Article

J. Biol. Regul. Homeost. Agents. 2024; 38(10): 5919–5926
https://doi.org/10.23812/j.biol.regul.homeost.agents.20243810.471

Prognostic Evaluation Value of Thyroid Function Tests plus B-type Natriuretic Peptide Tests for Patients with Heart Failure

Hongbo Yu[1,†], Nannan Li[2,†], Jie Li[3], Yaqun Liu[4], Qiong Zhang[5,*]

[1]Department of Cardiology, Qinhuangdao Military Hospital, 066001 Qinhuangdao, Hebei, China
[2]Department of Cardiology, The People's Hospital of Dongying District, 257000 Dongying, Shandong, China
[3]Department of Cardiology, The Fifth People's Hospital of Dongying, 257092 Dongying, Shandong, China
[4]Department of Neurology, Qinhuangdao Military Hospital, 066001 Qinhuangdao, Hebei, China
[5]The Fourth Department of Cardiology, Panjin Central Hospital, 124100 Panjin, Liaoning, China
*Correspondence: jinglantan79433@163.com (Qiong Zhang)
[†]These authors contributed equally.
Submitted: 25 September 2022 Revised: 13 June 2023 Accepted: 14 September 2023 Published: 1 October 2024

Objective: This research was performed to analyze the diagnostic and prognostic value of thyroid function tests plus B-type natriuretic peptide (BNP) tests in patients with heart failure (HF).

Methods: This study matched 120 patients with HF (HF group) at a single institution from January 2019 and January 2021 with 120 healthy subjects (control group) (1:1 ratio) during the same period. All eligible participants received BNP and thyroid function tests.

Results: Patients with HF exhibited markedly higher BNP levels than healthy controls ($p < 0.05$). Patients with HF showed remarkably lower concentrations of free triiodothyronine (FT_3) versus healthy controls ($p < 0.05$), while the concentrations of free thyroxine (FT_4) and thyroid-stimulating hormone (TSH) showed no marked alterations ($p > 0.05$). The aggravation of HF causes a remarkable decrease in FT_3 levels and an elevation in BNP levels ($p < 0.05$), while the alterations in the serum concentrations of FT_4 and TSH levels were mild ($p > 0.05$). After treatment, markedly elevations of FT_3 levels and a decline of BNP levels were found in the HF group ($p < 0.05$). Hybrid detection allows for a larger coverage of the detection area than the stand-alone test. The combined detection provided a larger area under the curve (AUC) and a higher 95% confidence interval and sensitivity versus single tests ($p < 0.05$), suggesting a superior diagnostic efficiency of the combined BNP and thyroid function tests.

Conclusion: The combination of BNP and thyroid function tests offers a viable diagnostic alternative for HF patients, with high diagnostic efficiency and prognostic assessment value.

Clinical Trial Registration: ChiCTR2200069567.

Keywords: B-type natriuretic peptide; thyroid function; HF; diagnosis; prognosis

Introduction

Heart failure (HF) is a cardiac circulatory disorder and is triggered by blood stasis and insufficient blood perfusion in the arterial system due to the systolic and diastolic dysfunctions of the heart, commonly manifested as pulmonary congestion and vena cava congestion [1,2]. HF is the end stage of cardiovascular disorders, such as coronary heart disease, and valvular heart disease. The prevalence of cardiovascular diseases has shown an increasing trend [3,4]. Thus, timely diagnosis and treatment are essential to boost the treatment effect and prognosis.

