Clinica Chimica Acta 445 (2015) 155–160

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Association of the biomarkers soluble ST2, galectin-3 and growth-differentiation factor-15 with heart failure and other non-cardiac diseases

Thomas Mueller *, Isabella Leitner, Margot Egger, Meinhard Haltmayer, Benjamin Dieplinger

Department of Laboratory Medicine, Konventhospital Barmherzige Brueder, Linz, Austria

ARTICLE INFO

Article history:
Received 14 February 2015
Received in revised form 27 March 2015
Accepted 27 March 2015
Available online 4 April 2015

Keywords:
Cardiac troponin
Galectins
Inflammation
Interleukin-1 receptor family
Natriuretic peptides
Transforming growth factor beta superfamily

ABSTRACT

Background: The biomarkers soluble ST2 (sST2), galectin-3, and growth-differentiation factor-15 (GDF-15) provide prognostic information in patients with heart failure (HF). The aim of this study was to evaluate to which extent plasma concentrations of these biomarkers are increased in HF compared with diverse non-cardiac conditions such as infectious disease or chronic kidney disease.

Methods: We recruited 15 patients in each of the following clinical categories: HF without co-morbidity, pneumonia without co-morbidity, chronic obstructive pulmonary disease (COPD) without co-morbidity, HF and a co-morbidity of pneumonia, renal disease without co-morbidity, and sepsis. We used 22 healthy individuals as control group. In each of the 112 study participants, we measured plasma concentrations of sST2 (Presage assay), galectin-3 (Abbott assay) and GDF-15 (Roche assay).

Results: Compared to controls, the median sST2 concentration was ~2.5-fold increased in HF, ~3.5-fold in pneumonia, ~5.0-fold in COPD, ~5.8-fold in HF + pneumonia, and ~70-fold in sepsis ($p < 0.001$ for all). sST2 was not significantly increased in renal disease. Compared to controls, the median galectin-3 concentration was ~1.5-fold increased in HF, ~1.4-fold in pneumonia, ~2.4-fold in HF + pneumonia, ~2.5-fold in renal disease, and ~2.7-fold in sepsis ($p < 0.001$ for all). Galectin-3 was not significantly increased in COPD. Compared to controls, the median GDF-15 concentration was ~4.4-fold increased in HF, ~5.4-fold in pneumonia, ~2.1-fold in COPD, ~8.3-fold in HF + pneumonia, ~5.1-fold in renal disease, and ~27-fold in sepsis ($p < 0.001$). In the 112 study participants, correlation analyses revealed a relatively strong association between galectin-3 and GDF-15 (correlation coefficient, 0.739; $p < 0.001$).

Conclusion: Because increased plasma concentrations of sST2, galectin-3, and GDF-15 are not specific for a distinct disease group, the three biomarkers are not useful for diagnostic purposes. The results of our study are novel with respect to sST2, galectin-3 and GDF-15 as markers of inflammatory diseases and should encourage further studies.

1. Introduction

The three proteins soluble ST2 (sST2), galectin-3, and growth-differentiation factor-15 (GDF-15) are currently gaining mounting interest as candidate biomarkers in heart failure (HF) [1–3]. There is increasing evidence that plasma concentrations of these three analytes provide prognostic information in HF patients independently of and additive to other established markers such as cardiac troponins or natriuretic peptides [1–4]. Among them, the biomarkers sST2 and galectin-3 have been included in the 2013 ACCF/AHA guideline for additive risk stratification of patients with acute and chronic HF [4].

To date, no comparative data has been published to which extent plasma concentrations of sST2, galectin-3, and GDF-15 are increased in clinical conditions often being associated with HF (e.g., pneumonia, chronic obstructive pulmonary disease [COPD], or renal failure). This is of interest because increased concentrations of the three biomarkers in various other diseases besides HF could modify the diagnostic and prognostic value of sST2, galectin-3, and GDF-15 for HF. The aim of this study was, therefore, to evaluate to which extent plasma concentrations of sST2, galectin-3, and GDF-15 are increased in HF compared with diverse non-cardiac conditions such as infectious disease, or chronic kidney disease.

2. Materials and methods

2.1. Study protocol

This is a single center study performed at the St. John of God Hospital in Linz, Austria. As part of an evaluation study of a novel high-sensitivity assay for measurement of sST2 [5], we recruited a cohort of patients

* Corresponding author at: Department of Laboratory Medicine, Konventhospital Barmherzige Brueder, Seilerstaette 2-4, A-4020 Linz, Austria. Fax: +43 732 7677 3799.
E-mail address: thomas.mueller@bs-lab.at (T. Mueller).

http://dx.doi.org/10.1016/j.cca.2015.03.033

with different diseases to evaluate whether sST2 was increased in diverse clinical conditions or not. In brief, we enrolled 15 inpatients each with 'heart failure (HF) without co-morbidity', 'pneumonia without co-morbidity', 'COPD without co-morbidity', 'HF with co-morbidity of pneumonia', 'renal disease without co-morbidity', and 'sepsis'. Using this approach, we aimed at disentangling various clinical conditions suspected to increase the concentrations of sST2 as accurately as possible. In addition, we used 22 healthy members of our laboratory staff as the control group. From each of the 112 study participants, several plasma aliquots were stored at −80 °C. This was done to give us the opportunity to determine other novel biomarkers of potential interest from this cohort in the future. The local ethics committee approved this study protocol in accordance with the Declaration of Helsinki [5]. All study participants gave informed consent [5].

