BRITISH JOURNAL OF
HOSPITAL MEDICINE

ARTICLE

Expression and Clinical Implications of pro-BNP and Soluble ST2 in Chronic Heart Failure

Xing Meng[1], Kai Zhang[1], Wan-Jie Zeng[1], Zhen-Hua Hu[1,*]

[1]Clinical Laboratory, Suzhou Kowloon Hospital Affiliated with Shanghai Jiaotong University School of Medicine, Suzhou, Jiangsu, China

*Correspondence: huzhenhua84@163.com (Zhen-Hua Hu)

Abstract

Aims/Background Chronic heart failure (CHF) is a complex clinical syndrome resulting from various cardiac diseases, characterized by weakened cardiac pumping capacity and inadequate blood supply to body tissues. This study aims to investigate the expression and clinical implications of pro-B-type natriuretic peptide (pro-BNP) and soluble suppression of tumorigenicity 2 (sST2) in CHF to explore their potential in early diagnosis and severity assessment of the pathological condition.

Methods This study included 146 CHF patients treated at our hospital from January 2022 to December 2023, who were classified in the observation group, and 150 concurrent healthy people categorized in the control group. pro-BNP and sST2 levels in the observation and control groups were compared. The diagnostic value of pro-BNP and sST2 in CHF was determined using receiver operating characteristic (ROC) curves. Besides, pro-BNP and sST2 levels in patients with different New York Heart Association (NYHA) grades were compared, and their relationships with left ventricular ejection fraction (LVEF), left atrial diameter (LAD), and left ventricular end-diastolic diameter (LVEDD) were assessed by means of Pearson's correlation.

Results CHF cases showed markedly higher pro-BNP and sST2 levels than healthy controls ($p < 0.05$). The area under the ROC curves for pro-BNP and sST2 in diagnosing CHF was 0.826 (95% CI: 0.778–0.875) and 0.733 (95% CI: 0.674–0.791), respectively. pro-BNP and sST2 levels were similar in grades I and II patients ($p > 0.05$), but lower when compared with those in grades III and IV patients ($p < 0.05$). Grade III patients showed lower pro-BNP and sST2 expression than grade IV patients ($p < 0.05$). Additionally, pro-BNP and sST2 had an inverse connection with LVEF (r = –0.764 and r = –0.535, respectively) and a positive correlation with LAD (r = 0.752 and r = 0.535, respectively) and LVEDD (r = 0.721 and r = 0.544, respectively).

Conclusion pro-BNP and sST2 exhibit good diagnostic value for CHF, owing to their close association with patients' cardiac function. These biomarkers can be used as effective indicators to evaluate the severity of heart failure.

Key words: pro-BNP; soluble ST2; chronic heart failure; cardiac function

Submitted: 29 July 2024 Revised: 17 September 2024 Accepted: 22 September 2024

How to cite this article:
Meng X, Zhang K, Zeng W, Hu Z. Expression and Clinical Implications of pro-BNP and Soluble ST2 in Chronic Heart Failure. Br J Hosp Med. 2024. https://doi.org/10.12968/hmed.2024.0465

Copyright: © 2024 The Author(s).

Introduction

Chronic heart failure (CHF) is a complex cluster of clinical symptoms resulting from various cardiac diseases, mainly manifested as weakened pumping capacity of the heart that results in an inadequate blood supply to various parts of the body (Mascolo et al, 2022). With a strong link to aging, the prevalence of the disease increases with age, with particularly higher rate in older adults (Zuo et al, 2023).

Given the accelerated aging on a global scale, the incidence of CHF is also showing an upward trend, with 2% to 3% of the adult population in Western nations and 5% to 9% of individuals aged 65 years and older being affected by CHF (Girerd et al, 2022; Roger, 2021; van Riet et al, 2016). CHF has a significant impact on patients' quality of daily life, causing typical symptoms such as reduced exercise tolerance, shortness of breath, and limb edema, which not only pose a physical challenge to patients but also place significant strain on the household finances and healthcare resources (Lin et al, 2023). Given the complexity and progressive nature of CHF, timely diagnosis, proactive treatment measures, and continuous disease management are crucial for improving patient survival and quality of life (Heidenreich et al, 2022). However, the diversity of clinical manifestations of CHF and the fact that its symptoms are indistinguishable from those of other conditions, such as chronic obstructive pulmonary disease and asthma, make differential diagnosis more challenging (Harjola et al, 2020; Liu et al, 2022). Therefore, accurate diagnosis and effective management of CHF require comprehensive clinical judgment, application of auxiliary examinations, and consideration of the patient's overall condition.

The expression of the B-type natriuretic peptide (*BNP*) gene is significantly enhanced when the ventricles are subjected to a high-pressure load or when the myocardium is in a state of ischemia and hypoxia (Primessnig et al, 2022; Redfors et al, 2018). The resulting precursor protein of *BNP*, following the transcription and translation of this gene, is subjected to specific enzymatic action to yield pro-BNP by removing the N-terminal signal peptide (Han et al, 2020). Despite not being biologically active, pro-BNP boasts high clinical application value by virtue of its long half-life (about 1 to 2 hours), stable expression *in vivo* (relatively constant levels within 24 hours), and measurement not being affected by factors such as daily activities and body position changes (Onoe et al, 2023). As a peptide hormone secreted by the heart, pro-BNP plays a key role in the diagnosis, treatment response monitoring, and prognosis evaluation of cardiovascular diseases (Sani et al, 2021).

