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ORIGINAL ARTICLE

Correlations between soluble ST2 concentration and the nutritional status in patients with heart failure with reduced ejection fraction — cross-sectional study

Correlations between sST2 and nutritional status in HFrEF patients

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Abstract

Background: Heart failure (HF) is a global problem that stimulates research on markers associated with the diagnosis and course of the disease. Soluble suppression of tumorigenicity-2 (sST2) is a receptor for interleukin-33 and is associated with increased mortality rates in HF patients. Malnutrition in HF is also connected with inflammation and is

associated with worse prognosis. The present study aimed to evaluate the relationship between sST2 concentration and the nutritional status of patients with HF with reduced ejection fraction (HFrEF).

Material and methods: 138 patients with HFrEF were enrolled in this cross-sectional study. Nutritional status was assessed using Geriatric Nutritional Risk Index (GNRI) and Controlling Nutritional Status (CONUT). The mean age was 53.6 ± 10.8 years.

Results: In the group with sST2 > 32.9 ng/mL, the GNRI score was higher and the associated risk of malnutrition was more common (29% vs. 12%; p = 0.011). Coherently in the group with sST2 > 32.9 ng/mL the median CONUT score was worse (2 [IQR 1–3] vs. 1 [IQR 0–2]; p = 0.0016) and the risk of malnutrition defined by this tool was also more prevalent (p = 0.0079). This relationship was independent of the concentration of natriuretic peptides, age and sex.

Conclusions: According to available research, this research is the first study showing that sST2 concentration is related with nutritional status in HFrEF patients. sST2 may help to evaluate the necessity for nutritional intervention in HFrEF patients.

Keywords: biomarkers, heart failure, HFrEF, nutritional status, suppression of tumorigenicity-2, ST2, malnutrition

Introduction

Heart failure (HF) remains a common and demanding problem in everyday clinical practice. Its increasing prevalence and poor prognosis despite new treatment methods stimulates further research, for example to characterize the impact of poor nutritional status on HF outcomes [1]. Moreover, in recent years the multi-marker approach in diagnosing and assessing the HF prognosis has been gaining interest [2, 3]. Natriuretic peptides, namely N-terminal pro-B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP),

are established diagnostic and prognostic HF markers [1]. Furthermore, many new biochemical markers have been found. The suppression of tumorigenicity-2 (ST2) is one of them. It is a member of the interleukin-1 receptor family released by myocardial and endothelial cells in response to cardiovascular stress [4, 5].

The interleukin-33/transmembrane ST2 (IL-33/ST2L) system **(Figure 1)** plays a part in the cardioprotective pathway, which prevents fibrosis, hypertrophy and apoptosis of cardiomyocytes, while also inhibiting the inflammatory response [6–9]. IL-33 is released into the extracellular space after tissue damage or necrosis and binds to the ST2L receptor. Through this interaction, IL-33 can initiate different inflammatory response pathways depending on the type of cell it acts on. Soluble ST2 (sST2) acts as a decoy receptor, directly bound to IL-33, and suppresses activation of JNK (c-Jun N-terminal kinase), NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and ERK (extracellular signal-regulated kinases), reversing the beneficial effects of the IL-33/ST2 system, thus destabilizing the defense mechanism. The association between sST2 and mortality rates was confirmed in patients with acute [10–13], chronic decompensated [14] and chronic HF [3, 15, 16]. Moreover, the association was observed regardless of the left ventricular ejection fraction (LVEF) values, as well as in patients with reduced ejection fraction (HFrEF) [3, 17, 18]. Higher sST2 concentration is connected with worse survival rate independently from parameters known for their association with worse prognosis in HF, for example natriuretic peptides, NYHA functional class or kidney function [17, 19, 20]. Recent studies suggest that the predictive value of sST2 is additive to NT-proBNP [21, 22].

Malnutrition is a common condition in HF patients and occurs when body cells receive insufficient energy, vitamins or macro- and microelements [1, 23] and it can lead to the worsening of heart performance and decreased survival [24]. The assessment of nutritional status in patients with HF is not clearly defined by guidelines. It is challenging due to

fluctuations in patients' body mass caused by overhydration or dehydration connected with the intensification of diuretic therapy. Previous studies show malnutrition and HF to be linked with inflammation [25, 26]. Cardiac diseases can activate the innate immune response, leading to inflammatory reactions. Additionally, malnutrition associated with the underlying disease, including HF, increases inflammatory cytokines and biomarkers concentrations [8, 27].

According to some studies, nutritional status is associated with adverse outcomes and worse clinical status [28, 29]. However, the results depend on the study design and differ across the LVEF, HF symptoms severity and age [30]. It was proven that nutritional treatment in HF may improve the prognosis [31]. Therefore, it is important to identify the patients with HF who are malnourished or are at risk of malnutrition.

Moreover, the relations of sST2 with nutritional status have not yet been established. There is a recent study that presents an association of cachexia with elevated sST2 [32] and one that correlates sST2 concentration with the risk of malnutrition defined by the geriatric nutritional risk index (GNRI) [33]. However, both mentioned papers involved different populations – the first included only male patients recruited regardless of LVEF [32], while the second one concerned acute HF irrespectively of LVEF [33]. Research in homogenous populations according to LVEF is important in order to facilitate both the assessment of nutritional status and the use of sST2 as a prognostic parameter in HF patients, especially in the HFrEF population.