The present work is a retrospective explorative analysis because it was a post-hoc decision to measure galectin-3 and GDF-15 from the plasma aliquots stored at −80 °C. As detailed previously, the data on sST2 in this cohort have been already published [5]. We now intended to compare these results on sST2 with the results of galectin-3 and GDF-15 measurements in those same patients of our well characterized cohort.

2.2. Definitions

Arterial hypertension was defined as resting systolic blood pressure ≥140 mm Hg, or resting diastolic blood pressure ≥90 mm Hg or the use of any antihypertensive medication. Diabetes mellitus was defined as fasting blood glucose levels ≥126 mg/dL or the use of any glucose-lowering medication. Current smoking was defined as any amount of tobacco use. Left ventricular ejection fraction (LVEF) was determined by echocardiography and was quantified as ≥50% or <50%. Coronary artery disease (CAD) was defined as previous myocardial infarction or unstable angina by history, or as previous percutaneous transluminal coronary angioplasty or coronary bypass surgery. The diagnosis of atrial fibrillation was defined as first episode, paroxysmal, persistent, or permanent.

'HF without co-morbidity' was defined as clinical condition with typical symptoms and signs of acute destabilized HF (e.g., dyspnea, jugular venous distension, pulmonary rales, edema of the legs or feet) according to the Framingham criteria for the clinical diagnosis of HF [5,6], evidence of heart enlargement by chest radiograph and/or evidence of systolic dysfunction by echocardiography, response to adequate HF therapy, and B-type natriuretic peptide (BNP) plasma concentrations >500 pg/mL, but without a clinical diagnosis of pneumonia, COPD or renal disease and without any laboratory evidence of inflammation or renal disease (i.e., C-reactive plasma protein [CRP] ≤1.0 mg/dL, procalcitonin [PCT] ≤0.5 ng/mL, interleukin-6 [IL-6] ≤15.0 pg/mL, and estimated glomerular filtration rate [eGFR] >90 mL/min/1.73 m^2) [5].

'Pneumonia without co-morbidity' was defined as community-acquired pneumonia with symptoms and signs consistent with a lower respiratory tract infection (e.g., cough, sputum production, dyspnea, fever, auscultatory findings of abnormal breath sounds and crackles) associated with a new pulmonary opacity on chest radiograph compatible with pneumonia and response to antimicrobial therapy [5,7] but without a clinical diagnosis of HF, COPD or renal disease and without any laboratory evidence of renal disease or HF (i.e., eGFR >90 mL/min/1.73 m2, and BNP ≤100 pg/mL) [5].

'COPD without co-morbidity' was defined as exacerbated disease with acute worsening of respiratory symptoms (e.g., increased dyspnea, productive cough with altered sputum, wheezing, fever, fatigue) [5,8], and was based on clinical history, physical examination, and spirometric criteria (FEV_1 < 50% predicted and FEV_1/VC ratio <70%) and response treatment with oral corticosteroids or antibiotics, or both but without a clinical diagnosis of HF, pneumonia or renal disease and without any laboratory evidence of renal disease or HF (i.e., eGFR >90 mL/min/1.73 m2, and BNP ≤100 pg/mL) [5].

'HF with co-morbidity of pneumonia' was defined as HF with additional pneumonia according to the definitions as described previously in this chapter [5].

'Renal disease without co-morbidity' was defined as non-dialysis chronic kidney disease [5,9] associated with an eGFR <60 mL/min/1.73 m2 but without a clinical diagnosis of HF, pneumonia, or COPD and without any laboratory evidence of HF or inflammation (i.e., BNP ≤100 pg/mL, CRP ≤1.0 mg/dL, PCT ≤0.5 ng/mL, and IL-6 ≤ 15.0 pg/mL) [5].

'Sepsis' was defined as severe sepsis or septic shock according to the criteria of the American College of Chest Physicians/Society of Critical Care Medicine consensus conference [5,10].

2.3. Blood collection, routine analyte determination, and aliquot storage

We obtained blood by venipuncture avoiding venous stasis. Using VACUETTE® polyethylene terephthalate glycol blood collection tubes (Greiner Bio-One, Kremsmuenster, Austria), we collected one EDTA anticoagulated blood sample and one serum sample. We quantified serum concentrations of CRP, PCT, IL-6, and creatinine, plasma concentrations of BNP, and eGFR within 4 h of blood collection in clinical routine, as described previously [5]. Several plasma aliquots from each study participant were frozen at −80 °C and stored until analysis. Plasma concentrations of sST2 were measured from a thawed aliquot in 2009 [5]. Plasma concentrations of galectin-3 and GDF-15 were measured in one batch from another thawed aliquot in 2014. Plasma concentrations of high sensitive cardiac troponin I (hs-cTnI) were measured in one batch from another thawed aliquot on an Architect system (Abbott Diagnostics, Vienna, Austria) in 2015. Based to the analytical sensitivity of this assay reported in the package insert, hs-cTnI concentrations ≤1.5 ng/L were reported as 1.5 ng/L.