B-type natriuretic peptide (BNP) is a polypeptide secreted by ventricular myocytes, containing 32 amino acids [5–7]. It can act on the renin-angiotensin-aldosterone system (RAAS), has a diuretic function, removes sodium, and suppresses RAAS and the sympathetic nervous system [8]. When ventricular volume load or pressure load is increased, BNP mRNA is first translated into precursor protein of BNP (proBNP) containing 134 amino acids [9]. ProBNP was cleaved to inactive NT-proBNP and active BNP under the action of endonuclease [10]. Studies have shown that cardiac function classification is associated with thyroid hormone levels and brain natriuretic peptide (BNP) [9,11–13]. In severe cases, thyroid function would be altered with decreased levels of serum free triiodothyronine and normal or reduced concentrations of free thyroxine and thyroid-stimulating hormone [14,15]. Increased cardiac volume load or ventricular dilation give rise to elevated BNP levels, and higher BNP levels indicate poorer prognosis and a greater risk of cardiogenic death or HF in patients [16,17]. As a result, BNP and thyroid hormones in the diagnosis,

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treatment, and prognosis of HF patients has grown in importance. This research explores the application of simultaneous BNP and thyroid function tests in the diagnosis, treatment and prognosis of HF patients.

Materials and Methods

Participants

The current study matched 120 patients with HF (HF group) at a single institution from January 2019 and January 2021 with 120 healthy subjects (control group) (1:1 ratio) during the same period. According to the New York Heart Association classification of stages of HF, 16 patients in the HF group were classified as grade I, 32 patients grade II, 48 patients grade III, and 24 patients grade IV.

The sample size calculation estimated that 100 patients in each group would be required to determine a 3-point difference between groups in a two-sided test of significance with a power of 0.8 and an alpha error level of 0.05.

The protocol was ratified by the Ethics Committee of Panjin Central Hospital, No. 1979291-1. Clinical registration number: ChiCTR2200069567. All participants submitted written informed consent in accordance with the Declaration of Helsinki.

Inclusion and Exclusion Criteria

Inclusion criteria: ① patients met the diagnostic criteria forHF; ② complete clinical data; ③ normal cognitive and communication skills. The patients and their families were informed of the study and signed informed consent forms.

Exclusion criteria: ① patients with thyroid disease; ② liver and kidney functional diseases; ③ mental illness; ④ received medications that affected BNP levels, such as Sacubitril/Valsartan.

Methods

The patients in the HF group were given conventional treatment for HF. In the acute phase, they were intravenously injected with 0.2–0.4 mg of cedilanid (Shanghai Xudong Haipu Pharmaceutical Co., Ltd.; Approval No.: H31021178, Shanghai, China) and 20–40 mg of furosemide injection (Ji'an Yisheng Pharmaceutical Co., Ltd.; Approval No.: H22021500, Ji'an City, Jilin Province, China). After symptoms were relieved, the patients received 20–40 mg of furosemide tablets (Jiangsu Yabang Epson Pharmaceutical Co., Ltd.; Approval No.: H32021428, Yancheng City, Jiangsu Province, China) daily, and 20–40 mg of spironolactone tablets (Guangdong Huanan Pharmaceutical Co., Ltd.; Approval No.: H44020686, Dongguan, Guangdong 523325., China) daily. All patients were treated with angiotensin-converting enzyme inhibitors (ACEI).

Morning fasting venous blood (3 mL) was collected upon admission and tested within 1 h. After centrifugation for 10 minutes, the serum was obtained, and the serum BNP level was measured using a 12000SR automatic chemical reflector (Abbott, Green Oaks, IL, USA). The kit was from Suzhou Lianjian Technology Co., Ltd., Suzhou, Jiangsu Province, China and the operation was in strict accordance with the instructions. E170 electrochemiluminescence analyzer was used to determine free triiodothyronine (FT_3), free thyroxine (FT_4), and thyroid-stimulating hormone (TSH). Telephone follow-up and review of patient records were conducted to learn about patient survival, and death cases were recorded.

