Soluble ST2 and its relation to inflammatory, vascular atherosclerotic, and calcification markers in patients with atrial fibrillation or heart failure at moderate-to-high cardiovascular risk

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ABSTRACT

Background: Cardiovascular diseases (CVDs) are the major cause of death globally. Among them, heart failure (HF) and atrial fibrillation (AF) result in poor prognosis and quality of life. Standard methods for assessing AF and HF, through history and physical examination, have limited sensitivity and specificity, which lead to delayed diagnosis and high risk of mortality. The identification of biomarkers able to detect the early stages of disease and/or their progression is of great importance for improving the clinical outcome. As AF and HF often coexist, it would be of great importance to find a biomarker with diagnostic utility in predicting HF in AF patients. Soluble suppression of tumorigenesis-2 (sST2) is a part of the cardioprotective IL-33/ST2 signaling pathway and may serve as a candidate biomarker for HF and AF. We aimed to evaluate sST2 serum levels in patients with AF and HF with preserved ejection fraction (HFpEF) and to explore potential relationships with traditional CVD risk factors and with novel biomarkers for vascular calcification such as undercarboxylated matrix Gla-protein (ucMGP). **Materials and Methods:** This study included 99 patients stratified into three groups: HFpEF (n=19), paroxysmal or persistent AF in sinus rhythm (n=33), and control group without CVD but at moderate-to-high CVD risk (n=47). Hemodynamic and anthropometric measures, coronary artery calcification (CAC), routine laboratory parameters, circulating ucMGP, and sST2 were measured. **Results:** sST2 levels were highly elevated in HFpEF patients. Significant positive correlation was found between sST2 and CAC-score (r=0.237, p=0.039), negative relations with serum lipids in AF patients, and positive association with serum C-reactive protein (r=0.609, p=0.018) in HFpEF patients. Soluble ST2 positively correlates with ucMGP in the entire studied population (r=0.252, p=0.006) and in the combined CVD group (AF+HFpEF) (r=0.254, p=0.036). **Conclusions:** sST2 levels emerge as a novel biomarker in CVD and may have prognostic importance for HF prediction in AF patients.

Key words: *Cardiovascular diseases, Lipids, Matrix Gla protein, ST2 protein, Vascular calcification*

Cardiovascular diseases (CVDs) are the major cause of death globally. Among them, heart failure (HF) and atrial fibrillation (AF) result in poor prognosis and quality of life for the patient. Despite the advances in the control of CVDs, HF and AF incidences and prevalence continue to increase [1,2]. HF with preserved ejection function (HFpEF) comprises approximately 50% of all cases of HF [3] and may account for up to two-thirds of cases in patients older than 70 years [4]. Regardless of age, the lifetime risk of developing HF is approximately 20% for all patients older than 40 years [5]. AF is the most common arrhythmia encountered in clinical practice that can cause major cardiovascular complications, including stroke and HF [6]. The mechanism of AF is still not completely understood. Nowadays, inflammation, cardiac fibrosis, and remodeling are considered to play an important role in the development and progression of atrial fibrillation [7,8]. Standard methods for assessing AF and HF, through history and physical examination, have limited sensitivity and specificity, which lead to delayed diagnosis and high risk of mortality [9].

The identification of biomarkers able to detect the early stages of disease and/or their progression is of great importance to take measures for improving the clinical outcome [10]. There is no single diagnostic test for HF and AF. As AF and HF often coexist and interact with each other, it would be of great importance to find a biomarker with diagnostic utility in predicting HF in AF patients [8]. The current guidelines recommend the measurement of natriuretic peptides and cardiac troponin for the diagnosis and prognosis of HF [11,12]. In addition to these well-established cardiovascular biomarkers, a novel biomarker, soluble suppression of tumorigenesis-2 (sST2), integrating inflammation, fibrosis, and cardiac stress are attracting the attention for its potential utility in HF and AF management.