2.4. Measurement of sST2, galectin-3 and GFD-15 plasma concentrations

We measured sST2 plasma concentrations on a BEP 2000 instrument (Siemens Medical Solutions Diagnostics, Vienna, Austria) with the Presage ST2 assay (Critical Diagnostics, San Diego, CA, USA) as previously described [5]; this enzyme-linked immunosorbent assay has a measurement range of 2.8–180 ng/mL (based on a 45-fold dilution of patient samples). We measured galectin-3 plasma concentrations with a chemiluminescent microparticle immunoassay on an ARCHITECT I2000SR analyzer (Abbott Laboratories, Abbott Park, IL, USA) [11]; according to the package insert this assay has a measurement range of 4–114 ng/mL. We measured GDF-15 plasma concentrations with a pre-commercial chemiluminescent microparticle immunoassay on a Hitachi cobas e411 analyzer (Roche Diagnostics, Mannheim, Germany); according to the manufacturer, this assay has a measurement range of 400–20,000 pg/mL.

If the analyte concentration of a patient sample exceeded the analytical range of one of the three assays, the respective sample was assayed in various dilutions if necessary to obtain the actual value. Based to the analytical sensitivity of the assays, sST2 concentrations ≤2.8 ng/mL were reported as 2.8 ng/mL, galectin-3 concentrations ≤4 ng/mL were reported as 4 ng/mL, and GDF-15 concentrations ≤400 pg/mL were reported as 400 pg/mL in the present work.

We evaluated the precision of the sST2 assay in 2009, and the precision of the GDF-15 and galectin-3 assays in 2014, applying the same protocol according to the Clinical and Laboratory Standards Institute (CLSI; formerly NCCLS) guideline EP5-A [12]. For each of the three assays, we used the same three pooled patient plasma samples (pools 1–3) which we had aliquoted into twenty plastic tubes for each concentration level and frozen at −80 °C. We analyzed these samples in duplicate in one run per day for 20 days with the three assays. Within-run and total analytical imprecision (CV) was calculated with the CLSI single-run precision evaluation test [12] for each assay.

As previously reported [5], the Presage ST2 assay had a within-run CV of 2.4% and a total CV of 4.0% at a mean concentration of 11 ng/mL (pool 1), a within-run CV of 2.0% and a total CV of 3.9% at a mean concentration of 87 ng/mL (pool 2), and a within-run CV of 2.2% and a total CV of 3.9% at a mean concentration of 140 ng/mL (pool 3).

The Abbott galectin-3 assay had a within-run CV of 3.6% and a total CV of 4.9% at a mean concentration of 16 ng/mL (pool 1), a within-run CV of 1.8% and a total CV of 2.6% at a mean concentration of 22 ng/mL (pool 2), and a within-run CV of 2.8% and a total CV of 4.5% at a mean concentration of 32 ng/mL (pool 3).

The Roche GDF-15 assay had a within-run CV of 2.1% and a total CV of 5.4% at a mean concentration of 483 pg/mL (pool 1), a within-run CV of 1.4% and a total CV of 6.5% at a mean concentration of 5659 pg/mL (pool 2), and a within-run CV of 0.8% and a total CV of 6.1% at a mean concentration of 7719 pg/mL (pool 3).

2.5. Statistical analyses

We analyzed our data with the SPSS 13.0 software (SPSS Inc., Chicago, IL, USA) and the MedCalc 13.0.0.0 package (MedCalc Software, Mariakerke, Belgium). Dichotomous variables are given as absolute numbers and continuous variables as median (range). Comparisons of continuous variables between patient groups were performed with the non-parametric Mann–Whitney U test. Relationships between continuous variables are described by means of the Spearman coefficient of rank correlation with 95% confidence intervals (95% CI). Obtained p values were not adjusted for multiple comparisons and are therefore descriptive only.

3. Results

The results of our clinical evaluation study are detailed in Table 1. The distribution of sST2, galectin-3 and GDF-15 plasma concentrations in the control group and in the disease groups are displayed in Fig. 1.

The results indicate that there is no relevant difference of sST2 plasma concentrations between the control group and the patients with renal disease ($p = 0.065$). In contrast, increased sST2 concentrations were obtained in the patients with HF ($p < 0.001$), pneumonia ($p < 0.001$), COPD ($p < 0.001$), and sepsis ($p < 0.001$). Compared to healthy controls, the median plasma concentrations of sST2 are ~2.5-fold increased in HF, ~3.5-fold increased in pneumonia, ~5.0-fold increased in COPD, ~5.8-fold increased in HF with co-morbidity of pneumonia, and ~70-fold increased in sepsis.

For galectin-3, increased analyte concentrations are evident in the patients with HF ($p < 0.001$), pneumonia ($p = 0.001$), renal disease ($p < 0.001$), and sepsis ($p < 0.001$). In contrast, galectin-3 plasma concentrations are not significantly different in healthy controls and patients with COPD ($p = 0.070$). Compared to healthy controls, the median plasma concentrations of galectin-3 are ~1.5-fold increased in HF, ~1.4-fold increased in pneumonia, ~2.4-fold increased in HF with co-morbidity of pneumonia, ~2.5-fold increased in renal disease, and ~2.7-fold increased in sepsis.

Table 1
Characteristics of the study participants according to the different disease groups.