Nutritional status may be quantified with dedicated scales. Geriatric Nutritional Risk Index (GNRI) is based on two variables: body mass index (BMI) and albumin concentration. A recent meta-analysis validated it as a predictor of mortality rates in HF patients [34]. This relation was also present in relatively younger patients under 75 years old [34]. Controlling Nutritional Status (CONUT) score takes into account concentrations of total cholesterol (TC),

albumin, and lymphocytes [35]. CONUT was confirmed to be associated with prognosis in HF patients [36–38].

The study aimed to evaluate the relationship between sST2 concentration and nutritional status in HFrEF patients.

Material and methods

Study population

A group of 160 consecutive patients with HF hospitalized at the cardiology department was enrolled in this prospective single-center observational study. After excluding patients with LVEF > 40% and with missing laboratory results, the final analysis included 138 patients with HFrEF (**Figure 2**). All patients were tested for the serum sST2 concentration. The inclusion criteria were: 1) age of 18 years or older; 2) HF diagnosis according to the International Classification of Diseases (ICD-10 code for the main diagnosis I50); 3) HF diagnosis at least three months or more before enrollment in the study; and 4) reduced LVEF ≤ 40%. Additionally, epidemiological, biochemical and echocardiographic data were gathered and analyzed.

Clinical, laboratory, and echocardiographic data

On admission to hospital, patients underwent laboratory tests, including electrolytes, lipid profile, complete blood count, fasting glucose, creatinine, total protein, and albumin. Natriuretic peptides such as BNP or NT-proBNP were also measured. The estimated glomerular filtration rate (eGFR) was calculated with the MDRD formula. Blood sST2 concentration was assessed using the Aspect-PLUS Rapid ST2 Test by Critical Diagnostics [39]. Additionally, all patients underwent echocardiographic examination. LVEF was assessed

using the Simpson method, according to the most recent European Society of Cardiology (ESC) guidelines [40].

Nutritional status evaluation

Nutritional status was assessed using scales depending on biochemical and clinical parameters: Geriatric Nutritional Risk Index (GNRI) and Controlling Nutritional Status (CONUT). GNRI score is a simple tool based on body mass index (BMI) and albumin concentration. It is calculated as follows: (1.489 × serum albumin [g/L]) + (41.7 × body weight/ideal body weight (IBW) [kg]); IBW was calculated with the formula: IBW = height^2 [m] × 22 [41]. When the body weight to IBW ratio was higher than 1, this ratio was set to 1. Patients with GNRI scores below 98 were classified as having no nutritional risk.

CONUT is derived from concentrations of total cholesterol (TC), albumin and lymphocytes count [35]. For each of these parameters, patients could get various numbers of points (0–6 for albumin, 0–3 for both TC and lymphocytes) and the total number of points could vary from 0 (best possible nutritional status) to 12 (severe malnutrition). Patients were classified according to CONUT score as normal nutrition (0–1 points), mild malnutrition (2–4), moderate malnutrition (5–8) and severe malnutrition (9–12) [35, 42].

Statistical analysis

Patients were divided into two equal-size groups to assess the relationship between serum sST2 concentration and nutritional status: the first group with low sST2 level (lower or equal to the median, ≤ 32.9 ng/mL) and the second group with high sST2 level (higher than the median, > 32.9 ng/mL). Parameters connected to the nutritional status were compared between the two groups: GNRI, CONUT and the elements of these scales. Epidemiologic data, such as age, BMI, comorbidities and prescribed medications, were also analyzed.

Continuous variables were checked for normal distribution using the Kolmogorov–Smirnov test and are presented as mean values with the standard deviation or as median values with the interquartile range, according to the normality of their distribution. Categorical variables are presented as the number of patients and percentages (%). Depending on the characteristic of the variable, the Mann–Whitney U test, Student's t-test or the Fisher's exact test were used to compare the variables. To further assess the relationship between sST2 and GNRI score and between sST2 and components of the CONUT and GNRI formulas (albumin, BMI, lymphocyte, TC), the Spearman correlation coefficient test was used. Linear regression models comprising sST2, NT-proBNP, sex and age were deployed to further assess the relationship between sST2 and nutritional status.

Results

Baseline characteristics

The study population consisted of 138 HFrEF patients (**Figure 2**) with a mean age of 53.6 ± 10.8 years. The group was comprised of 12 (8.7%) women. The median LVEF was 20% (IQR 20–30). Over half of the analyzed group (51.5% of patients) presented ischemic HF etiology. Most patients were classified as NYHA II or III (47.1% and 45.7%, respectively). NYHA I was observed in 2.9% of patients and ambulatory NYHA IV class — in 4.3%. All patients were stable — they required no hospitalization or administration of intravenous diuretics due to exacerbation/decompensation of HF in the prior 4 weeks. The median value of serum sST2 level was 32.9 (IQR 21.4–56.4) ng/mL. The baseline characteristics of the studied group are presented in **Table 1**.