Suppression of tumorigenicity 2 (ST2), which belongs to the interleukin-1 receptor (IL-1R) family, binds with interleukin-33 (IL-33) to exert its biological effects, mainly by inhibiting the hypertrophy, necrosis, and fibrosis of cardiomyocytes, thus playing a cardioprotective role (Dattagupta and Immaneni, 2018; Zhang et al, 2021). On the other hand, soluble ST2 (sST2)—a soluble variant of ST2—can competitively bind with IL-33, thus counteracting the cardioprotective effect of ST2 (Vitali et al, 2021). In patients with cardiovascular diseases, elevated sST2 levels are strongly associated with cardiac remodeling, myocardial fibrosis, and exacerbation of inflammatory responses (Dudek et al, 2023). Although sST2 has shown great potential as a biomarker for cardiovascular disease, its value in clinical application requires further evaluation taking into account the comprehensive information, such as clinical symptoms and signs, as well as expression of other biomarkers, to substantiate its accuracy in disease diagnosis and treatment.

Left atrial diameter (LAD), left ventricular end-diastolic diameter (LVEDD), and left ventricular ejection fraction (LVEF) are critical indices used to evaluate cardiac function and structure (Yu et al, 2024). LAD refers to the maximum internal diameter of the left atrium during systole, providing insight into atrial size and

potential remodeling (Bouzas-Mosquera et al, 2011). LVEDD, on the other hand, represents the maximum left ventricular internal diameter at end-diastole, indicating ventricular dilation or hypertrophy (Gać et al, 2022). LVEF, which indicates the percentage of blood ejected from the left ventricle with each contraction, serves as a key measure of systolic function (Packer, 2024). These indices hold significant importance as they enable the quantification of cardiac remodeling and dysfunction in patients with CHF.

This study aims to investigate the expression levels of pro-BNP and sST2 in CHF patients, explore their correlation with different grades of heart failure, and analyze the relationships between these biomarkers and cardiac function indices, thereby providing references and insights into clinical evaluation and treatment of CHF.

Methods

Patient Information

In this retrospective study, we enrolled and selected 146 patients with CHF treated at the Suzhou Kowloon Hospital Affiliated with Shanghai Jiaotong University School of Medicine from January 2022 to December 2023. These cases were grouped under the observation group, and for comparison, 150 healthy individuals treated in our hospital during the same period of time were recruired and categorized into the control group. This study was approved by the Ethics Committee of the Suzhou Kowloon Hospital Affiliated with Shanghai Jiaotong University School of Medicine (NO. 2023021515183465) and was conducted in accordance with the Declaration of Helsinki. Due to the retrospective nature of the study, informed consent was waived by the Ethics Committee of the Suzhou Kowloon Hospital Affiliated to Shanghai Jiaotong University School of Medicine.

Inclusion and Exclusion Criteria

All the subjects in the observation group were patients diagnosed with CHF upon confirmation against their medical history, physical examination results, imaging findings, electrocardiograms, and other examination results (McDonagh et al, 2021). On the other hand, the subjects in the control group showed no abnormality in all the laboratory tests administered. All recruited participants were subjected to pro-BNP and sST2 measurements. Only the subjects with complete medical records were included.

For this study, patients with severe hepatic and renal insufficiency, cardiac insufficiency caused by congenital heart disease, acute heart failure, mental retardation, language communication disorders, psychiatric disorders, or previous history of mental illness were excluded. These criteria were applied to both the observation group and the control group.

Data Collection

The clinical data required for this study were collected from the hospital's electronic medical record system. These data encompass demographic characteristics (sex, age, body mass index [BMI], and heart rate), laboratory parameters (levels of

pro-BNP and sST2), echocardiographic indices (LVEF, LAD, and LVEDD), complications (hypertension, coronary heart disease, diabetes mellitus, dyslipidemia, stroke, and prior myocardial infarction), and the New York Heart Association (NYHA) functional classification.

Blood samples from patients were collected to determine the levels of pro-BNP and sST2 using human pro-BNP ELISA kits (Abcam, London, UK) and human sST2 ELISA kits (Sangon Biotech, Shanghai, China), respectively, in accordance with the manufacturer's instructions. Echocardiographic measurements of LAD and LVEDD were performed in the parasternal long-axis view using M-mode, while LVEF was calculated by employing the Simpson's biplane method. The severity of cardiac dysfunction was graded according to the NYHA functional classification, which categorizes patients into four grades (I–IV) based on the degree of limitation in physical activity due to their symptoms.