Observation Indicators

The levels of BNP and thyroid hormone were compared between the two groups. The prognostic value of individual BNP tests, individual thyroid hormone tests and combined BNP and thyroid hormone tests was analyzed, and the sensitivity and specificity of different test methods were calculated. The calculation method is as follows:

Sensitivity = True Positive/(True Positive + False Negative)

Specificity = True Negative/(True Negative + False Positive)

B-Type Natriuretic Peptide (BNP)

We used enzyme-linked immunosorbent assay (ELISA) kit (EHNPPB, Thermo Fisher, Waltham, MA 02451, USA) to detect BNP in patients' blood. The kit has a sensitivity of 14 pg/mL and a detection range of 15.63–1000 pg/mL. A patient's blood sample is centrifuged to separate the serum. The kit containing BNP antibody and test substance was thoroughly mixed and added to the well plate. The sample is then added to the well plate and incubated in a temperature-controlled mixture to promote the binding of BNP to specific antibodies. Remove any unbound proteins or chemicals that are not bound to specific antibodies by adding a buffer and washing the orifice plate with a scrubber. An enzyme-labeled secondary antibody (also specific antibody) is added and incubated at a constant temperature in order to bind to the BNP/anti-BNP antibody complex. An enzyme-labeled substrate is then added and allowed to bind to the enzyme in order to generate an optical signal. The optical signal was read using ELISA automated microplate reader (ERBA LisascanTM EM SR 120710, Germany) to determine BNP concentration and the absorbance is 450 nm. The results are usually plotted with a standard curve and reported as pg/mL or ng/L.

Thyroid Function Tests

A 2 mL syringe was used for drawing venous blood from the antecubital vein under aseptic precautions and blood transferred to a plain sterile vial after removing the needle hub. After centrifugation of the blood samples at 2000 ×g for 10 minutes in a centrifuge, the serum were prepared and stored in freezer compartment of refrigerator at –2 °C to –10 °C. Prior to use, all the samples were brought to

Table 1. Comparison of the clinical data of the two groups of patients [n (%)].

	Control group (n = 120)	Heart failure (HF) group (n = 120)	t/χ^2	p
Gender			0.067	0.654
Male	64 (53.33)	68 (56.67)		
Female	56 (46.67)	52 (43.33)		
Mean age (year)	63.42 ± 13.25	64.21 ± 11.57	0.250	0.703
Grade I	0	16 (13.3)		
Grade II	0	32 (26.67)		
Grade III	0	48 (40.00)		
Grade IV	0	24 (20.00)		
Drinking	40 (33.33)	44 (36.67)	8.097	0.861
Smoking	32 (26.67)	28 (23.33)	7.679	0.805
Hypertension	68 (56.67)	60 (50.00)	2.680	0.655
Diabetes	48 (40.00)	56 (46.67)	7.272	0.702