In the analysis of nutritional status, 80% of patients had no risk of malnutrition according to the GNRI score with a score greater or equal to 98. 28 patients (20%) had any level of risk of malnutrition (GNRI score < 98). According to the CONUT score, 64 patients

(46.4%) belonged to the normal nutrition category, 69 (50%) — to the group with mild risk of malnutrition, 4 (2.9%) — to the moderate risk patients and 1 patient (0.7%) was at severe risk of malnutrition.

Nutritional status and laboratory findings are presented in **Table 2**.

Correlation between sST2 and other parameters

A cutoff point according to the median sST2 value was established at 32.9 ng/mL. It allowed us to divide the study population into two equal groups: those with sST2 above 32.9 ng/mL (high sST2 group) and those with sST2 below or equal to 32.9 ng/mL (low sST2 group). No differences were reported regarding gender, age, BMI and HF etiology (**Tables 1 and 2**). NYHA functional classes were higher in the high sST2 group. This was most noticeable in NYHA classes I and IV. All patients (n = 4) with NYHA I class had sST2 below or equal to 32.9 ng/mL and 83% of patients with NYHA IV class had sST2 > 32.9 ng/mL. The systolic and diastolic blood pressure (SBP and DBP) values were significantly higher and heart rate (HR) values were lower in the low sST2 group. The analysis of BNP and NT-proBNP revealed considerably higher concentrations in the high sST2 group (430 vs. 155 pg/mL; $p < 0.0001$; 2275 vs. 690 pg/mL; $p < 0.0001$ respectively). Regarding the nutritional risk, the GNRI score was lower (**Figure 3**) and the associated nutritional risk was more common (29% vs. 12%; $p = 0.011$) in the group with sST2 above 32.9 ng/mL. Moreover, the nutritional status according to CONUT score was worse (2 [IQR 1–3] vs. 1 [IQR 0–2]; $p = 0.0016$) and the risk of malnutrition defined with CONUT score was also more common in the group with sST2 > 32.9 ng/mL ($p = 0.0079$). Patients with moderate (n = 4) and severe risk (n = 1) were reported only in the high sST2 group (**Figure 4**).

Biomarkers classically associated with nutritional status were also analyzed according to sST2. Albumin (41.8 ± 3.1 vs. 39.9 ± 3.9 g/L; $p = 0.0017$), TC (4.6 ± 1.2 vs. 4.0 ± 1.0

mmol/L; p = 0.0016) and triglycerides (TG) (1.46 [IQR 1.07–2.32] vs. 1.24 [IQR 0.92–1.61] mmol/L; p = 0.032) were higher in the low sST2 group. No differences were found in lymphocyte count, LDL, HDL or hemoglobin concentrations. Considering comorbidities, there were no statistically significant differences reported. Patients with high sST2 used more commonly thiazides; statin use was more abundant in the low sST2 group. Despite the broader use of lipid-lowering drugs, this group had higher TC and TG levels (**Tables 1 and 2**).

The serum concentration of sST2 protein significantly correlated with the CONUT score, which indicated worse nutritional status. There was an inverse correlation between sST2 and serum albumin, TC and GNRI score. No significant relation was observed with BMI nor lymphocyte count (**Table 3**). GNRI and CONUT scores were related to sST2 concentrations independently from NT-proBNP concentration, age and sex of the patients (**Table 4**).

Discussion

According to available research, the present study is the first to evaluate the association between serum sST2 concentration and nutritional status in HFrEF patients. HF patients are characterized by multi-morbidity. Among non-cardiological diseases, diabetes mellitus type II, thyroid diseases, depression, as well as frailty and malnutrition syndrome should be highlighted [1]. Moreover, biomarkers such as NT-proBNP or sST2 are independent predictors of cardiovascular death [43]. Therefore, a multidimensional approach is essential in that population. Using two tools to assess nutritional status allows for a more credible assessment. Those scales (GNRI and CONUT) were previously used in numerous studies to assess the nutritional risk in HF patients [42, 44–47].

sST2 is probably one of the most promising new prognostic markers to be used in clinical practice. Together with NT-proBNP, it may be useful to better assess the probability of an unfavorable outcome [21, 22]. However, there is limited information from previous studies, involving different populations [32, 33]. Other papers reveal only the relation of sST2 with parameters related to malnutrition as secondary results rather than considering nutritional status as the primary point of the study [22, 33, 48].

Other authors also showed the correlation between nutritional risk according to GNRI and CONUT and well-established prognostic factors like NT-proBNP and BNP [42, 45, 49]. The risk of malnutrition of any level was present at 20% in accordance with GNRI and 53.6% when assessed with CONUT.

In this research, the population was relatively young (mean age: 53.6 ± 10.8 years) and well-nourished. This is a strength of the study, as previous research focused mainly on elderly patients, while relatively younger HF patients were understudied. Moreover, due to the relatively young age of the analyzed population, senility-related problems, including loss of appetite and malnutrition, did not influence the results. Multi-morbidity is less common in younger patients, which is also essential, especially when assessing sST2 concentration. This biomarker is also increased in diabetes [50] and COPD and correlates with the disease's severity and prognosis [51]. On the other hand, the population's age and nutritional status should be taken into consideration when compared with other studies. The results cannot be extrapolated to elderly patients, who constitute most HF patients. Moreover, only HFrEF patients were included, excluding patients with HF with preserved ejection fraction (HFpEF) and HF with moderately reduced ejection fraction (HFmrEF), which ensured a homogenous population.