Outcome Measures

The diagnostic value of pro-BNP and sST2 in CHF was determined using receiver operating characteristic (ROC) curves. The area under the ROC curve was calculated for quantifying the discriminatory power of each biomarker. Additionally, sensitivity and specificity were determined to assess the accuracy of these markers in diagnosing CHF. Furthermore, the current study explored the correlations of pro-BNP and sST2 levels with the key echocardiographic indices of cardiac function (LVEF, LAD, and LVEDD).

Statistical Analysis

All statistical analyses were carried out using SPSS 20.0 (SPSS Inc., Chicago, IL, USA), and the statistical significance threshold was set at $p < 0.05$. Prior to statistical analysis, normality of the data was assessed using the Kolmogorov-Smirnov test. The normally distributed data are presented as means and standard deviations (mean $\pm$ SD). Independent samples *t*-tests were employed to compare continuous variables between the observation group and the control group. Categorical data were analyzed using the Chi-square test (denoted by (χ^2), and are expressed as percentages (%) in this paper. One-way analysis of variance (ANOVA) was used to compare pro-BNP and sST2 levels across patient groups with different NYHA grades. In the case when significant differences ($p < 0.05$) were detected in the ANOVA, a Tukey's post-hoc test was conducted to specifically compare differences between two patient groups of different NYHA grades. Pearson's correlation was utilized to analyze the relationships of pro-BNP and sST2 levels with cardiac function indices such as LVEF, LAD, and LVEDD. ROC curves were constructed to evaluate the diagnostic value of pro-BNP and sST2 in CHF.

Results

Baseline Data

The analysis of the patient's baseline data, presented in Table 1, revealed no statistically significant inter-group differences in terms of sex, age, and BMI ($p >$ 0.05). However, notable statistical significance was identified in several key pa-

Table 1. Baseline data of observation and control groups.

Baseline characteristics	Observation group (n = 146)	Control group (n = 150)	t/χ^2	p-value
Sex			0.455	0.500
Male	79 (54.11)	87 (58.00)		
Female	67 (45.89)	63 (42.00)		
Age (years)	71.51 ± 7.34	69.93 ± 8.64	1.690	0.092
Body mass index (kg/m^2)	22.42 ± 2.73	22.96 ± 3.23	1.560	0.120
Heart rate (bpm)	72.50 ± 4.46	81.01 ± 5.39	14.780	<0.001
LVEF (%)	43.36 ± 2.22	60.57 ± 2.24	66.385	<0.001
LAD (mm)	59.82 ± 4.42	47.99 ± 2.70	27.715	<0.001
LVEDD (mm)	38.30 ± 3.33	30.26 ± 2.12	24.716	<0.001
Hypertension	51 (34.93)	32 (21.33)	6.780	0.009
Coronary heart disease	64 (43.84)	28 (18.67)	21.880	<0.001
Diabetes mellitus	57 (39.04)	39 (26.00)	5.742	0.016
Dyslipidemia	68 (46.58)	46 (30.67)	7.907	0.005
Stroke	29 (19.86)	8 (5.33)	14.280	<0.001
Prior myocardial infarction	38 (26.03)	14 (9.33)	14.240	<0.001
NYHA classification				
I	29 (19.86)			
II	59 (40.41)			
III	31 (21.23)			
IV	27 (18.49)			

Notes: Categorical data are expressed as count (percentage), whereas quantitative data are expressed as mean ± standard deviation.
Abbreviations: LVEF, left ventricular ejection fraction; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; NYHA, New York Heart Association.

rameters, including LVEF, LAD, and LVEDD ($p < 0.05$). The observation group exhibited a significantly lower LVEF (43.36 ± 2.22%) compared to the control group (60.57 ± 2.24%), indicating a substantial difference in left ventricular function between the groups ($p < 0.001$). Similarly, LAD and LVEDD were significantly higher in the observation group (59.82 ± 4.42 mm and 38.30 ± 3.33 mm, respectively) than in the control group (47.99 ± 2.70 mm and 30.26 ± 2.12 mm, respectively) ($p < 0.001$). Additionally, significant inter-group differences were observed in heart rate, hypertension, coronary heart disease, diabetes mellitus, dyslipidemia, stroke, and prior myocardial infarction ($p < 0.05$), further emphasizing the distinct clinical profiles and complications between the observation and control groups.

pro-BNP and sST2 Expression in CHF

By comparing pro-BNP and sST2 levels between the observation and control groups (Fig. 1), we found that pro-BNP and sST2 levels were higher in CHF cases than in controls ($p < 0.05$).