	Controls (n = 22)	HF (n = 15)	Pneumonia (n = 15)	COPD (n = 15)	HF + pneumonia (n = 15)	Renal disease (n = 15)	Sepsis (n = 15)
Male gender	12	11	13	14	12	12	9
Age (years)	38 (22–59)	72 (57–85)	57 (25–84)	63 (51–82)	80 (55–96)	74 (55–83)	70 (35–83)
BMI (kg/m^2)	23 (19–34)	24 (17–35)	25 (19–35)	24 (19–33)	24 (20–36)	22 (19–30)	25 (18–40)
Hypertension	0	11	5	6	10	13	7
Diabetes mellitus	0	3	4	3	7	7	1
Current smoking	7	4	4	5	0	0	3
LVEF <50%	0	15	0	0	15	0	7
CAD	0	8	1	2	9	4	7
Atrial fibrillation	0	7	3	1	4	1	5
CRP (mg/dL)	0.1 (0.1–1.0)	0.6 (0.1–1.0)	14 (2.8–29)	0.3 (0.1–18)	8.4 (5.8–30)	0.1 (0.1–1.0)	25 (7.6–35)
PCT (ng/mL)	0.1 (0.1–0.2)	0.1 (0.1–0.4)	0.2 (0.1–2.8)	0.1 (0.1–0.4)	0.1 (0.1–2.2)	0.1 (0.1–0.4)	32 (7.0–280)
IL-6 (pg/mL)	2.0 (2.0–14)	4.6 (2.0–15)	48 (7–245)	2.0 (2.0–16)	43 (10–1088)	2.1 (2.0–10)	1132 (112–65,500)
eGFR (mL/min/ 1.73 m^2)	>90 (>90–>90)	>90 (>90–>90)	>90 (>90–>90)	>90 (>90–>90)	>90 (>90–>90)	29 (10–56)	43 (12–>90)
BNP (pg/mL)	17 (10–95)	880 (519–3109)	66 (17–96)	48 (10–91)	864 (539–4793)	51 (30–96)	697 (37–2575)
hs-cTnI (ng/L)	1.8 (1.5–15.7)	34.8 (2.6–116.0)	5.0 (1.5–33.0)	2.5 (1.5–24.9)	40.8 (8.9–106.1)	7.8 (2.3–35.6)	71.1 (12.7–180.9)
sST2 (ng/mL)	11 (6–33)	27 (11–132)***	39 (19–765)***	56 (8–341)***	64 (21–158)***	13 (8–34)‡	745 (111–4056)***
sST2 values > URL[a]	0	3	5	9	10	0	15
Galectin-3 (ng/mL)	13 (7–21)	20 (10–42)***	18 (9–49)**	14 (10–24)‡	31 (12–85)***	33 (17–68)***	35 (11–107)***
Galectin-3 values > URL[b]	0	3	5	0	8	10	11
GDF-15 (pg/mL)	602 (400–1144)	2636 (843–6889)***	3212 (400–17,986)***	1269 (596–2158)***	4974 (2218–15,054)***	3090 (2167–9174)***	16,127 (4775–33,454)***
GDF-15 values > URL[c]	1	7	10	1	10	9	15

Abbreviations: BMI, body mass index; BNP, B-type natriuretic polypeptide; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; GDF-15, growth-differentiation factor-15; HF, heart failure; hs-cTnI, high-sensitivity cardiac troponin I; IL-6, interleukin-6; LVEF, left ventricular ejection fraction; PCT, procalcitonin; sST2, soluble ST2; URL, upper reference limit.

Data are presented as number or median (range). Difference of sST2, galectin-3 and GDF-15 concentrations of the control group vs. each of the disease groups were calculated with the Mann–Whitney-U test (p-values were not corrected for multiple comparisons): ***$p < 0.001$, **$p < 0.01$, and ‡$p > 0.05$.

[a] The number of patients with sST2 plasma concentrations greater than the upper reference limits as derived from the package insert of the Presage ST2 assay (Critical Diagnostics, San Diego, CA, USA). Based on the 95th percentiles of a healthy reference population, the age-independent upper reference limits for sST2 are 49.3 ng/mL for male individuals and 33.5 ng/mL for female individuals.

[b] The number of patients with galectin-3 plasma concentrations greater than the upper reference limits as derived from the package insert of the galectin-3 assay (Abbott Laboratories, Abbott Park, IL, USA). Based on the 97.5th percentiles of a healthy reference population, the age-independent upper reference limits for galectin-3 are 26.1 ng/mL for male individuals and 28.7 ng/mL for female individuals.

[c] The number of patients with GDF-15 plasma concentrations greater than the upper reference limits as derived from a study by Ho and co-workers using a pre-commercial chemiluminescent microparticle immunoassay (Roche Diagnostics, Mannheim, Germany) [31]. Based on 97.5th percentiles by 10-year age and sex categories of a healthy reference population, the upper reference limits for galectin-3 were ranging from 1498 ng/L for male individuals in the 4th decade to 5006 ng/L in the 8th decade and from 1085 ng/L for female individuals in the 4th decade to 2562 ng/L in the 8th decade.