Sobieszek et al. [32] proved that cachexia in chronic HF was associated with a higher concentration of sST2. The highest sST2 concentrations were correlated with worse prognosis

in the whole group involving all chronic HF patients and when considering only malnourished patients [32]. Moreover, the authors used C-reactive protein, which was highly correlated with sST2 ($R = 0.524$; $p < 0.001$) as one of the criteria of cachexia [32]. Such an approach could generate artificial relations between cachexia and sST2, which could be only caused by a relatively strong correlation between sST2 and CRP. Both biomarkers relate to the inflammatory state present in chronic HF. Furthermore, Sobieszek et al. involved only male patients, excluding females [32]. Yamamoto et al. indicated a moderate correlation of nutritional parameters: GNRI and albumin with sST2 ($R = 0.320$; $p < 0.001$ and $R = –0.160$; $p < 0.001$, respectively) in 616 acute decompensated HF patients [33]. This was consistent with the presented results. BMI was also related to the biomarker concentration ($R = –0.160$; $p < 0.001$). The disagreement between results ($R = –0.111$; $p = 0.19$) is probably associated with a more numerous study population in the cited paper [33]. Nonetheless, the population of this study was a much more homogeneous group. Only HFrEF patients with a median LVEF of 20% and median sST2 of 32.9 ng/mL were enrolled, compared to Yamamoto et al., who involved patients irrespective of LVEF (median: 46%) with median sST2 of 17.3 ng/mL [33]. Another interesting article that raised the issue of biomarkers in HF, such as sST2 and BNP was published by Sugano et al. [48]. The authors presented correlations of sST2 with various parameters, including those related to nutritional status (serum albumin, BMI). Sugano et al. reported that higher sST2 concentration was associated with systemic inflammation, low BMI and hypoalbuminemia [48]. The present study observed a similar correlation of sST2 with albumin and other parameters of nutritional status except for BMI. The most significant difference between the Japanese study and this research is the analyzed population. In this study relatively young patients with reduced LVEF were included (mean age 53.6 ± 10.8 years and median LVEF of 20% [IQR 20–30]), while Sugano et al. enrolled older patients with HFpEF (mean age 76.4 ± 11.9 years and mean LVEF 60 ± 7.6%) [48].

The last study considering parameters related to nutrition and sST2 was published by Zhang et al. and included 1528 HF patients, but only 51.5% with LVEF ≤ 40% [22]. Besides revealing the accurate predictive value of sST2, correlations with other continuous parameters were checked for sST2 in the HFrEF group [22]. As a result, weak reverse correlations between sST2 and albumin ($R = –0.293$; $p < 0.001$), TC ($R = –0.205$; $p < 0.001$) and BMI ($R = –0.140$; $p < 0.001$) were found [22]. It corresponds to the data reported in the presented study. However, the relationship with BMI in this paper is probably insignificant due to the less numerous population compared to Zhang et al. [22].

Additionally, higher NYHA classes were observed in patients with high sST2. It was found that concentrations of this biomarker correspond to HF advancement [52, 53]. Lower SBP, DBP and higher HR revealed in the group with biomarker concentration above the median were previously described as associated with unfavorable outcomes, disease severity and frailty syndrome [54, 55]. In the study high sST2 was associated with lower LVEF values. Similar results were reported previously [22, 33]. Nevertheless, this relation was not observed in HFpEF patients [48].

Study limitations

The study presented here is an observational study and establishing a causative relationship on this basis is inadequate. Secondly, it is a single-center study with a limited population; however, it was sufficient to reveal a statistically significant relationship between parameters of interest. Finally, women constituted only a small part of the population (8.7%). Nonetheless, it was caused by including only HFrEF and the relatively young age of the studied population. In such groups, males are decisively more prevalent [56, 57].

Conclusions

This research is the first study showing that sST2 concentration is related to nutritional status in HFrEF patients. sST2 may help to evaluate the necessity for nutritional intervention in HFrEF patients. Further studies with larger analyzed groups are required to assess the issue in different HF patient populations and determine the causative relationship between sST2 and the nutritional risk.

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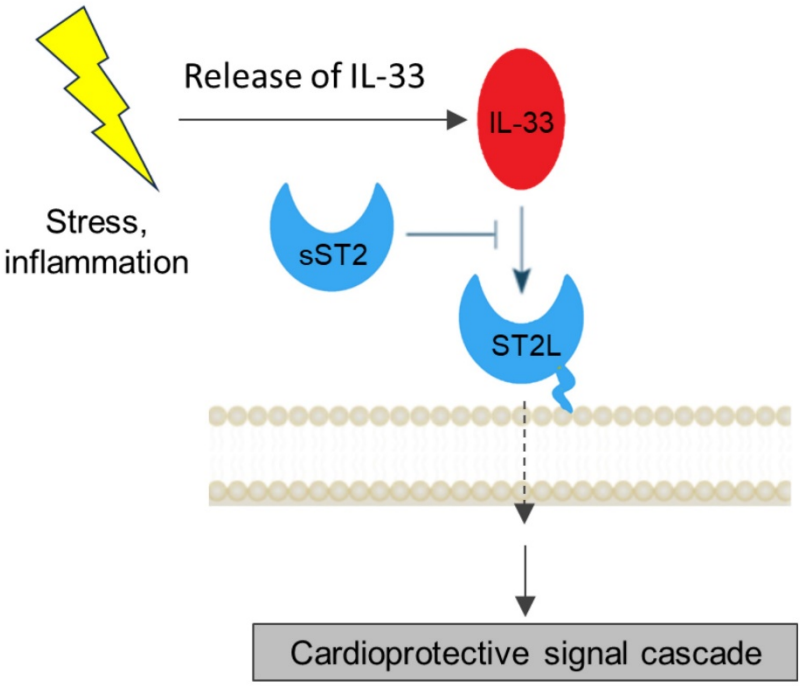