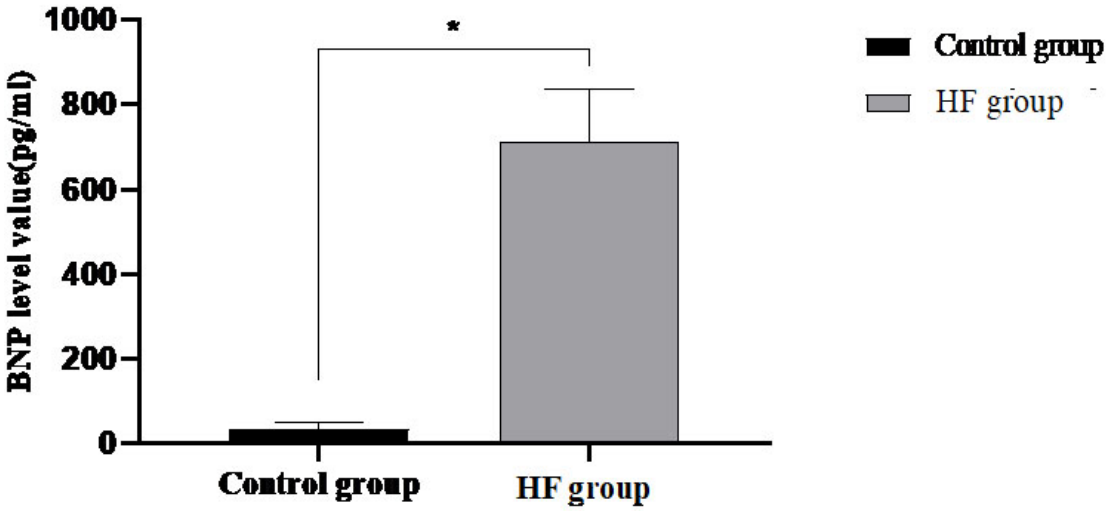

Fig. 1. Comparison of B-type natriuretic peptide (BNP) levels of two groups ($\bar{x} \pm s$). The abscissa represents the control group and the HF group, and the ordinate represents the BNP level; * indicates that there is a significant difference in BNP level between the control group and the HF group (t = 29.540, $p < 0.001$)

room temperature and analyzed for thyroid profile studies, which included FT_3, FT_4 and TSH estimation using ELISA automated microplate reader (ERBA LisascanTM EM SR 120710, Germany) with adsorbance at 450 nm and commercially available ELISA thyro-kit (BeneSphera Avantor Inc, Gurgaon-122002, Haryana, India) with the analytical sensitivity for serum FT_3, serum FT_4 and serum TSH assays as 0.05 picogram per decilitre (pg/dL), 0.05 nanogram per decilitre (ng/dL) and 0.027 micro international unit per milliliter (μIU/mL) respectively.

Endpoints and Follow-up

The clinical endpoint of this study is the final clinical diagnosis of the patient. In this process, relevant laboratory results of BNP and thyroid function tests were collected during the patient's illness. We have fully explained the purpose, content and sample handling of this clinical trial to the subjects, all of whom have signed informed consent.

Statistical Analysis

The data were processed by software SPSS 20.0, and GraphPad Prism 7 (GraphPad Software, San Diego, CA 92108, USA) was used to plot graphics. The count data were expressed as [n (%)] and tested by *chi*-square test. Measurement data were expressed as means ± variance ($\bar{x} \pm s$) and examined by *t*-test. For data before and after treatment, paired *t*-tests were used. Significant differences were indicated by a *p*-value of <0.05.

Results

Clinical Data

This study matched 120 patients with HF (HF group) (68 males and 52 females, aged 64.21 ± 11.57 years) at a single institution from January 2019 and January 2021 with 120 control subjects (64 males and 56 females, aged 63.42 ± 13.25 years) (1:1 ratio) during the same period. In the HF