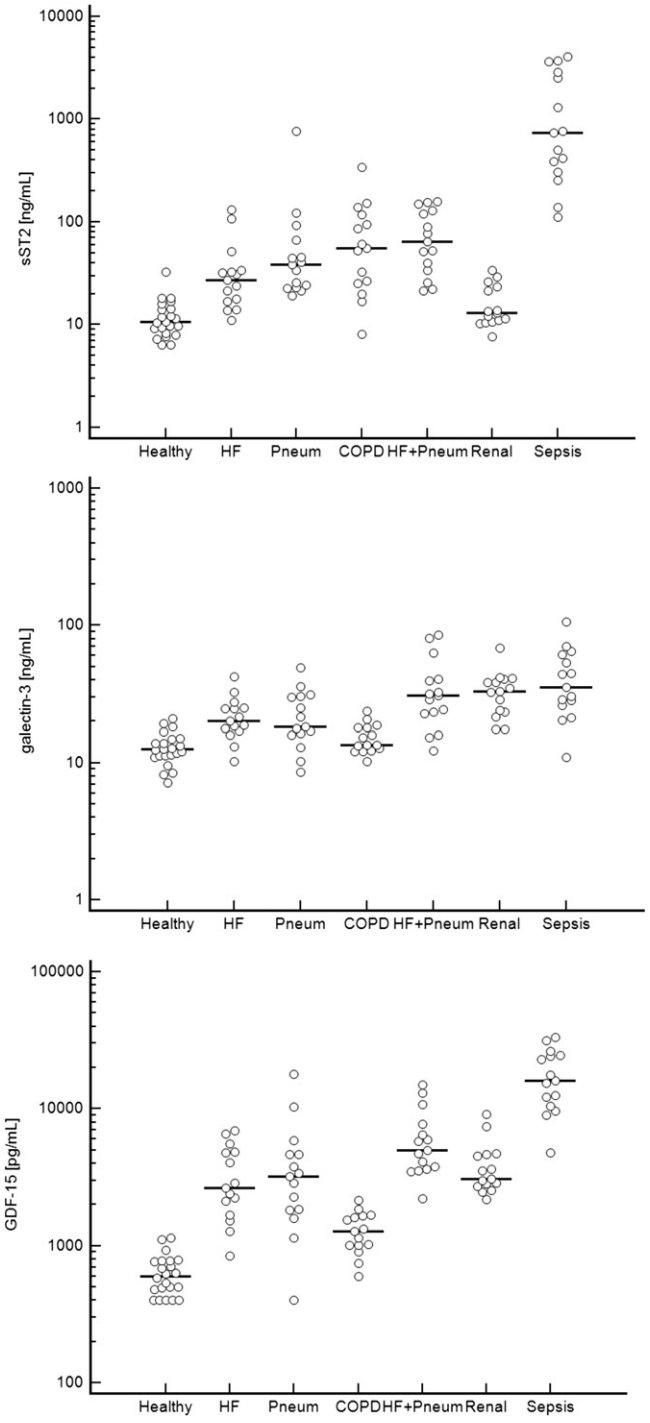

Fig. 1. Distribution of (A) sST2, (B) galectin-3, (C) and GDF-15 plasma concentrations in healthy individuals vs. diseased patients. The multiple comparison graphs show the distribution of the three biomarkers in healthy individuals (Healthy, n = 22) compared to patients with heart failure (HF, n = 15), to patients with pneumonia (Pneum, n = 15), to patients with chronic obstructive pulmonary disease (COPD, n = 15), to patients with HF and co-morbidity of pneumonia (HF + Pneum, n = 15), to patients with renal disease (Renal, n = 15), and to patients with sepsis (Sepsis, n = 15), respectively. In each disease category all data were plotted as open circles, and the horizontal lines represent the median analyte concentration of each disease category.

GDF-15 plasma concentrations are increased in all disease groups evaluated in this study ($p < 0.001$ for each). Compared to healthy controls, the median plasma concentrations of GDF-15 are ~4.4-fold increased in HF, ~5.4-fold increased in pneumonia, ~2.1-fold increased in COPD, ~8.3-fold increased in HF with co-morbidity of pneumonia, ~5.1-fold increased in renal disease, and ~27-fold increased in sepsis.

As a secondary finding, hs-cTnI plasma concentrations are markedly increased in HF (with or without co-morbidity of pneumonia) and in sepsis as shown in Table 1.