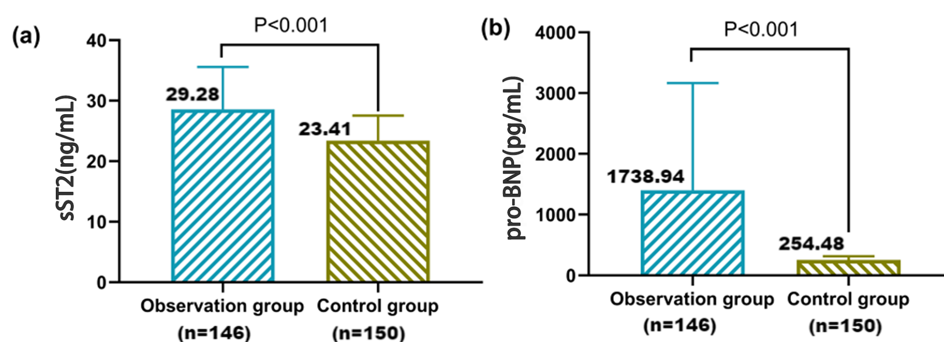

Fig. 1. pro-BNP and sST2 expression in chronic heart failure. (a) The observation groups showed higher pro-BNP level than the control group ($p < 0.001$). (b) The observation groups showed higher sST2 level than the control group ($p < 0.001$). Abbreviations: pro-BNP, pro-B-type natriuretic peptide; sST2, soluble suppression of tumorigenicity 2.

Diagnostic Value of pro-BNP and sST2 in CHF

To assess the diagnostic value of pro-BNP and sST2 in CHF, ROC curves were constructed and analyzed. The results, presented in Fig. 2, demonstrated that the area under the curve (AUC) for pro-BNP was 0.826 (95% CI: 0.778–0.875), while the AUC for sST2 was 0.733 (95% CI: 0.674–0.791). Specifically, pro-BNP demonstrated a sensitivity of 89.33% and a specificity of 68.49%, whereas sST2 showed a sensitivity of 94.00% and a specificity of 50.00%. These results suggest that both pro-BNP and sST2 possess application value in CHF diagnosis.

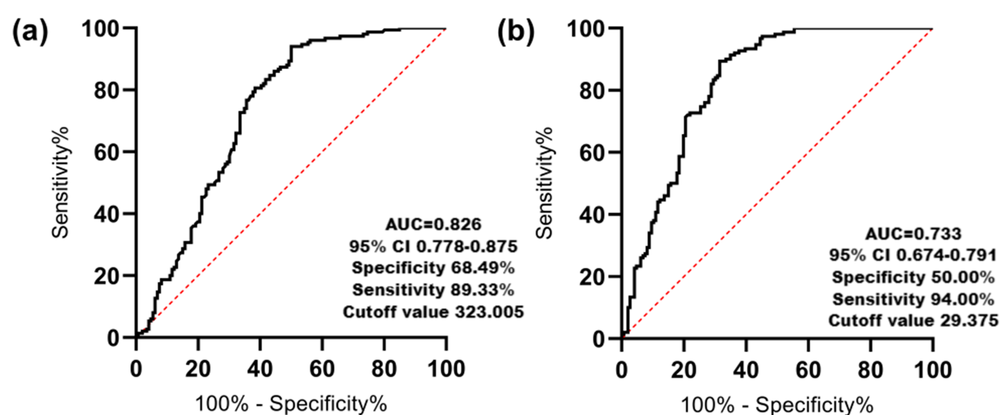

Fig. 2. ROC curves for evaluating the diagnostic value of pro-BNP and sST2 in chronic heart failure (CHF). (a) ROC curve for pro-BNP in CHF diagnosis. (b) ROC curve for sST2 in CHF diagnosis. Abbreviations: ROC, receiver operating characteristic; pro-BNP, pro-B-type natriuretic peptide; sST2, soluble suppression of tumorigenicity 2.

Table 2. pro-BNP and sST2 levels across different NYHA grades.

Grade	sST2 level (ng/mL)	pro-BNP level (pg/mL)
I	26.77 ± 6.36	299.30 ± 80.62
II	26.10 ± 5.89	313.73 ± 75.42
III	31.10 ± 6.58^{ab}	1531.04 ± 368.47^{ab}
IV	33.16 ± 7.29^{abc}	$4811.69 \pm 1003.22^{abc}$
F value	9.928	645.77
p-value	<0.001	<0.001

Notes: ^{a} $p < 0.05$ versus grade I patients; ^{b} $p < 0.05$ versus grade II patients; ^{c} $p < 0.05$ versus grade III patients.
Abbreviations: pro-BNP, pro-B-type natriuretic peptide; sST2, soluble suppression of tumorigenicity 2.

pro-BNP and sST2 Levels in Patients Across Different NYHA Grades

The comparison of pro-BNP and sST2 levels across different NYHA grades revealed that patients in NYHA grades I and II had comparable levels of both pro-BNP and sST2 ($p > 0.05$). However, when compared to patients in NYHA grades III and IV, those in grades I and II had significantly lower levels of pro-BNP and sST2 ($p < 0.05$). Furthermore, patients in NYHA grade III had significantly lower levels of pro-BNP and sST2 compared to those in grade IV ($p < 0.05$; Table 2).

Association of pro-BNP and sST2 with Cardiac Function Indices

The correlation of pro-BNP and sST2 with LVEF, LAD, and LVEDD in CHF patients was determined by Pearson's correlation, which revealed an inverse association of pro-BNP and sST2 with LVEF and a positive correlation of these markers with LAD and LVEDD, as shown in Fig. 3.