Figure 1. IL-33/ST2L system in the cardioprotective pathway; IL-33 — Interleukin-33; sST2 — soluble suppression of tumorigenicity-2 receptor; ST2L — transmembrane suppression of tumorigenicity-2 receptor.

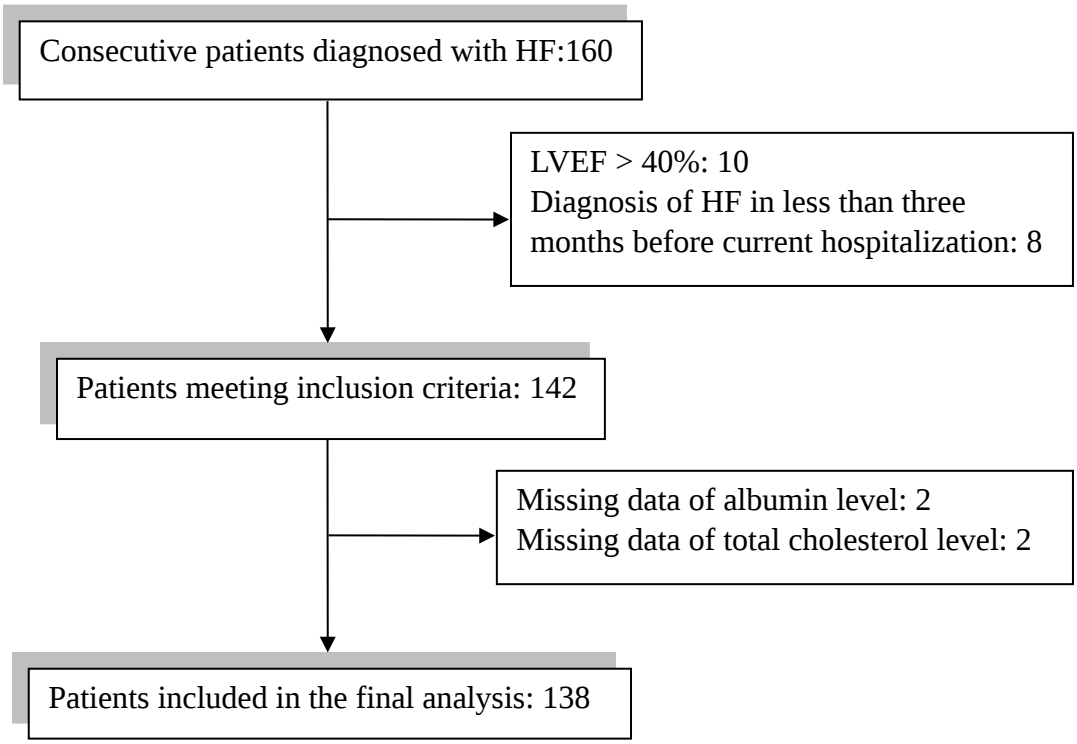

Figure 2. Study flowchart; HF — heart failure; LVEF — left ventricular ejection fraction.