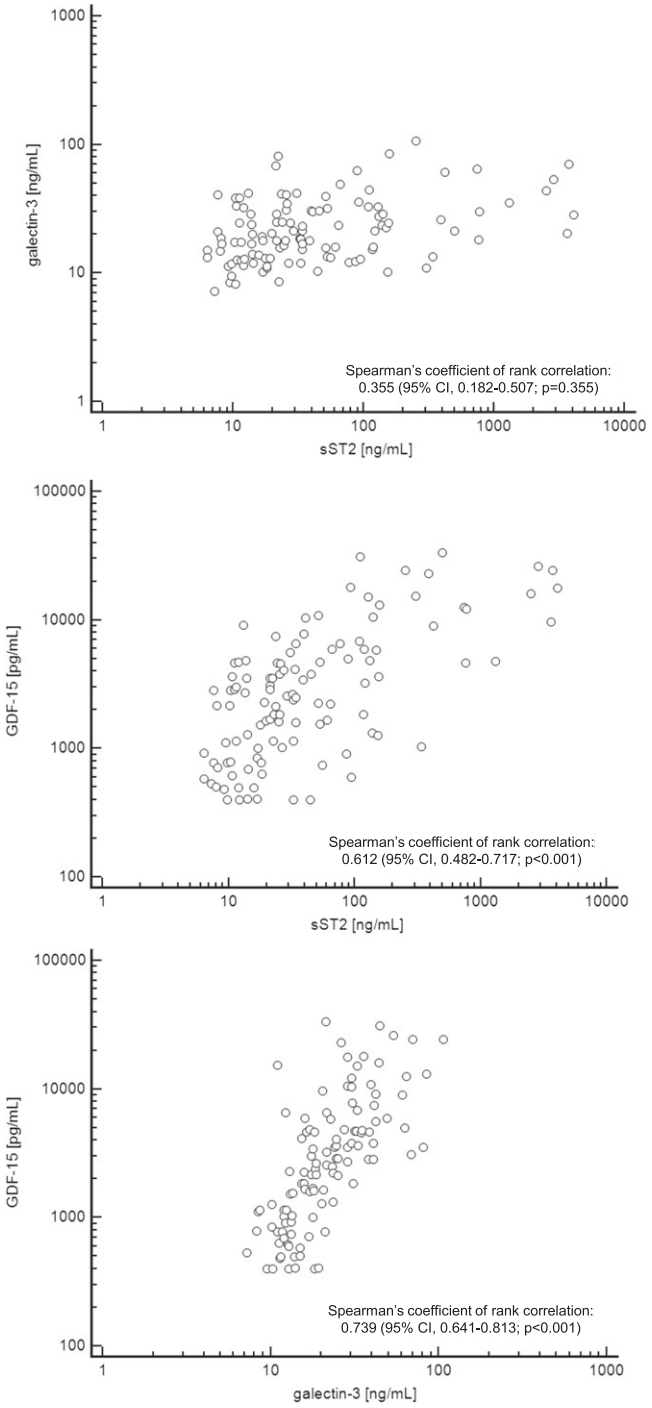

Fig. 2. Scatterplots of (A) sST2 plasma concentrations vs. galectin-3 plasma concentrations; (B) sST2 plasma concentrations vs. GDF-15 plasma concentrations; and (C) galectin-3 plasma concentrations vs. GDF-15 plasma concentrations in the 112 study participants. In each graph, the plasma concentrations of each of the 112 study participant were plotted as open circles. The method comparison graphs display the results of Spearman rank correlation.

Fig. 2 demonstrates the association between sST2 and galectin-3, between sST2 and GDF-15, and between galectin-3 and GDF-15, respectively, in the entire cohort of the 112 study participants. Non-parametric correlation analyses revealed Spearman's coefficient of rank correlations of 0.355 (95% CI, 0.182–0.507; $p = 0.355$) for sST2 vs. galectin-3, of 0.612 (95% CI, 0.482–0.717; $p < 0.001$) for sST2 vs. GDF-15, and of 0.739 (95% CI, 0.641–0.813; $p < 0.001$) for galectin-3 vs. GDF-15.

4. Discussion

The main finding of the present study was that the plasma concentrations of the three biomarkers sST2, galectin-3, and GDF-15 were increased not only in HF but also in several other non-cardiac diseases. In HF and other diverse non-cardiac conditions such as infectious disease, or chronic kidney disease, however, the magnitude of the increment for sST2, galectin-3, and GDF-15 differs considerably. Compared to healthy controls, sST2 was increased ~2.5-fold in HF, galectin-3 ~1.5-fold, and GDF-15 ~4.4-fold. In pneumonia for example, sST2 was increased ~3.5-fold, galectin-3 ~1.4-fold, and GDF-15 ~5.4-fold; and in sepsis, sST2 was increased ~70-fold, galectin-3 ~2.7-fold, and GDF-15 ~27-fold. In general, across most of the disease groups of this study, sST2 and GDF-15 plasma concentrations seem to have a greater amount of increase compared with plasma concentrations of galectin-3. Thus, there is a different behavior of the three analytes in various medical conditions which can be explained by different pathophysiological functions of these biomarkers. Nevertheless, we saw associations between the three markers as demonstrated by correlation analyses; especially the relationship between galectin-3 and GDF-15 was relatively strong in our study.

It is well known from the literature that cardiac troponins are often increased in HF [1,3] and in sepsis [13], and that cardiac troponins are considered prognostic markers in both conditions [1,3,13]. Similarly, hs-cTnI plasma concentrations were markedly increased in HF and in sepsis in our study as well.

ST2 is an interleukin-1 receptor family member with transmembrane (ST2L) and soluble isoforms (sST2) [14–17]. ST2L is a membrane bound receptor, and interleukin-33 (IL-33) is the functional ligand for ST2L [14–17]. In principle, IL-33 functions as a danger signal or an alarmin by signaling the presence of tissue damage to local immune cells after exposure to pathogens, injury-induced stress, or death by necrosis [15–17]. IL-33/ST2L signaling leads to inflammatory gene transcription and ultimately to the production of inflammatory cytokines/chemokines and induction of immune response [16,17]. sST2, a soluble truncated form of ST2L, is secreted into the circulation and is believed to function as a "decoy" receptor for IL-33, inhibiting the effects of IL-33/ST2L signaling [14–17]. Thus, increased concentrations of sST2 in the circulation attenuate the systemic biologic effects of IL-33. Blood concentrations of sST2 are significantly increased, e.g., in inflammatory/infectious diseases, in cancer and in cardiac disease but not in chronic kidney disease [1–3,5,16,17]. The major source of circulating sST2 in healthy individuals and in patients with distinct diseases (especially in human cardiac disease) is, however, currently not established [16,17].