Discussion

The indistinct symptoms of CHF present considerable challenges in early detection and diagnosis, leading to late treatment and poor prognosis in heart failure patients (Buckley et al, 2023). Given the importance of early diagnosis, the present study investigated the clinical significance of pro-BNP and sST2 levels in CHF patients, particularly focusing on their diagnostic value and correlation with cardiac function parameters.

The comparison of pro-BNP and sST2 levels between the observation and control groups revealed that the levels of these markers were markedly higher in CHF patients than in healthy controls. The elevated levels of pro-BNP in heart failure patients are attributed to cardiac stretch and pressure overload due to myocardial dysfunction, resulting in the release of BNP from cardiomyocyte (Boulogne et al, 2017). A previous study has shown that cardiomyocytes undergo remodeling during heart failure, including cardiomyocyte hypertrophy and extracellular matrix deposition, resulting in increased synthesis and release of pro-BNP (Chang et al, 2023). Patients with heart failure are often accompanied by chronic inflammation, and the activation of inflammatory cells and cytokines can stimulate the produc-

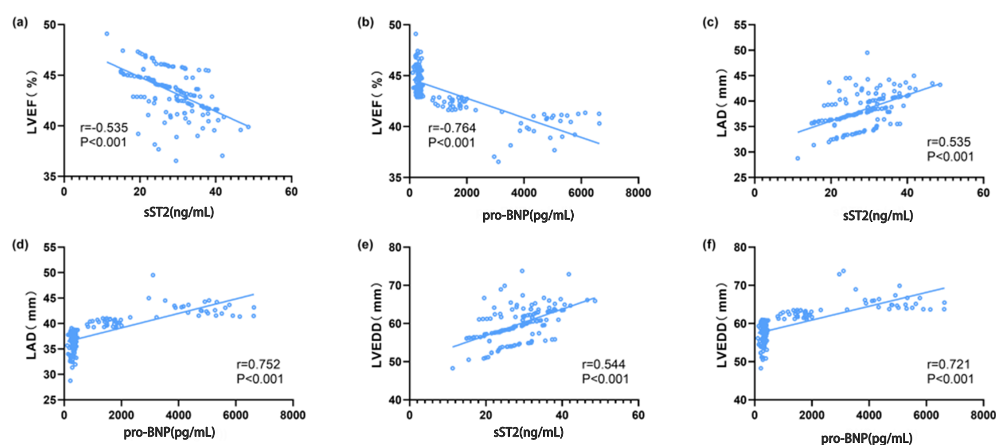

Fig. 3. Correlation of pro-BNP and sST2 with cardiac function indices. (a) sST2 was negatively correlated with LVEF (r = –0.535). (b) pro-BNP was negatively correlated with LVEF (r = –0.764). (c) sST2 was positively correlated with LAD (r = 0.535). (d) pro-BNP was positively correlated with LAD (r = 0.752). (e) sST2 was positively correlated with LVEDD (r = 0.544). (f) pro-BNP was positively correlated with LVEDD (r = 0.721). Abbreviations: pro-BNP, pro-B-type natriuretic peptide; sST2, soluble suppression of tumorigenicity 2; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter.

tion of sST2 by cardiomyocytes and fibroblasts (Uchida et al, 2022). These findings highlight that the determination of pro-BNP and sST2 levels may be useful for the diagnosis of CHF, whose diagnostic potential for CHF was assessed in the present study using ROC curves. Both pro-BNP (0.826) and sST2 (0.733) exhibit high AUCs, highlighting their diagnostic potential for CHF. Our results indicate that these biomarkers may serve as valuable clinical tools for the early detection of CHF. Our findings align with previous studies that emphasize the importance of pro-BNP and sST2 in diagnosing cardiovascular diseases (Rabkin and Tang, 2021; Zhang et al, 2021).

In our subsequent comparative analysis of pro-BNP and sST2 levels across different NYHA grades, we found that the levels of these biomarkers were significantly elevated in grades III and IV patients than in grade I and II patients, while patients with grade IV had significantly higher pro-BNP and sST2 levels than those with grade III. At the end of the study, we used Pearson's correlation to detect the correlation of pro-BNP and sST2 with LVEF, LAD, and LVEDD in CHF patients. Importantly, we observed an inverse correlation between these biomarkers and LVEF, which represents the percentage of blood ejected from the left ventricle with each contraction. LVEF is a key indicator of left ventricular systolic function, and a decrease in LVEF indicates a reduction in the amount of blood pumped out by the heart during each contraction, which is tantamount to a decrease in myocardial contractility (Srivastava et al, 2022). Conversely, pro-BNP and sST2 levels were positively correlated with LAD and LVEDD, markers of atrial and ventricular dilation. This result can be accounted for by the reduced myocardial contractility, which can trigger insufficient ventricular emptying during systole, ultimately increasing the volume of blood retained within the ventricles and exacerbating the

pressure load on the ventricular wall (Aimo et al, 2019; Kuwahara, 2021). The increase in LAD and LVEDD typically reflects the remodeling process of the heart, including hypertrophy of the atrial and ventricular walls, as well as enlargement of the heart cavity (Jia et al, 2023). This remodeling is an adaptive response to the long-term high-volume load on the heart. The elevation in capacity load leads to the dilatation of the atria and ventricles, thereby raising the filling pressure of the heart, exacerbating the workload of the heart, and aggravating the severity of heart failure (Rossi et al, 2014).