sST2 is a member of the interleukin-1 (IL-1) receptor family. It possesses two major isoforms: a transmembrane receptor (ST2L) and a soluble receptor (sST2), detected in the blood plasma. *In vitro* studies have shown that cardiomyocytes subjected to mechanical stress express ST2 [13]. IL-33, secreted by many cells in response to damage, acts as a functional ligand for ST2L. Recently, IL-33 is found to be an important part of IL-33/ST2 signaling pathway [13]. When IL-33 is bound to ST2L, it exerts cardioprotective effect (anti-hypertrophic and anti-fibrotic effects). Soluble ST2 acts as a decoy receptor for IL-33 and its binding results in neutralization the beneficial activity of circulating IL-33 and suppression of its cardioprotective activity [14]. sST2 is produced by the myocardial and vascular cells, as well as in lungs and other organ tissues [15]. A lot of research is recently focused on IL-33/ST2 pathway as a novel area of interest in CVD and potential therapeutic target in the prevention and treatment of HF and AF [16,17].

The aim of the present study was to evaluate the serum sST2 levels in AF and HFpEF patients and to explore potential relationships with traditional risk factors for CVD and with novel biomarkers for vascular calcification such as ucMGP.

MATERIALS AND METHODS

Patients

The methodology of the study was presented elsewhere [18]. Briefly, we included 99 patients who were admitted at the Cardiology Clinics of the University Hospital – Varna between October 2018 and January 2020. The patients were stratified into three definite groups: with HF with preserved ejection fraction (HFpEF) (n=19), patients with paroxysmal or persistent AF in sinus rhythm (n=33), and control group of people without CVD and cancer but at moderate-to-high CVD risk (n=47). Demographic data and history of hypertension, diabetes, and hyperlipidemia were recorded by structured interview. Hemodynamic and anthropometric measures were taken from all participants, including blood pressure, heart rate, weight, height, and waist circumference (WC). Body mass index (BMI) was calculated according the established formula weight/height^2 (kg/m^2) [19]. Patients with proven ischemic heart disease or stroke, cardiomyopathy, type 1 diabetes mellitus, chronic renal disease IV stage or more (with estimated glomerular filtration rate [eGFR]<30 mL/min/1.73 m^2), known thyroid gland diseases, and active cancer were excluded from the study.

Coronary Artery Calcification (CAC) Assessment

CAC was assessed by dual-source multislice computer tomography and overall and separate arterial CAC score (CACS) were evaluated using Agatston's method [20].

Laboratory Measurements

Routine laboratory parameters – glucose, urea, creatinine, uric acid (UA), total cholesterol (TC), triglycerides (TG), HDL-cholesterol (HDL-C), and LDL-cholesterol (LDL-C) for each patient were extracted from the medical documentation. Castelli risk indexes (TC/HDL-C and LDL-C/HDL-C) and eGFR were calculated. The plasma levels of circulating ucMGP were determined by a commercial ELISA kit based on competitive mono-antibody assay (Cusabio, Wuhan, China). Soluble sST2 concentrations in human blood plasma were assayed by commercial sandwich-type ELISA kit with detection range 31.25–2000 pg/ml, sensitivity 18.75 pg/ml, and coefficient of variation <10% (Elabscience, Wuhan, China).

Statistical Analysis

Data analysis was performed on GraphPad Prism v. 8.3. (GraphPad Software, San Diego, CA USA) and SPSS v.23 (SPSS Inc., Chicago, IL, USA). Standard statistical methods, such as descriptive statistics and one-way analysis of variance including Bonferroni correction, were used. For categorical data, Chi-square test or Fisher's exact test were applied. The relationship between continuous variables was evaluated by Pearson's correlation analysis, and if significant relation was found, a linear regression analysis was applied to test the associations of sST2 with other tested parameters. Receiver operating characteristic (ROC) analysis was performed for evaluation the predictive power of serum sST2. All statistical analyses were two-tailed and statistical significance was considered at $p<0.05$.

Ethical Issues

The study was approved by the Local Ethical Committee (Protocol No 75/07.06.2018). Written informed consent was obtained from all participants in the study.

