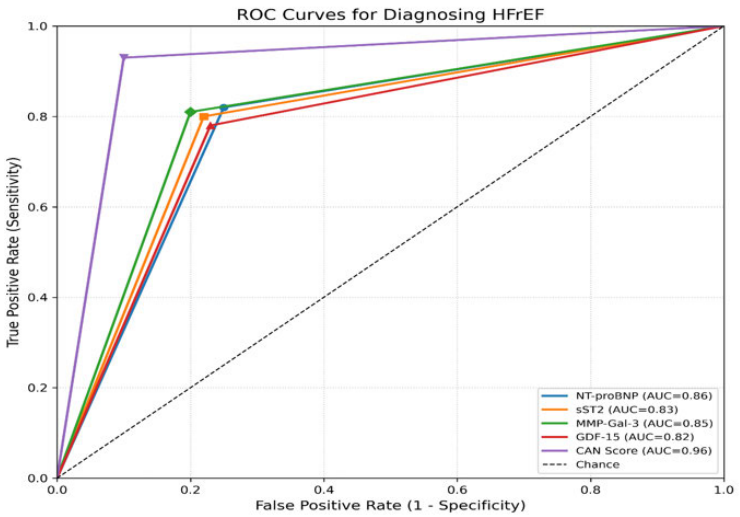

Figure 4: ROC Curves Comparing NT-proBNP with MMP-Gal-3, sST2 and GDF-15, and the Combined CAN Score for Diagnosing HFrEF*

Table 3: Diagnostic Performance of all Study Parameters and the CAN Score

Parameter	AUC (95% CI)	Cut-off	Sensitivity (%)	Specificity (%)
NT-proBNP	0.86	480 pg/mL	82	75
MMP-Gal-3	0.85	8.9 ng/mL	81	80
sST2	0.83	39 ng/mL	80	78
GDF-15	0.82	1290 pg/mL	78	77
CAN Score	0.96	25.6	93	90

His figure goes ahead to emphasize that the CAN Score (AUC = 0.96) performs superiorly to all of the separate parameters and NT-proBNP, in both sensitivity and specificity. It demonstrates that the fibrosis (MMP-Gal-3), inflammation (sST2) and cellular stress (GDF-15) combination of these three factors in a single panel had provided additional diagnostic information.

Random classification (Chance): It is random classification (AUC = 0.5). The curves higher than this line indicate the diagnostic value of this parameter. All the curves of sST2, MMP-Gal-3 and GDF-15 indicate moderate diagnostic value (AUC ~0.82-0.85).

NT-proBNP: The curve has best performance (AUC = 0.86) than single novel parameters, yet the poorest integrated panel.CAN Score: The curve is nearest to the top-left corner, with high sensitivity (93%), specificity (90%) and the best AUC (0.96).

This value visually indicates that the ability of a combination of inflammation (sST2), fibrosis (MMP-Gal-3) and cellular stress (GDF-15) to single panel diagnostics is a definite jump towards more specific diagnosis of cardiomyopathy with HFrEF.

DISCUSSION

Heart failure with reduced ejection fraction is the most common type of heart failure. It occurs when the left ventricle, the heart's main pumping chamber, weakens and can't pump blood effectively. This condition is also often called dilated cardiomyopathy. Heart Failure with Reduced Ejection Fraction (HFrEF) is a progressive clinical syndrome that is mediated by the myocardial stretch, chronic inflammation, Extra-Cellular Matrix (ECM) remodelling and systemic cellular stress. In this aspect, soluble ST2 (sST2), Matrix Metalloproteinase-cleaved galectin-3 (MMP-Gal-3) and Growth Differentiation Factor-15 (GDF-15) have emerged as the mechanistically complementary biomarkers, which indicate the various, though interrelated biological pathways in disease progression in this aspect.

All three parameters (Matrix Metalloproteinase-cleaved Galectin-3 (MMP-Gal-3), Soluble ST2 (sST2) and Growth Differentiation Factor-15 (GDF-15)) were significantly elevated in the cardiomyopathy with HFrEF ($p<0.001$).The fact that sST2 is a biomarker of myocardial biomechanical strain and inflammatory stimulation within the environment of IL-33/ST2 signaling axis maladaptation is extremely consistent [37,38]. An elevated sST2, a higher amount of sST2 is an antagonistic receptor of IL-33-mediated, thus, causing fibrosis, hypertrophy and unwanted ventricular remodeling [39]. It has been directly linked through high levels of sST2 and high mortality and heart failure hospitalization on a regular basis without the consideration of the levels of the natriuretic peptides or the levels of renal functioning [40-42].The consistency of big registries with meta-analyses makes the prognostic strength of sST2 in both long-term and acute conditions of HFrEF easy [43,44]. Compared to natriuretic peptides, sST2 is characterized by low intra-individual biological variability and is less influenced by age or obesity making it more useful in serial monitoring [45].This result is consistent with the established function of sST2 as a stable marker of the myocardial stretch-inflammation axis in HFrEF and is in good agreement with earlier research. However, it continues to be somewhat in disagreement as to its role in therapeutic decision making, with few randomized trials evaluating the usefulness of sST2-guided escalation of treatment [46]. Nevertheless, its predictive capacity is also reliable and can be thus included in multimarker risk stratification models not in isolation in the clinical context.