In this study, the pro-BNP and sST2 levels were found to be elevated with the cardiac function grade, indicating their significance in reflecting the severity of heart failure. This phenomenon can be attributed to the increasing pressure load and volume load of the central chamber during the pathogenic process of heart failure, which activates related genes and promotes the production of sST2 and pro-BNP (Romeo et al, 2010). Consistent with this observation, Apandi et al (2023) have also reported that pro-BNP increases in response to heightened left and right ventricular pressure and volume load. sST2, as a novel biomarker, reflects myocardial fibrosis and remodeling processes, which are often underlying factors in CHF progression (Miller et al, 2016). Moreover, given that sST2 is minimally influenced by age and renal function, its inclusion in the diagnostic protocol can further enhance diagnostic accuracy (Bayes-Genis et al, 2013; Maisel and Di Somma, 2017). The current combined analysis of these two biomarkers not only confirms their roles in CHF but also underscores their synergistic effect in the early identification of CHF. This approach enables clinical detection of CHF at an earlier stage, facilitating prompt interventions that can potentially slow disease progression and improve patient outcomes. Furthermore, continuous monitoring of these biomarkers over time can offer valuable insights into disease activity and treatment response, aiding in the timely adjustment of therapeutic strategies as needed.

Several shortcomings of this study are worthy of discussion. First, the retrospective research design of this study may inadvertently introduce bias in patient selection, which reduces the generalizability of the current set of findings. Second, the impact of pro-BNP and sST2 on the long-term outcomes in patients remains unclear due to the short period of follow-up with the patients. Further studies may consider extending the follow-up period to analyze patient outcomes. Third, the sample size of this study is relatively small. Therefore, further research should increase the sample size.

Conclusion

In conclusion, our findings confirm that pro-BNP and sST2 exhibit remarkable potential in CHF diagnosis. The levels of these biomarkers can reflect the severity of heart failure, thus giving valuable information for conducting timely and accurate clinical diagnosis. Future studies should aim to validate these findings in larger, prospective cohorts, and to explore the potential role of these biomarkers in monitoring treatment response and predicting long-term outcomes in CHF patients.

Key Points

- Our study highlights the clinical significance of pro-BNP and sST2 as biomarkers for the early diagnosis and severity assessment of chronic heart failure (CHF).
- These biomarkers enable early identification of CHF and accurate assessment of cardiac dysfunction, thereby facilitating timely interventions to improve patient outcomes.
- The inverse correlation with left ventricular ejection fraction and positive correlation with atrial and ventricular dilation markers emphasize their role in guiding patient management and treatment decisions.
- The findings of this study underscore the clinical significance of incorporating pro-BNP and sST2 measurements into routine CHF assessment protocols.

Availability of Data and Materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

XM contributed to the conception and design of the study, and made the first draft. KZ performed the research and analysis the data. WJZ and ZHH collected data and interpreted the data. All authors contributed to editorial important changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work. All authors have reviewed and finally approved the version.

Ethics Approval and Consent to Participate

The study was reviewed and approved by the Ethics Committee of Suzhou Kowloon Hospital Affiliated with Shanghai Jiaotong University School of Medicine (NO. 2023021515183465). Due to the retrospective nature of the study, informed consent was waived by the Ethics Committee of Suzhou Kowloon Hospital Affiliated with Shanghai Jiaotong University School of Medicine. The study was conducted in accordance with the Declaration of Helsinki.

Acknowledgement

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

Aimo A, Januzzi JL Jr, Bayes-Genis A, Vergaro G, Sciarrone P, Passino C, et al. Clinical and Prognostic Significance of sST2 in Heart Failure: JACC Review Topic of the Week. Journal of the American College of Cardiology. 2019; 74: 2193–2203. https://doi.org/10.1016/j.jacc.2019.08.1039

Apandi PR, Djer MM, Kuswiyanto RB, Wijaya EA, Artiko B, Rahayuningsih SE. NT-proBNP levels as a predictor of higher left ventricular end-diastolic pressure in children with small perimembranous ventricular septal defect. Cardiology in the Young. 2023; 33: 2604–2609. https://doi.org/10.1017/S1047951123000756

Bayes-Genis A, Zamora E, de Antonio M, Galán A, Vila J, Urrutia A, et al. Soluble ST2 serum concentration and renal function in heart failure. Journal of Cardiac Failure. 2013; 19: 768–775. https://doi.org/10.1016/j.cardfail.2013.09.005

Boulogne M, Sadoune M, Launay JM, Baudet M, Cohen-Solal A, Logeart D. Inflammation versus mechanical stretch biomarkers over time in acutely decompensated heart failure with reduced ejection fraction. International Journal of Cardiology. 2017; 226: 53–59. https://doi.org/10.1016/j.ijcard.2016.10.038