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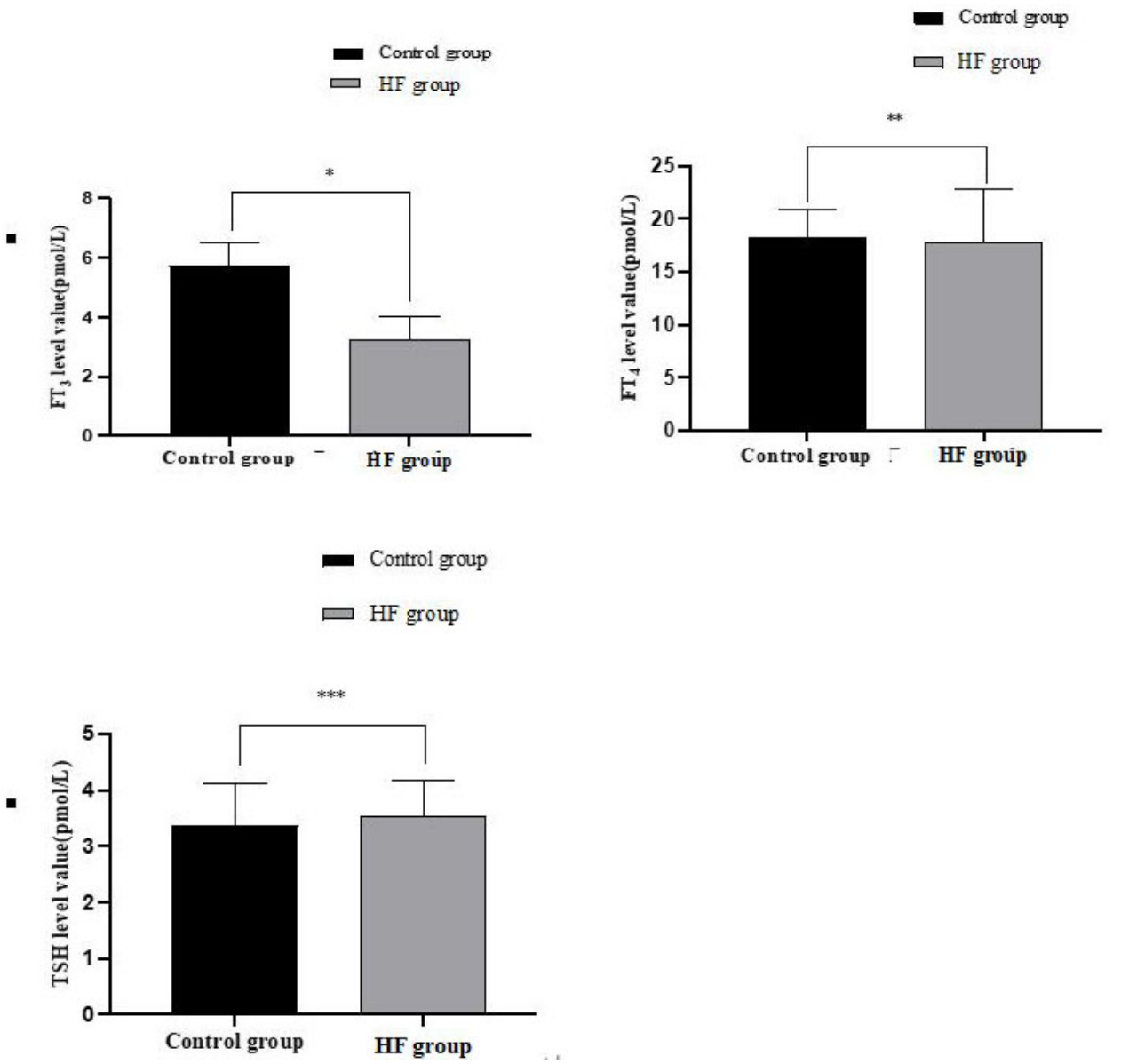

Fig. 2. Comparison of thyroid hormone levels between the two groups ($\bar{x} \pm s$). The abscissa represents the control group and the heart failure (HF) group, and the ordinate represents the level of thyroid hormone; * indicates that there is a significant difference between the control group and the HF group in the free triiodothyronine (FT_3) level before treatment (t = 12.441, $p < 0.001$); ** indicates that there is no statistical difference between the control group and the HF group in the free thyroxine (FT_4) level before treatment (t = 0.491, $p > 0.05$); *** means that there is no statistical difference between the control group and the HF group in the thyroid-stimulating hormone (TSH) level before treatment (t = 0.957, $p > 0.05$).

group, 16 patients were classified as grade I, 32 cases grade II, 48 cases grade III, and 24 cases grade IV. The two groups were comparable in terms of baseline patient profiles ($p > 0.05$) (Table 1).

BNP Levels

The BNP level of the control group was (35 ± 15) pg/mL. The BNP level before treatment in the HF group was (714 ± 125) pg/mL. Patients with HF exhibited markedly higher BNP levels than healthy controls ($p < 0.05$) (Fig. 1).