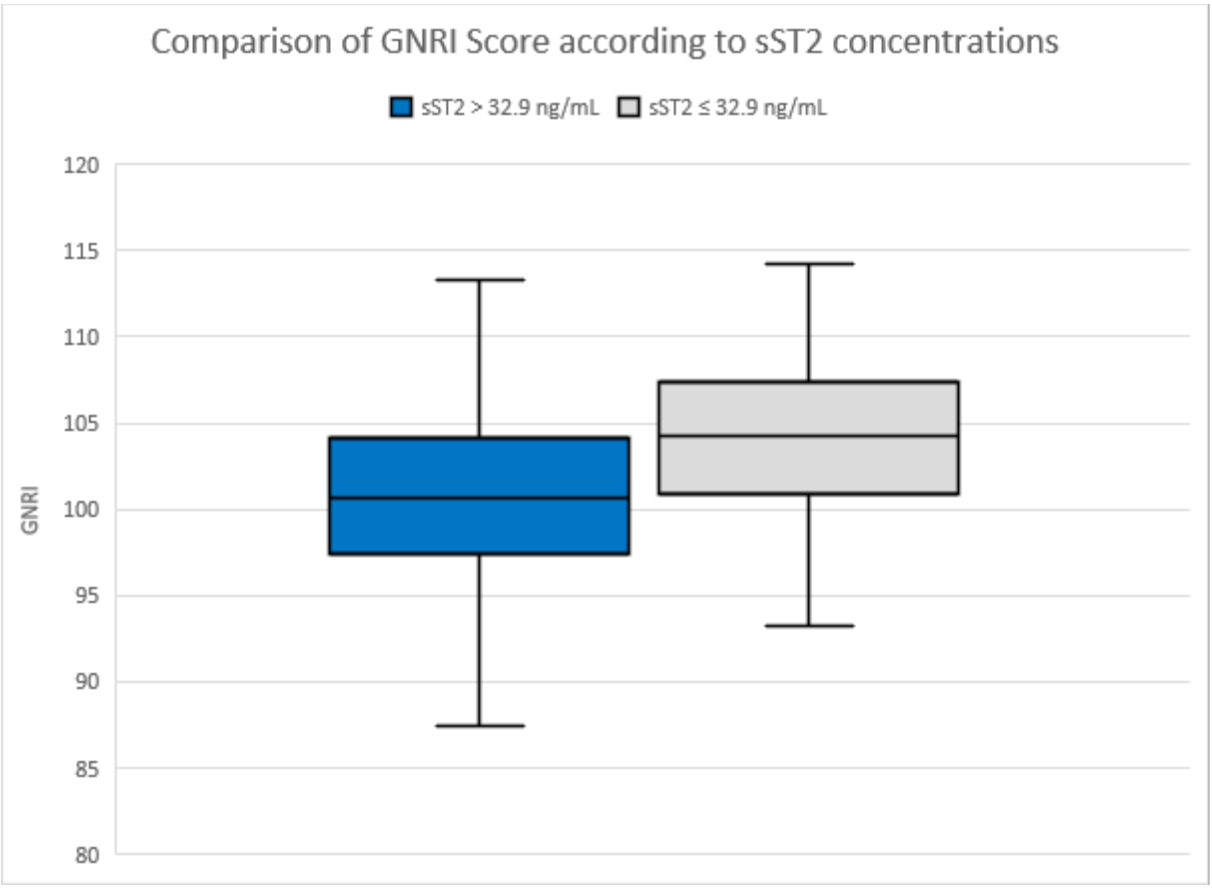

Figure 3. Comparison of GNRI score between low and high sST2 levels; GNRI — Geriatric Nutritional Risk Index; IQR — interquartile range; sST2 — soluble suppression of tumorigenicity 2 protein.

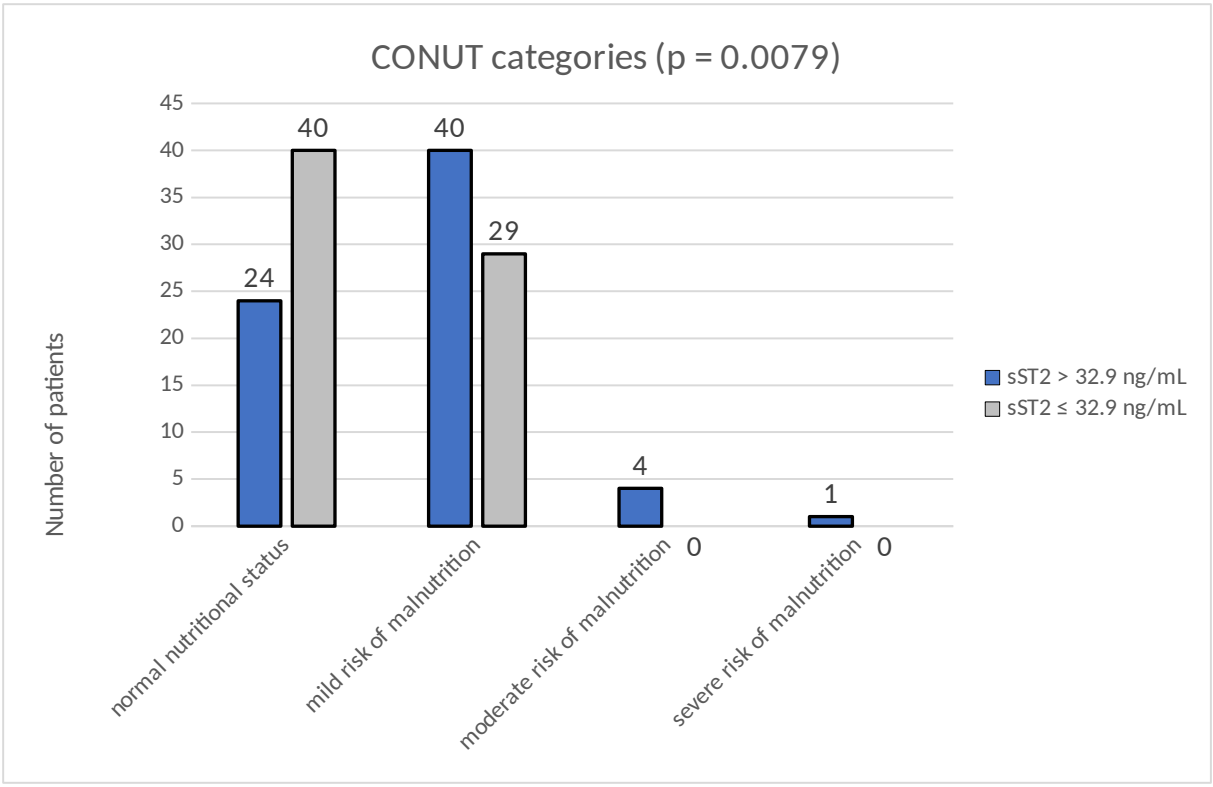

Figure 4. Comparison of nutritional risk according to CONUT classification between patients with sST2 higher and lower than 32.9 ng/mL; CONUT — Controlling Nutritional Status Score; sST2 — soluble suppression of tumorigenicity 2 protein.