Bouzas-Mosquera A, Broullón FJ, Álvarez-García N, Méndez E, Peteiro J, Gándara-Sambade T, et al. Left atrial size and risk for all-cause mortality and ischemic stroke. CMAJ: Canadian Medical Association Journal. 2011; 183: E657–E664. https://doi.org/10.1503/cmaj.091688

Buckley LF, Claggett BL, Matsushita K, McMahon GM, Skali H, Coresh J, et al. Chronic Kidney Disease, Heart Failure, and Adverse Cardiac Remodeling in Older Adults: The ARIC Study. JACC. Heart Failure. 2023; 11: 523–537. https://doi.org/10.1016/j.jchf.2023.01.029

Chang CC, Cheng HC, Chou WC, Huang YT, Hsieh PL, Chu PM, et al. Sesamin suppresses angiotensin-II-enhanced oxidative stress and hypertrophic markers in H9c2 cells. Environmental Toxicology. 2023; 38: 2165–2172. https://doi.org/10.1002/tox.23853

Dattagupta A, Immaneni S. ST2: Current status. Indian Heart Journal. 2018; 70: S96–S101. https://doi.org/10.1016/j.ihj.2018.03.001

Dudek M, Kałużna-Oleksy M, Migaj J, Sawczak F, Krysztofiak H, Lesiak M, et al. sST2 and Heart Failure-Clinical Utility and Prognosis. Journal of Clinical Medicine. 2023; 12: 3136. https://doi.org/10.3390/jcm12093136

Gać P, Waszczuk Ł, Kurcz J, Poręba R. Optimization of the method of measuring left ventricular end-diastolic diameter in cardiac magnetic resonance as a predictor of left ventricular enlargement. Scientific Reports. 2022; 12: 8425. https://doi.org/10.1038/s41598-022-12359-2

Girerd N, Mewton N, Tartière JM, Guijarro D, Jourdain P, Damy T, et al. Practical outpatient management of worsening chronic heart failure. European Journal of Heart Failure. 2022; 24: 750–761. https://doi.org/10.1002/ejhf.2503

Han X, Zhang S, Chen Z, Adhikari BK, Zhang Y, Zhang J, et al. Cardiac biomarkers of heart failure in chronic kidney disease. Clinica Chimica Acta. 2020; 510: 298–310. https://doi.org/10.1016/j.cca.2020.07.040

Harjola P, Miró Ò, Martín-Sánchez FJ, Escalada X, Freund Y, Penaloza A, et al. Pre-hospital management protocols and perceived difficulty in diagnosing acute heart failure. ESC Heart Failure. 2020; 7: 289–296. https://doi.org/10.1002/ehf2.12524

Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022; 145: e895–e1032. https://doi.org/10.1161/CIR.0000000000001063

Jia J, Zhao XA, Tao SM, Wang JW, Zhang RL, Dai HL, et al. Icariin improves cardiac function and remodeling via the TGF-β1/Smad signaling pathway in rats following myocardial infarction. European Journal of Medical Research. 2023; 28: 607. https://doi.org/10.1186/s40001-023-01588-4

Kuwahara K. The natriuretic peptide system in heart failure: Diagnostic and therapeutic implications. Pharmacology & Therapeutics. 2021; 227: 107863. https://doi.org/10.1016/j.pharmthera.2021.107863

Lin B, Siskin M, Wang B, Natarajan S. Does exercise training improve exercise tolerance, quality of life, and echocardiographic parameters in patients with heart failure with preserved ejection fraction? A systematic review and meta-analysis of randomized controlled trials. Heart Failure Reviews. 2023; 28: 795–806. https://doi.org/10.1007/s10741-022-10285-z

Liu T, Si Y, Yang W, Huang J, Yu Y, Zhang G, et al. Inter-Patient Congestive Heart Failure Detection Using ECG-Convolution-Vision Transformer Network. Sensors. 2022; 22: 3283. https://doi.org/10.3390/s22093283

Maisel AS, Di Somma S. Do we need another heart failure biomarker: focus on soluble suppression of tumorigenicity 2 (sST2). European Heart Journal. 2017; 38: 2325–2333. https://doi.org/10.1093/eurheartj/ehw462

Mascolo A, di Mauro G, Cappetta D, De Angelis A, Torella D, Urbanek K, et al. Current and future therapeutic perspective in chronic heart failure. Pharmacological Research. 2022; 175: 106035. https://doi.org/10.1016/j.phrs.2021.106035

McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal. 2021; 42: 3599–3726. https://doi.org/10.1093/eurheartj/ehab368

Miller WL, Saenger AK, Grill DE, Slusser JP, Bayes-Genis A, Jaffe AS. Prognostic Value of Serial Measurements of Soluble Suppression of Tumorigenicity 2 and Galectin-3 in Ambulatory Patients With Chronic Heart Failure. Journal of Cardiac Failure. 2016; 22: 249–255. https://doi.org/10.1016/j.cardfail.2015.07.017