RESULTS

Patients' Characteristics

BMI and WC were higher in AF and HFpEF groups versus controls. Smokers were more frequently present among controls (55.3%) and were the least common among HFpEF patients (31.6%). The CACS reached highest values in the HF group. The prevalence of comorbidities, such as arterial hypertension, hyperlipidemia, diabetes, and family history of ischemic heart disease was similar in both AF and HFpEF patients. Significantly higher creatinine ($p<0.0001$) and UA ($p=0.049$) levels were found in HFpEF patients compared to controls. ucMGP was with highest median value in the HF group (5.5 mg/L, IQR 2.9 – 9.6 mg/L, $p=0.06$) (Table 1).

sST2 and CVD Pathology

Significant and gradual increase was indicated for serum sST2 in dependence of CVD pathology. The mean value was highest for the HFpEF patients (0.98±0.67 ng/ml), lower in AF (0.64±0.43 ng/ml), and lowest for the controls (0.57±0.38 ng/ml) (Fig. 1).

Table 1: General characteristics of the studied patients

Parameter	Controls	AF patients	HFpEF patients
n	47	33	19
Gender (male/female)	18/29	11/22	5/14
Body mass index (kg/m^2)	27.5±5.4	29.9±5.6	30.2±5.9
Waist circumference (cm)	91.3±15.3	101.0±14.3	103.8±14.0
Smoking (%)	55.3%	36.4%	31.6%
CAC score (AU)	77.3±268.8	351.4±591.2	358.2±473.3
TG (mmol/L)	1.1 (0.8–1.6)	1.1 (10.8–5.9)	1.6 (1.0–2.6)
TC (mmol/L)	5.3±0.9	4.6±1.0	5.2±1.4
HDL-C (mmol/L)	1.4±0.4	1.4±0.5	1.4±0.3
LDL-C (mmol/L)	3.2±0.7	2.6±0.9	3.1±1.1
CRP (mg/L)	15.2 (0.9–29.5)	6.3 (2.2–11.1)	2.8 (1.0–7.0)
Urea (mmol/L)	5.8±0.8	7.3±3.7	9.1±6.3
Creatinine (μmol/L)	68.2±13.6	81.4±17.8	89.2±30.7
Uric acid (mmol/L)	321.5±109.5	379.7±142.6	382.0±86.8
ucMGP (mg/L)	2.9 (1.8–7.7)	4.8 (1.2–8.7)	5.5 (2.9–9.6)
sST2 (ng/ml)	0.57±0.38	0.64±0.43	0.98±0.67

Data are presented as mean ± SD, median (IQR) or number and percentage (%), as appropriate. AF: Atrial fibrillation, HFpEF: Heart failure with preserved ejection function, CAC: Coronary arterial calcium, TC: Total cholesterol, TG: Triglycerides, HDL-C: High density lipoprotein cholesterol, LDL-C: High density lipoprotein cholesterol, CRP: C-reactive protein, ucMGP: Uncarboxylated matrix Gla-protein, sST2: Soluble suppression of tumorigenesis-2

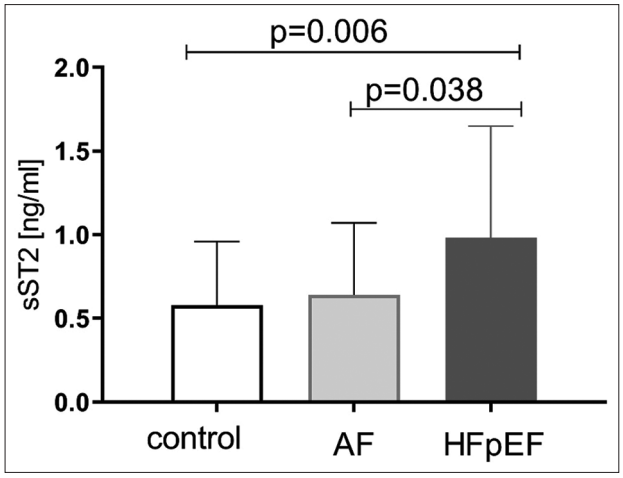

Figure 1: Changes of sST2 serum levels by CVD pathology. Data are given as mean±SD. Statistical significance was encountered at p<0.05. CVD: Cardiovascular disease, AF: Atrial fibrillation, HFpEF: Heart failure with preserved ejection fraction