Thyroid Hormone Levels

The levels of FT_3, FT_4, and TSH in the control group were (5.74 ± 0.79) pmol/L, (18.30 ± 2.62) pmol/L, and (3.37 ± 0.75) pmol/L, respectively. The levels of FT_3, FT_4, and TSH in the HF group before treatment were (3.25 ± 0.76) pmol/L, (17.8 ± 4.93) pmol/L, (3.54 ± 0.62) pmol/L, respectively. Patients with HF showed remarkably lower concentrations of FT_3 versus healthy controls ($p < 0.05$), while the concentrations of FT_4 and TSH showed no marked alterations ($p > 0.05$) (Fig. 2).

Table 2. Comparison of BNP and thyroid hormone levels in patients with different cardiac function grading ($\bar{x} \pm s$).

Cardiac functional grading	n	FT_3 (pmol/L)	FT_4 (pmol/L)	TSH (pmol/L)	BNP (pg/mL)
Grade I	16	4.89 ± 0.76	16.97 ± 5.37	2.87 ± 1.74	86.48 ± 20.41
Grade II	32	4.14 ± 0.45	16.32 ± 4.65	3.30 ± 2.46	675.54 ± 230.02
Grade III	48	3.36 ± 1.12	16.10 ± 5.48	3.41 ± 2.15	1321.52 ± 630.58
Grade IV	24	2.52 ± 1.24	15.84 ± 5.67	3.79 ± 1.90	2144.26 ± 1031.17
F		3.383	0.315	0.774	3.908
p		<0.05	>0.05	>0.05	<0.05

Table 3. Comparison of changes in BNP and thyroid hormone levels before and after treatment in the HF group ($\bar{x} \pm s$).

Groups	n	FT_3 (pmol/L)	FT_4 (pmol/L)	TSH (pmol/L)	BNP (pg/mL)
Before treatment	120	3.27 ± 0.91	17.85 ± 5.72	3.50 ± 0.65	723 ± 135
After treatment	120	4.39 ± 0.60	17.74 ± 5.13	3.64 ± 0.69	144 ± 90
t		4.074	0.074	0.809	19.546
p		<0.05	>0.05	>0.05	<0.05