Onoe H, Tanaka K, Tsuchiya N, Miyata K, Kitaoka M, Nakayama M, et al. Maximum carotid intima-media thickness and NT-pro BNP in association with retinal vein occlusion. PLoS ONE. 2023; 18: e0291456. https://doi.org/10.1371/journal.pone.0291456

Packer M. Left Ventricular Ejection Fraction in Heart Failure: Crazy, Stupid Love-and Maybe, Redemption. Journal of the American Heart Association. 2024; 13: e034642. https://doi.org/10.1161/JAHA.124.034642

Primessnig U, Deißler PM, Wakula P, Tran KL, Hohendanner F, von Lewinski D, et al. Effects of BNP and Sacubitrilat/Valsartan on Atrial Functional Reserve and Arrhythmogenesis in Human Myocardium. Frontiers in Cardiovascular Medicine. 2022; 9: 859014. https://doi.org/10.3389/fcvm.2022.859014

Rabkin SW, Tang JKK. The utility of growth differentiation factor-15, galectin-3, and sST2 as biomarkers for the diagnosis of heart failure with preserved ejection fraction and compared to heart failure with reduced ejection fraction: a systematic review. Heart Failure Reviews. 2021; 26: 799–812. https://doi.org/10.1007/s10741-020-09913-3

Redfors B, Chen S, Crowley A, Ben-Yehuda O, Gersh BJ, Lembo NJ, et al. B-Type Natriuretic Peptide Assessment in Patients Undergoing Revascularization for Left Main Coronary Artery Disease: Analysis From the EXCEL Trial. Circulation. 2018; 138: 469–478. https://doi.org/10.1161/CIRCULATIONAHA.118.033631

Roger VL. Epidemiology of Heart Failure: A Contemporary Perspective. Circulation Research. 2021; 128: 1421–1434. https://doi.org/10.1161/CIRCRESAHA.121.318172

Romeo R, Scalisi C, Tafuri L, Romeo A, Maugeri D, Sorace R. Different characteristics of chronic heart failure (CHF) in elderly diabetics and non-diabetics. Archives of Gerontology and Geriatrics. 2010; 50: 101–104. https://doi.org/10.1016/j.archger.2009.02.008

Rossi A, Gheorghiade M, Triposkiadis F, Solomon SD, Pieske B, Butler J. Left atrium in heart failure with preserved ejection fraction: structure, function, and significance. Circulation. Heart Failure. 2014; 7: 1042–1049. https://doi.org/10.1161/CIRCHEARTFAILURE.114.001276

Sani MU, Damasceno A, Davison BA, Cotter G, Mayosi BM, Edwards C, et al. N-terminal pro BNP and galectin-3 are prognostic biomarkers of acute heart failure in sub-Saharan Africa: lessons from the BA-HEF trial. ESC Heart Failure. 2021; 8: 74–84. https://doi.org/10.1002/ehf2.13032

Srivastava S, Girandola RN, Abedon B. Effect of E-OJ-01 on Left Ventricular Ejection Fraction and Myocardial Oxygen Consumption: A Randomized, Double-Blind, Placebo-Controlled Study. Journal of Multi-

disciplinary Healthcare. 2022; 15: 2511–2525. https://doi.org/10.2147/JMDH.S381028

Uchida AM, Ro G, Qiang L, Peterson KA, Round J, Dougan M, et al. Human differentiated eosinophils release IL-13 in response to IL-33 stimulation. Frontiers in Immunology. 2022; 13: 946643. https://doi.org/10.3389/fimmu.2022.946643

van Riet EES, Hoes AW, Wagenaar KP, Limburg A, Landman MAJ, Rutten FH. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. European Journal of Heart Failure. 2016; 18: 242–252. https://doi.org/10.1002/ejhf.483

Vitali E, Piccini S, Trivellin G, Smiroldo V, Lavezzi E, Zerbi A, et al. The impact of SST2 trafficking and signaling in the treatment of pancreatic neuroendocrine tumors. Molecular and Cellular Endocrinology. 2021; 527: 111226. https://doi.org/10.1016/j.mce.2021.111226

Yu Y, Ding L, Huang H, Cheng S, Deng Y, Cai C, et al. Effect of short-term cardiac function changes after cardiac resynchronization therapy on long-term prognosis in heart failure patients with and without diabetes. Therapeutic Advances in Chronic Disease. 2024; 15: 20406223231223285. https://doi.org/10.1177/20406223231223285

Zhang T, Xu C, Zhao R, Cao Z. Diagnostic Value of sST2 in Cardiovascular Diseases: A Systematic Review and Meta-Analysis. Frontiers in Cardiovascular Medicine. 2021; 8: 697837. https://doi.org/10.3389/fcvm.2021.697837

Zuo X, Li X, Tang K, Zhao R, Wu M, Wang Y, et al. Sarcopenia and cardiovascular diseases: A systematic review and meta-analysis. Journal of Cachexia, Sarcopenia and Muscle. 2023; 14: 1183–1198. https://doi.org/10.1002/jcsm.13221