To evaluate how the severity of vascular calcification affects the sST2 levels, we stratified the participants according to their CAC score into two groups: without coronary calcium (CACS=0) and with calcium deposits (CACS>0). Although non-significant, a weak trend for an increase of sST2 values in the patients with coronary arterial calcification was observed (0.66±0.44 ng/ml vs. 0.69±0.52 ng/ml, p=0.48). Correlation analysis revealed significant positive associations between sST2 and CACS for both CACS groups (Pearson r=0.288, p=0.036 for CACS=0; Pearson r=0.237, p=0.039 for CACS>0).

sST2 and Risk Factors for CVD

Soluble ST2 levels were higher, although insignificantly in female versus male (1.11±0.69 ng/ml vs. 0.62±0.52 ng/ml, p=0.30) and in abdominally obese versus non-obese (1.06±0.69 ng/ml vs. 0.87±0.69 ng/ml, p=0.86) HFpEF patients. Age, BMI, AH, smoking status, presence of hyperlipidemia, or diabetes did not affect sST2 levels in both AF and HFpEF patients.

A significant decrease in sST2 serum levels in AF patients was indicated for the groups with UA, LDL-C, and LDL-C/HDL-C levels above the corresponding median values. The same tendency for sST2 levels with UA and LDL-C above their median values was observed for HFpEF patients. On the contrary, a slightly increase of sST2 levels (by 12.6% and 11.1%, respectively) was found in HFpEF patients with TC/HDL-C and LDL-C/HDL-C above their median values (Fig. 2a and b).

Correlation analysis revealed significant negative relationships between sST2 serum levels TC/HDL-C (Pearson r=−0.395, p=0.015), and LDL-C/HDL-C (Pearson r=−0.358, p=0.026) in AF patients. In HFpEF patients, significant positive association was found only between sST2 and serum CRP values (Pearson r=0.609, p=0.018) (Fig. 3a-c).

sST2 and Circulating ucMGP Levels

Studying the relationship between sST2 and ucMGP as a novel marker for vascular calcification, we found a significant positive relation between these two parameters for the entire studied population (Pearson r=0.252, p=0.006) and for the patients of the combined CVD group (AF+HFpEF) (Pearson r=0.254, p=0.036). Association with borderline significance was indicated only for the HFpEF patients (Pearson r=0.359, p=0.066) (Fig. 4a and b).

Predicting Power of sST2

ROC analysis was performed to evaluate the diagnostic utility of sST2 for detection HFpEF in AF patients. The area under the ROC curve was 0.666, p=0.049 (Fig. 5).

DISCUSSION

In the present study, we have shown that the serum levels of sST2 gradually increase with CVD pathology demonstrating highest levels in HFpEF patients. Similar results revealing higher sST2 levels in HF patients' versus controls comprising non-CVD healthy individuals, above 50 years of age, were reported by [14,21]. These higher sST2 levels in HF patients are not surprising, as sST2 increases in conditions with high cardiomyocyte load and stretch, activated inflammation and increased macrophages' activity, and activated cardiac