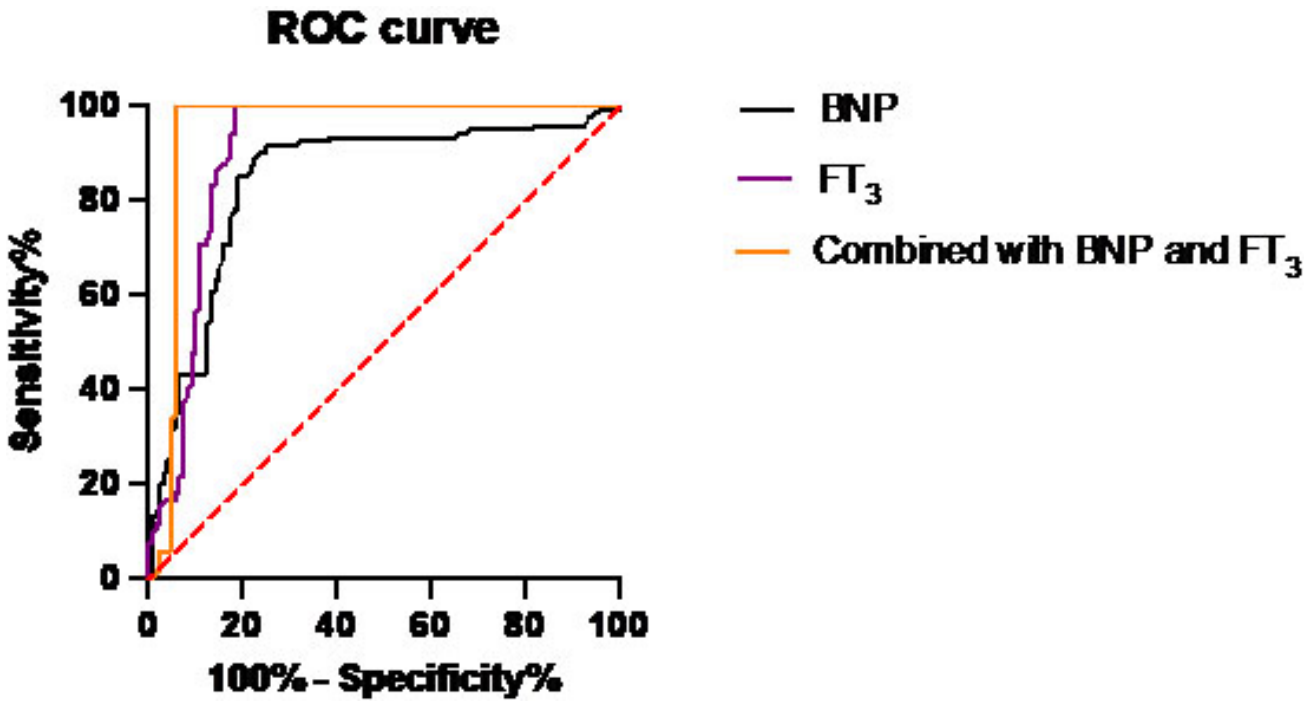

Fig. 3. Comparison of the prognostic value of BNP and FT_3 single detection and hybrid detection for patients with HF.

BNP and Thyroid Hormone Levels among Patients with Different Cardiac Function Grades

The aggravation of HF causes a marked decline in FT_3 levels and an elevation in BNP levels ($p < 0.05$), while the alterations in the serum concentrations of FT_4 and TSH levels were mild ($p > 0.05$) (Table 2).

Changes in BNP and Thyroid Hormone Levels

After treatment, markedly elevations of FT_3 concentrations and a decline of BNP concentrations were found in the HF group ($p < 0.05$). No marked disparity in FT_4 and TSH levels before and after treatment was found ($p > 0.05$, Table 3).

Prognostic Value of Single BNP or FT_3 Test Versus Combined Tests

The ROC curve (AUC) for diagnosis of HF using BNP alone was 0.833, FT_3 alone was 0.883, and the AUC for diagnosis of HF combined with BNP and FT_3 was 0.950. Hybrid detection allows for a larger coverage of the detection area than the stand-alone test. The combined detection provided a larger area under the curve (AUC) and a higher 95% confidence interval and sensitivity versus a single test ($p < 0.05$, Fig. 3), suggesting a superior diagnostic efficiency of the combined BNP and thyroid function tests (Table 4).

The maximum Youden index of BNP was 0.667, and the diagnostic sensitivity and specificity of BNP were 0.892, 0.775, and the diagnostic threshold was 439.5

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Table 4. Comparison of the area under the curve and 95% confidence interval.

	Area	Standard error a	Asymptotic Sig.B	95% confidence interval	
				Lower limit	Upper limit
BNP	0.833	0.056	0	0.724	0.943
FT_3	0.883	0.048	0	0.789	0.978
Hybrid detection	0.95	0.033	0	0	1

Table 5. Optimal diagnostic threshold of BNP and FT_3.

	Sensitivity	Specificity	Youden index	Cut-off value
BNP	0.892	0.775	0.667	439.5
FT_3	1.000	0.817	0.817	3.99

pg/mL. The maximum Youden index of FT_3 was 0.817, and the diagnostic sensitivity and specificity of BNP were 1.000, 0.817, and the diagnostic threshold was 3.99 pmol/L (Table 5). The optimal thresholds for the combined diagnosis of BNP and FT_3 were 436.3 pg/mL and 4.05 pmol/L, respectively.