Galectin-3 is a unique member of chimera type galectins and is involved in a large number of disease processes [18,19]. Galectin-3 contains a carbohydrate-recognition-binding domain that enables the specific binding of β-galactosides [18,19]. Galectin-3 exhibits both intracellular and intracellular functions and it has a concentration dependent ability to be monomeric or form oligomers [18,19]. Galectin-3 is involved in cell adhesion, activation, proliferation, apoptosis as well as cell migration [18–20]. It plays an important role not only in cancer [21] but also in inflammation [18,19,21]. In this context, galectin-3 can be viewed as regulatory protein acting at several stages along the continuum from acute inflammation to chronic inflammation and tissue fibrinogenesis [18]. Indeed, the involvement of galectin-3 in various "inflammatory/fibrotic" conditions such as arthritis, asthma, pneumonia, atherosclerosis, and kidney disease has been described [18,19,21]. Even in the pathophysiology of HF, galectin-3 plays a biological role through inflammation and fibrosis [1–3,21].

GDF-15 is a protein belonging to the transforming growth factor beta superfamily that has a role in regulating inflammatory and apoptotic pathways in acute and chronic tissue injury [22–25]. The expression of GDF-15 in virtually all tissues suggests its importance in general and basic cellular functions [22,23]. The expression of GDF-15 is upregulated in many different pathological conditions, including inflammation, cancer, cardiovascular disease, pulmonary disease, diabetes, and renal disease [22–27]. On a molecular level, GDF-15 expression seems to be controlled by, e.g., the ubiquitous transcription factor p53, which responds to various cellular stress signals, such as hypoxia, ischemia, oxidative stress, inflammation, or acute tissue injuries [24,25]. Plasma concentrations of GDF-15 are believed to reflect these stressors and their role on disease progression and prognosis [25]. Notably, the receptor of GDF-15 and the downstream signaling pathways that drive its action are currently not established [22,24]. In addition, it is still unclear whether increased plasma concentrations of GDF-15 can cause direct damage or may represent a protective response to biologic stress [23].

Taken together, the three biomarkers sST2, galectin-3, and GDF-15 are not specific for a distinct medical condition but rather represent general markers of disease and mortality [16–27]. Because increased plasma concentrations of sST2, galectin-3, and GDF-15 are not specific for a distinct disease group as demonstrated in this study, we conclude that the three biomarkers are of limited value for diagnostic purposes. For example, in emergency patients with acute shortness of breath, neither of three biomarkers can be considered useful for differentiating between dyspnea attributable to acute HF and dyspnea attributable to other causes, e.g., pneumonia or COPD.

On the other hand, there is a large body of evidence indicating that these three markers are valuable prognosticators for mortality endpoints in a broad spectrum of diseases as well as in population-based cohorts [16,17,21–27]. In addition to this, we would like to draw the attention to another issue of the potential of the three markers for prognostic purposes. In an emergency setting of acute dyspnea, it is well known that coincidence of HF and pulmonary disease (e.g., pneumonia or COPD) is common and also related to worse outcome [28–30]. Because plasma concentrations of sST2, galectin-3 and GDF-15 were increased in our patients with HF and co-morbidity of pneumonia compared to the patients suffering from HF without any co-morbidity or from pneumonia without any co-morbidity, the increased plasma concentrations of the three analytes in HF and concomitant pneumonia might reflect the increased mortality rates in this group. However, these considerations deserve further study.

A limitation of our study is certainly the small number of study participants in each disease group. However, after screening a huge number of patients in our hospital, we were able to completely disentangle various clinical conditions suspected to increase the concentrations of the analytes with our study design. We further acknowledge that that proportion of male was greater in every group compared to the control group, and that the individuals of the control group were younger than those of the other groups. In addition, this study was designed to evaluate plasma concentrations of sST2 in various diseases, and it was a post-hoc decision to measure galectin-3 and GDF-15 plasma concentrations in our cohort. This was the reason why we decided to rely on descriptive statistics only in our evaluation study and not to adjust for multiple comparisons. However, our study should be considered explorative and hypothesis generating for future work. In addition, we would like to further acknowledge that we have measured the biomarkers of interest at one time point only. It would be intriguing to have multiple serial measurements in time course to see how the biomarkers behave as a consequence of treatment initiation. This knowledge could refine the prognostic value of the novel biomarkers sST2, galectin-3 and GDF-15 in the different disease groups evaluated in this study.

Conflict of interest statement

Author's conflict of interest disclosure

The authors stated that there are no conflicts of interest regarding the publication of this article. Critical Diagnostics (San Diego, CA, USA), Abbott Diagnostics (Abbott Park, IL, USA), and Roche Diagnostics (Mannheim, Germany) provided reagents for measurement of sST2, galectin-3 and GDF-15 plasma concentrations, respectively, free of charge. The three companies did not play a role (1) in the study design; (2) in the collection, analysis, and interpretation of data; (3) in writing of the report; or (4) in the decision to submit the report for publication.

Research funding

None declared.

Employment or leadership

None declared.

Honoraria

Thomas Mueller and Benjamin Dieplinger have received speaking fees from Abbott Diagnostics and Roche Diagnostics.