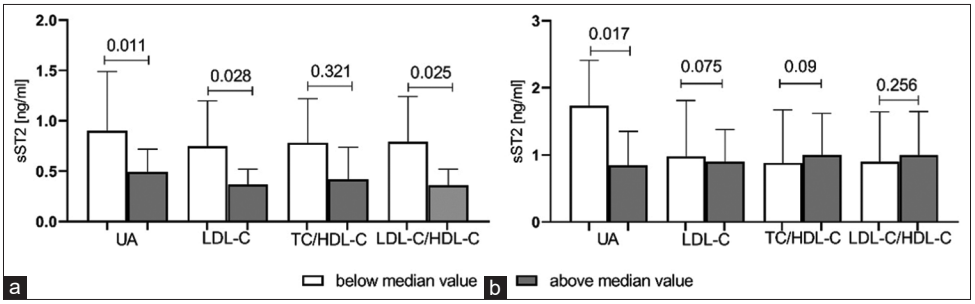

Figure 2: (a and b) Changes in sST2 serum levels in AF patients according to the tested conventional risk factors for CVD. Data are given as mean±SD. Statistical significance was considered at p<0.05. (a) Atrial fibrillation (AF) patients. (b) Heart failure with preserved ejection fraction (HFpEF) patients. CVD: Cardiovascular disease, UA: Uric acid (median value=350.0 mmol/L), LDL-C: Low-density lipoprotein cholesterol (median value=3.20 mmol/L), TC/HDL-C: Total cholesterol/high-density lipoprotein cholesterol ratio (median value=3.63), LDL-C/HDL-C: Low-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio (median value=2.27)

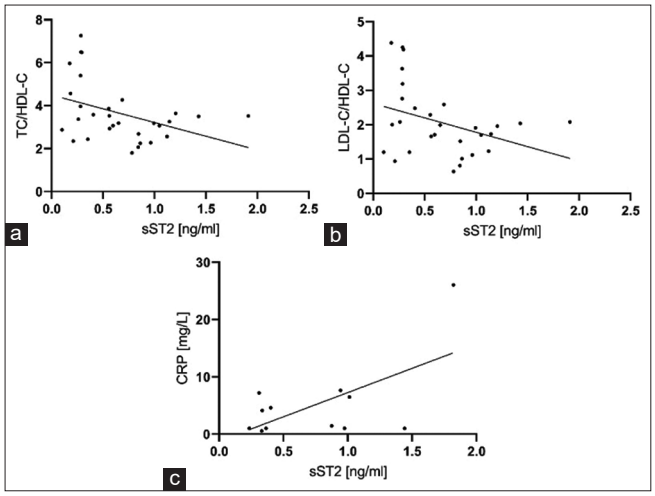

Figure 3: (a-c) Correlations between serum sST2, lipid indexes and hsCRP as conventional risk factors for CVD. Pearson correlation analysis was performed. Statistical significance was considered at p<0.05. (a) Atrial fibrillation patients. (b) HFpEF patients. CVD: Cardiovascular disease, TC/HDL-C: Total cholesterol/high-density lipoprotein cholesterol ratio (Pearson r=−0.395, p=0.015), LDL-C/HDL-C: Low-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio (Pearson r=−0.358, p=0.026), hsCRP: High sensitive C-reactive protein (Pearson r=0.609, p=0.018). HFpEF: Heart failure with preserved ejection fraction

fibrosis [21]. The prognostic importance of sST2 was established in acute HF patients, both with preserved and with reduced ejection fraction [23]. Prognostic significance of sST2 was also reported for patients with chronic HF [24].

We indicated a positive relationship with CRP for HFpEF participants. Consistent with our results are the findings of [25], showing a correlation of sST2 with inflammation parameters, such as temperature, leukocyte count, and CRP. Such association is not surprising as sST2 being a regulator of T-helper cell type 2 is involved in autoimmune and inflammatory response [26]. Other studies have also shown that in HF patients sST2 concentrations are associated with systemic inflammation [27]. Moreover, it is considered that circulating sST2, classified as an indicator for myocyte stress, in HF patients is mainly produced in extracardiac tissues in response to inflammatory and fibrotic stimuli and the subclinical inflammation is important factor for HF progression [27]. In addition, pro-inflammatory cytokines such as TNF-alpha or IL-6 also provoke sST2 release and enhanced sST2 levels reflect the involvement of inflammation in HF pathology [28].