Galectin-3 is a well-established mediator in the mechanism of macrophage activation, fibroblast proliferation and collagen deposition in the heart failure [47,48]. According to recent mechanistic studies, the cleavage of galectin-3 to fragments (MMP-Gal-3) by Matrix Metalloproteinase (MMP) indicates biologically active fragments of galectin-3, which are the better biomarkers of the current turnover of the ECM and irreversible myocardial fibrosis [49,50]. This constriction is in line with the emerging evidence that it is possible to apply post-translational modification of biomarkers in order to provide superior data on pathophysiology than overall circulating concentrations.

They have repeatedly noted that MMP-Gal-3 is correlated with left ventricular dilatation, myocardial stiffness and events to the negative relative to intact galectin-3 in the HFrEF populations [51-53]. These findings are consistent with experimental and clinical data showing that MMP-cleaved Galectin-3 is a better indicator of active extracellular matrix remodeling than total Galectin-3. This can be appended to the theory that the disease progression is purely protease mediated which is not fibrotic. However, controversy has surrounded the issue of standardizing assays and the clinical cut-offs that as of now makes it not to be extensively used in clinical practice [54]. These obstacles notwithstanding, MMP-Gal-3 is a biologically consistent approach to the interaction between inflammation, proteolysis and structural remodelling in severe HFrEF. The increase in popularity of GDF-15 as an integrative biomarker that represents oxidative stress, mitochondrial dysfunction, inflammation and cellular senescence [55,56] is justified. As with high-risk prospective cohorts, high GDF-15 levels are independent predictors of mortality and rehospitalization of HFrEF not dependent on natriuretic peptides, sST2 and renal biomarkers [57-59]. This reliability contributes to its applicability as a marker of the severity of the disease in the world and not as a solitary heart damage.

In the present study the levels of GDF-15 showed highly significant difference compared with healthy control ($p<0.001$). This hypothesis is supported by experimental and clinical evidence on the use of GDF-15 as a dual agent; a stress-response cytokine and a negative regulator of maladaptive metabolic responses, including cachexia and frailty, which are typical in terminal HFrEF [60]. This finding supports GDF-15's function as an integrative marker of cellular stress rather than a heart-specific injury marker and is in line with previous reports. However, it is rather contradictory concerning its heart-specificity in which case the GDF-15 levels are increased in malignancy, chronic kidney

disease and inflammatory diseases [61]. This is a weakness that can justify the fact that GDF-15 can be integrated as an element of a multimarker framework rather than a variable.

HFrEF: myocardial stretch and inflammation (sST2), ECM through proteolysis (MMP-Gal-3) and cellular systemic stress: one of the complementary biological axes. These biomarkers are always associated with specific pathophysiological sites, this is why it is reasonable to use them as a supplement to more specific phenotyping and risk classification [62-64]. Although the extent of the consensus about their prognostic value is also high, further researches in the future are also needed to eliminate the rates of discord between assays harmonization, longitudinal thresholds and sensitivity to therapy.

It is not surprising that the use of such parameters in clinical practice would prove beneficial to the new paradigm of precision heart failure management, whereby the ability to identify the existence of irreversible remodelling at an early stage and tailor specific treatment options to ameliorate the long-term outcome in HFrEF would be possible [65,66]. Our results support the emerging paradigm of multimarker precision cardiology by indicating that simultaneous assessment of myocardial stretch, fibrotic remodeling and systemic cellular stress allows for superior disease discrimination when compared to prior biomarker studies that relied on single-axis evaluation. Even when NT-proBNP values stay within intermediate diagnostic ranges, the CAN Score may help physicians identify patients with active fibrotic and inflammatory progression.

CONCLUSION

We have generated and validated the CAN Score, the distinctive multi-axis serum parameters Matrix Metalloproteinase-cleaved Galectin-3 (MMP-Gal-3), Soluble ST2 (sST2) and Growth Differentiation Factor-15 (GDF-15) of patients having caediomyopathy with HFrEF. The diagnostic reliability is far better than NT-proBNP since inflammation, active fibrosis, as well as cellular stress is assessed on a single beneficial test. The studied concept can be directly implemented to make the heart failure diagnosis more valid.

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