Nonstandard abbreviations

BMI	body mass index
BNP	B-type natriuretic peptide
CAD	coronary artery disease
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
eGFR	estimated glomerular filtration rate
GDF-15	growth-differentiation factor-15
HF	heart failure
hs-cTnI	high-sensitivity cardiac troponin I
IL-6	interleukin-6
LVEF	left ventricular ejection fraction
PCT	procalcitonin
sST2	soluble ST2
URL	upper reference limit

References

[1] Gaggin HK, Januzzi Jr JL. Biomarkers and diagnostics in HF. Biochim Biophys Acta 1832;2013:2442–50.
[2] Schmitter D, Cotter G, Voors AA. Clinical use of novel biomarkers in heart failure: towards personalized medicine. Heart Fail Rev 2014;19:369–81.
[3] Pouleur AC. Which biomarkers do clinicians need for diagnosis and management of heart failure with reduced ejection fraction? Clin Chim Acta 2015;443:9–16.
[4] Yancy CW, Jessup M, Bozkurt B, et al. American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147–239.
[5] Dieplinger B, Januzzi Jr JL, Steinmair M, et al. Analytical and clinical evaluation of a novel high-sensitivity assay for measurement of soluble ST2 in human plasma—the Presage ST2 assay. Clin Chim Acta 2009;409:33–40.
[6] Senni M, Tribouilloy CM, Rodeheffer RJ, et al. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. Circulation 1998;98:2282–9.
[7] Niederman MS, Mandell LA, Anzueto A, et al. American Thoracic Society. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med 2001;163:1730–54.
[8] Burge S, Wedzicha JA. COPD exacerbations: definitions and classifications. Eur Respir J 2003;21:46S–53S.
[9] Levey AS, Eckardt KU, Tsukamoto Y, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2005;67:2089–100.
[10] American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992;20:864–74.
[11] La'ulu SL, Apple FS, Murakami MM, Ler R, Roberts WL, Straseski JA. Performance characteristics of the ARCHITECT galectin-3 assay. Clin Biochem 2013;46:119–22.
[12] Standards Institute Laborator Clinical. Evaluation of precision performance of clinical chemistry devices; approved guideline. CLSI Document EP5-A. Wayne, PA: CLSI; 1999.
[13] Bessière F, Khenifer S, Dubourg J, Durieu I, Lega JC. Prognostic value of troponins in sepsis: a meta-analysis. Intensive Care Med 2013;39:1181–9.
[14] Liew FY, Pitman NI, McInnes IB. Disease-associated functions of IL-33: the new kid in the IL-1 family. Nat Rev Immunol 2010;10:103–10.
[15] Villarreal DO, Weiner DB. Interleukin 33: a switch-hitting cytokine. Curr Opin Immunol 2014;28C:102–6.
[16] Mueller T, Jaffe AS. Soluble ST2 — analytical considerations. Am J Cardiol 2015; 115(7S):8B–21B.
[17] Dieplinger B, Mueller T. Soluble ST2 in heart failure. Clin Chim Acta 2015;443C: 57–70.
[18] Henderson NC, Sethi T. The regulation of inflammation by galectin-3. Immunol Rev 2009;230:160–71.
[19] Gao P, Simpson JL, Zhang J, Gibson PG. Galectin-3: its role in asthma and potential as an anti-inflammatory target. Respir Res 2013;14:136.
[20] Song L, Tang JW, Owusu L, Sun MZ, Wu J, Zhang J. Galectin-3 in cancer. Clin Chim Acta 2014;431:185–91.
[21] Ravani P, Barrett BJ. Galectin-3 and new-onset CKD: marker or mediator? J Am Soc Nephrol 2013;24:1342–4.
[22] Corre J, Hébraud B, Bourin P. Concise review: growth differentiation factor 15 in pathology: a clinical role? Stem Cells Transl Med 2013;2:946–52.
[23] Lindahl B. The story of growth differentiation factor 15: another piece of the puzzle. Clin Chem 2013;59:1550–2.
[24] Mimeault M, Batra SK. Divergent molecular mechanisms underlying the pleiotropic functions of macrophage inhibitory cytokine-1 in cancer. J Cell Physiol 2010;224: 626–35.
[25] Kempf T, Wollert KC. Risk stratification in critically ill patients: GDF-15 scores in adult respiratory distress syndrome. Crit Care 2013;17:173.
[26] Wollert KC, Kempf T. Growth differentiation factor 15 in heart failure: an update. Curr Heart Fail Rep 2012;9:337–45.
[27] Unsicker K, Spittau B, Krieglstein K. The multiple facets of the TGF-β family cytokine growth/differentiation factor-15/macrophage inhibitory cytokine-1. Cytokine Growth Factor Rev 2013;24:373–84.
[28] Dieplinger B, Gegenhuber A, Kaar G, Poelz W, Haltmayer M, Mueller T. Prognostic value of established and novel biomarkers in patients with shortness of breath attending an emergency department. Clin Biochem 2010;43:714–9.
[29] Thomsen RW, Kasatpibal N, Riis A, Nørgaard M, Sørensen HT. The impact of preexisting heart failure on pneumonia prognosis: population-based cohort study. J Gen Intern Med 2008;23:1407–13.
[30] Macchia A, Monte S, Romero M, D'Ettorre A, Tognoni G. The prognostic influence of chronic obstructive pulmonary disease in patients hospitalised for chronic heart failure. Eur J Heart Fail 2007;9:942–8.
[31] Ho JE, Mahajan A, Chen MH, et al. Clinical and genetic correlates of growth differentiation factor 15 in the community. Clin Chem 2012;58:1582–91.