Table 1. Baseline characteristics of the studied group (n = 138).

Characteristic	**Whole study population N = 138**	**High sST2 group (sST2 > 32.9 ng/m|L) N = 69**	**Low sST2 group (sST2 ≤ 32.9 ng/mL) N = 69**	**P**
Age, years	53.6 (10.8)	54.2 (11.7)	52.9 (10.0)	0.47
Women	12 (8.7%)	7 (10.1%)	5 (7.2%)	0.38
Men	126 (91.3%)	62 (88.9%)	64 (92.8%)	
LVEF, %	23 (8.0)	21.8 (7.4)	25.2 (8.3)	0.03
Ischemic HF	71 (51.5%)	35 (51%)	36 (52%)	0.86
NYHA class				
I	4 (2.9%)	0 (0%)	4 (6%)	0.04
II	65 (47.1%)	29 (42%)	36 (52%)	
III	63 (45.7%)	35 (51%)	28 (41%)	
IV	6 (4.3%)	5 (7%)	1 (1%)	
III–IV	69 (50%)	40 (58%)	29 (42%)	0.06
Comorbidities				
Diabetes	41 (29.7%)	31 (45%)	36 (52%)	0.39
Chronic kidney disease	21 (15.2%)	23 (33%)	18 (26%)	0.35
Hypertension	67 (48.6%)	14 (20%)	7 (10%)	0.10
AF persistent or permanent	23 (16.7%)	16 (23%)	7 (10%)	0.08
AF paroxysmal	28 (20.3%)	15 (22%)	13 (19%)	
COPD	18 (13%)	10 (14%)	8 (12%)	0.61
Medications				
Loop diuretics	126 (91.3%)	65 (94%)	61 (88%)	0.23
Thiazides	17 (10%)	11 (16%)	3 (4%)	0.02
Beta-blockers	136 (98.6%)	68 (99%)	68 (99%)	–
ACEI/ARB	113 (81.9%)	56 (81%)	57 (83%)	0.83
ARNI	18 (13.0%)	7 (10%)	11 (16%)	0.31
MRA	122 (88.4%)	61 (88%)	61 (88%)	–
Statins	58 (42%)	33 (48%)	47 (68%)	0.02
SGLT2 inhibitors	3 (2.1%)	0	3 (4.3%)	0.24

Data are presented as mean (SD), median (interquartile range) or n (%). High sST2 group: patients with sST2 concentration above 32.9 ng/mL (median value in the study population), low sST2 group — patients with sST2 below or equal to 32.9 ng/mL; ACEI — angiotensin-converting-enzyme inhibitors; AF — atrial fibrillation; ARB — angiotensin receptor blockers; ARNI — angiotensin receptor-neprilysin inhibitors; COPD — chronic

obstructive pulmonary disease; HF — heart failure; LVEF — left ventricular ejection fraction; MRA — mineralocorticoid receptor antagonists; NYHA — New York Heart Association; SGLT — sodium-glucose linked transporter

Table 2. Nutritional status and laboratory findings.

Characteristic	**Whole study population N = 138**	**High sST2 group (sST2 > 32.9 ng/mL) N = 69**	**Low sST2 group (sST2 ≤ 32.9 ng/mL) N = 69**	**P**
Nutritional status				
BMI, kg/m^2	28.5 (4.9)	27.9 (5.4)	29.2 (4.2)	0.11
GNRI score	102.2 (5.5)	100.6 (5.9)	103.8 (4.6)	< 0.001
No nutritional risk (GNRI score ≥ 98)	110 (80%)	49 (71%)	61 (88%)	0.01
Any level of nutritional risk (GNRI score < 98)	28 (20%)	20 (29%)	8 (12%)	
CONUT score	2 (1–3)	2 (1–3)	1 (0–2)	0.002
CONUT category (points of CONUT score)				
Normal nutrition (0–1)	64 (46.4%)	24 (35%)	40 (58%)	0.008
Mild risk of malnutrition (2–4)	69 (50%)	40 (58%)	29 (42%)	
Moderate risk of malnutrition (5–8)	4 (2.9%)	4 (6%)	0 (0%)	
Severe risk of malnutrition (9–12)	1 (0.7%)	1 (1%)	0 (0%)	
Vital signs				
SBP on admission, mmHg	110 (100–120)	103 (95–117)	110 (100–120)	0.04
DBP on admission, mmHg	70 (64–80)	70 (60–75)	70 (65–80)	0.04
MAP on admission, mmHg	83.3 (75–90)	80 (74–87)	87 (78–93)	0.02
HR on discharge, beats per minute	69 (61–75)	73 (65–80)	65 (60–75)	< 0.001
Biochemical parameters				
sST2, ng/mL	32.9 (21.4–56.4)	-	-	-