In agreement with other studies, our data also revealed no significant sex-related differences in circulating sST2 in HFpEF patients [29]. However, the results from the Framingham Heart Study showed higher values for males than in females [30]. The same sex difference in the sST2 values was also reported in a Korean population sample [31], in patients with HF and CVD and in the general population [32]. We did not found associations of sST2 with age, arterial hypertension, and obesity for both AF and HFpEF patients. Our results are supported by the findings that sST2 is independent of other factors such as arterial hypertension, renal dysfunction, obesity, or age [33].

We found significant negative associations of sST2 with TC/HDL-C and LDL-C/HDL-C for AF patients, and positive insignificant correlations in the HF group. Gül *et al*. [34] found significant negative correlation between TC, triglycerides, and sST2 and positive correlation between LDL-C in 130 patients with HFpEF followed for 1 year. The same negative association between TC/HDL-C and sST2 was also found in our control group. This is in agreement with the results from the cohort community-based study, where they found significant negative correlation between TC and LDL-C with sST2 [31]. On the contrary, the hsCRP was positively related with the TC and LDL-C in this general population of Asian origin. Another large population study (in more than 24,000 Koreans) showed similar negative association between sST2, TC, and TG. The same protective effect of IL-33 on lipids was observed in non-diabetic subjects, with negative correlations of IL-33 with TC, LDL-C, and TG [35].

The coronary calcification showed non-significant weak trend for an increase of sST2 in the patients with CAC in our sample. Correlation analysis revealed significant positive associations between sST2 and CACS for both CACS groups (Pearson r=0.288, p=0.036 for CACS=0; Pearson r=0.237, p=0.039 for CACS>0). Luo *et al*. reported similar results in patients with non-ST-elevation acute coronary syndrome [36]. They found higher serum sST2 levels among patients with spotty plaque calcification, than those with large calcification. A recent study in

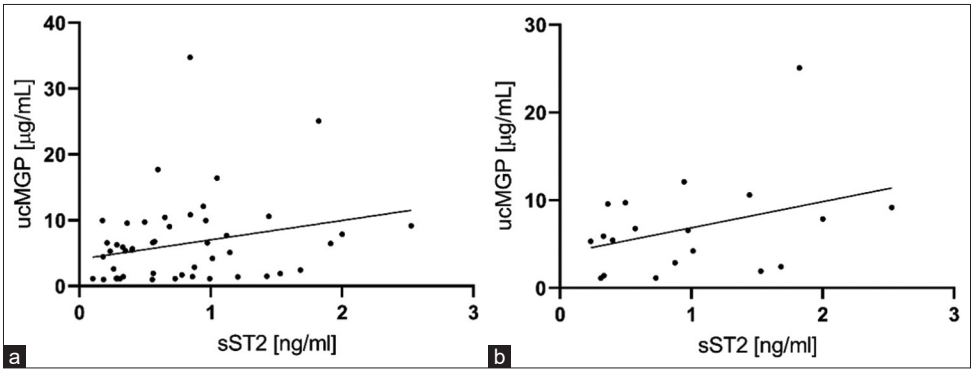

Figure 4: (a and b) Associations between serum sST2 and circulating ucMGP in CVD patients. Pearson correlation analysis was performed. Statistical significance was considered at p<0.05. (a) combined CVD group: atrial fibrillation and HFpEF patients (Pearson r=0.254, p=0.036), (b) HFpEF patients (Pearson r=0.359, p=0.066). CVD: Cardiovascular disease, ucMGP: Undercarboxylated matrix Gla-protein, HFpEF: Heart failure with preserved ejection fraction