BNP level, ng/mL	256.7 (106.7–474.3)	430 (288–691)	155 (58–264)	< 0.001
NT-proBNP level, pg/mL	1343 (533–2315)	2275 (1341–4304)	690 (296–1614)	< 0.001
Albumin, g/L	40.9 (3.7)	39.9 (3.9)	41.8 (3.1)	0.002
TP, g/L	73.2 (6.7)	72.4 (7.9)	73.9 (5.2)	0.37
Creatinine, μmol/L	102.8 (25.6)	104.3 (25.4)	101.3 (25.9)	0.50
eGFR MDRD, min/1.73m^2	69.2 (21.2)	67.9 (20.4)	70.5 (22.0)	0.48
Na+, mmol/L	140 (138–141)	139 (137–141)	140 (139–141)	0.08
K+, mmol/L	4.3 (4.1–4.6)	4.3 (4.0–4.6)	4.4 (4.2–4.5)	0.43
Fasting glucose, mmol/L	6.0 (5.4–6.7)	6.0 (5.3–6.8)	5.9 (5.5–6.6)	0.79
TC, mmol/L	4.3 (1.1)	4.0 (1.0)	4.6 (1.2)	0.002
LDL, mmol/L	2.49 (0.91)	2.40 (0.78)	2.58 (1.02)	0.23
HDL, mmol/L	1.24 (0.41)	1.20 (0.44)	1.27 (0.37)	0.29
TG, mmol/L	1.35 (0.98–1.89)	1.24 (0.92–1.61)	1.46 (1.07–2.32)	0.03
Hgb, mmol/L	9.0 (0.8)	9.0 (1.0)	9.1 (0.7)	0.92

Data are presented as mean (SD), median (interquartile range) or n (%). High sST2 group: patients with sST2 concentration above 32.9 ng/mL (median value in the study population), low sST2 group — patients with sST2 below or equal to 32.9 ng/mL; BMI — body mass index; BNP — B-type natriuretic peptide; DBP — diastolic blood pressure; eGFR MDRD — estimated glomerular filtration rate using the Modification of Diet in Renal Disease formula; HCT — hematocrit; HDL — high-density lipoprotein; HGB — hemoglobin; HR — heart rate; K+ — potassium; LDL — low-density lipoprotein; MAP — mean arterial pressure; MNA — Mini Nutritional Assessment; Na+ — sodium; NT-proBNP — N-terminal pro-B-type natriuretic peptide; SBP — systolic blood pressure; TC — total cholesterol level; TG — triglycerides; TP — total protein

Table 3. Correlations of sST2 and GNRI, CONUT, BMI, albumin, total cholesterol, and lymphocyte count.

Pair of variables	Spearman R	P-value
sST2 & BMI	–0.111	0.19
sST2 & serum albumin	–0.268	0.002
sST2 & total cholesterol	–0.269	0.001
sST2 & GNRI score	–0.297	< 0.001
sST2 & CONUT score	0.275	0.001
sST2 & lymphocyte count	–0.147	0.09

BMI — body mass index; CONUT — Controlling Nutritional Status Score; GNRI — Geriatric Nutritional Risk Index; sST2 — soluble suppression of tumorigenicity 2 protein

Table 4. Linear regression models comprising sST2 concentration for prediction of GNRI and CONUT scores.

Model 1 (GNRI score)	Univariable parameter estimate (95% CI)	p	Multivariable parameter estimate (95% CI)*	adjusted p
Intercept	multiple	multiple	107.7 (103.1; 112.3)	< 0.001
sST2, ng/mL	–0.044 (–0.020; –0.069)	< 0.001	–0.0281 (–0.0013; –0.0548)	0.040
NT-proBNP, pg/mL	–0.00045 (–0.00023; –0.00068)	< 0.001	–0.00032 (–0.00008; –0.00057)	0.010
female sex	–1.832 (–0.207; –3.458)	0.027	–1.838 (–0.256; –3.421)	0.023
age (years)	–0.075 (0.010; –0.160)	0.085	–0.092 (–0.013; –0.172)	0.023
Model 2 (CONUT score)	univariable parameter estimate (95% CI)	p	Multivariable parameter estimate (95% CI)*	adjusted p
Intercept	multiple	multiple	−0.947 (–2.160; 0.286)	0.13
sST2, ng/mL	0.0130 (0.006; 0.0196)	< 0.001	0.0076 (–0.00047; 0.00148)	0.037
NT-proBNP, pg/mL	0.00013 (0.00007; 0.00019)	< 0.001	0.00011 (0.00004; 0.00017)	0.002
female sex	–0.167 (–0.618; 0.285)	0.470	–0.178 (0.407; –0.601)	0.410
age (years)	0.0335 (0.0106; 0.0564)	0.0044	0.034 (0.011; 0.056)	0.0044

CONUT — Controlling Nutritional Status Score; GNRI — Geriatric Nutritional Risk Index; NT-proBNP — N-terminal pro-B-type natriuretic peptide; sST2 — soluble suppression of tumorigenicity 2 protein