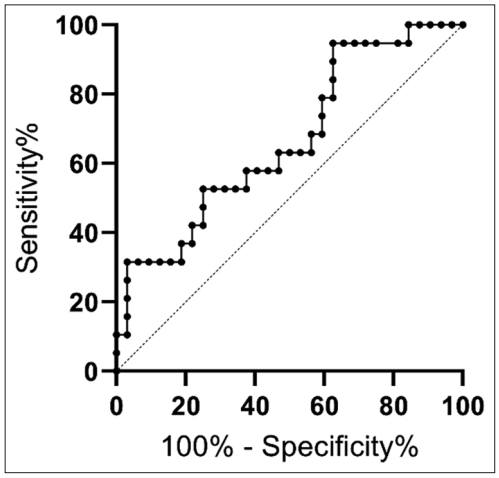

Figure 5: Predictive power of sST2 for detection HFpEF in AF patients. Area under the ROC curve (AUC)=0.67, p=0.049. AF: Atrial fibrillation, HFpEF: Heart failure with preserved ejection fraction

patients with chronic kidney diseases confirmed that the elevated levels in sST2 were associated with higher risk of incident CVD and of non-zero CAC score [37].

It is considered that macrophages may play a role in the relationship between sST2 and calcification. The previous studies have demonstrated that sST2 may suppress the differentiation of macrophages toward the anti-inflammatory phenotype and, thus, may facilitate calcification and plaque progression [38].

The Framingham Heart Offspring Study group examined the association between sST2 and subclinical atherosclerosis to clarify the relationship between sST2/IL-33 pathway and vascular biology. They did not found any significant association between sST2 levels and carotid intima-media thickness (IMT) or plaque formation in the general population [39]. The only biomarker which predicted the IMT and plaque change in internal carotid artery wall, but not of common carotid artery, was plasma growth differentiation factor-15, while sST2 and high-sensitive Troponin I failed to do that. Study on a Korean cohort did not found difference between the sST2 levels and the CACS category (high vs. low risk) [31]. However, they found a mild positive correlation with r=0.10 between sST2 and CACS, which are in agreement with our results (p=0.031) and (r=0.288, p=0.036 for CACS=0; r=0.237, p=0.039 for CACS>0).

In our study, we found a mild positive correlation between sST2 and ucMGP which were significant in the combined CVD group (p=0.032) and almost significant in the HF patients (p=0.066). This is the first time in the literature, as far as we know to find such an association between these two biomarkers. These two markers have different functions in the atherosclerotic process: the vitamin K-dependent ucMGP is a powerful inhibitor of vascular calcification while sST2, unlike membrane-bound ST2 is reducing the protective effects of IL-33 and, thus, increasing the possibility of cardiac fibrosis. One possible explanation may be that both can be produced by the vascular cells and may potentiate the secretion of each other. This is an interesting hypothesis, which renders further investigations.

Although the presence of AF increases the sST2 in our group with the arrhythmia, the difference was not significant from healthy controls and significantly lower than those with HF. Our results are in agreement with [40], who evaluated the role of sST2 to predict new-onset AF in healthy general population in Framingham, USA, and did not find any prognostic effect of sST2. On the contrary, there are data that high sST2 is related to AF occurrence [41] and progression [42] and predicts unfavorable result after ablation therapy [1,43]. Obviously, the level of fibrosis generation in the myocardium in AF is less than that in HF and does not result in significant sST2 elevation.

It is well established that coexisting of AF and HF is related to adverse prognosis [6,8]. There are data showing that AF occurs in more than half of individuals with HF, and HF occurs in more than one third of individuals with AF [44]. In addition, HF comprises 22% among patients with incident non-valvular AF [45]. There are limited studies examining the diagnostic utility of sST2 in predicting HF in AF patients. Similar to our results were reported by Chen *et al*. [8] who found for serum sST2 AUC=0.60, p=0.02 for predicting HF in non-valvular AF patients. It can be assumed that the determination of serum sST2 concentration may be a useful method for predicting HF development in patients with AF.

One limitation of the current study is that it was a single-centered study. The small sample size especially of HFpEF group is another limitation of this study.

CONCLUSION

Soluble ST2 levels are elevated in patients with HFpEF and, to lesser extent, in the patients with AF. This important biomarker of cardiac fibrosis is associated with other inflammatory markers, like hsCRP, as well as with other vascular atherosclerosis and calcification markers like lipids, CACS, and ucMGP. The definite role of sST2 in various CVD groups of patients is still to be further elucidated, as well as its prognostic implications in healthy people.

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