Discussion

As a common cardiovascular disease in clinical practice, HF is characterized by compromised myocardial contractility, decreased cardiac output, and reduced blood perfusion of tissues and organs [18,19]. As society ages, the incidence of HF in recent years has exhibited an uproar. Relevant studies have shown that 5-year mortality of patients with HF is approximately 50% [20,21]. For patients with HF, Western medicine typically treats patients with diuretics, angiotensin-converting enzyme inhibitors, and beta-receptor antagonists to prevent myocardial remodeling, thereby improving the cardiac function and life quality of patients [22]. The primary cause of HF is the deficiency of kidney yang and heart yang. Thus, the treatment should focus on the replenishment of the yang and the alleviation of water retention.

BNP is a polypeptide hormone secreted by ventricular myocytes that stabilizes blood volume and reflects ventricular function [23,24]. A previous study [25] revealed a high expression of BNP in patients with HF. Here, strikingly higher BNP levels were found in the HF group. The higher the BNP level, the less the circulating blood volume in patients with HF, and the worse the long-term prognosis. Thyroid hormones can act on the cardiovascular system by regulating the sympathetic adrenal system, ventricular function, peripheral vascular resistance, arginine vasopressin, and atrial natriuretic peptide levels [26].

In the current study, we assigned 120 patients with HF of varying severity to the HF group and selected 120 healthy individuals as controls. In order to exclude the influence of drug factors on the experimental results, observe the ethics of clinical research and protect the rights of patients, the use of cedilan and diuretics in patients with HF is limited to the acute stage of HF. In addition, patients with hypertension and diabetes in the two groups should take medicine according to relevant doctor's advice, and diuretics and Angiotensin-Converting Enzyme Inhibitors (ACEI) are preferred. Lower FT_3 levels were seen in the HF group before treatment versus controls, while the alterations in the serum concentrations of FT_4 and TSH were mild. After treatment, markedly elevations of FT_3 and a decline of BNP were visible in the HF group. HF patients are in the terminal stages of various heart diseases, and most of them are susceptible to abnormal endocrine metabolism. The decrease in FT_3 levels in patients with HF can be attributable to the following factors. (1) As the patient is in a stressed state, the secretion of catecholamines and glucocorticoids increases, 5′-deiodinase is inhibited, and the conversion of triiodothyronine (T_3) is compromised. (2) The patient has acidosis, which increases the utilization of FT_3. (3) The patient's thyroid receptor density increases significantly. (4) The patient is in a state of hypoxia and lacks nutrients, which reduces the synthesis of FT_3.

In the present study, the aggravation of HF causes a remarkable reduction in FT_3 levels and an elevation in BNP levels ($p < 0.05$), while the alterations in the serum concentrations of FT_4 and TSH levels were mild, which was in line with the study conducted by Wang K *et al*. [27]. All these results suggest that the cardiac function classification of patients with HF is associated with the levels of BNP and thyroid hormones. Moreover, hybrid detection allows for a larger coverage of the detection area than the stand-alone test. The combined detection provided a larger area under the curve and a higher 95% confidence interval and sensitivity versus a single test, suggesting a superior diagnostic efficiency of the combined BNP and thyroid function tests.

This study has the following limitations, such as the small sample size and short long-term follow-ups. In addition, this clinical study is still unable to explain the mechanism of parameter changes of FT_3, FT_4, BNP in patients with HF, and further basic research is needed to explain this phenomenon. Future clinical studies based on larger samples will be conducted to provide more reliable evidence.

Conclusion

In conclusion, the combination of BNP and thyroid function tests offers a viable diagnostic alternative for HF patients, with high diagnostic efficiency and prognostic assessment value.

Availability of Data and Materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Author Contributions

HY, NL designed the research study. JL, YL performed the research. QZ conducted experiments, analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

This study was approved by the ethics committee of Panjin Central Hospital, No. 1979291-1. Informed consent was obtained from all study participants. All the methods were carried out in accordance with the Declaration of Helsinki.

Acknowledgment

Not applicable.

Funding

The study was supported by Qinhuangdao science and technology research and development plan project No. 201805A097.

Conflict of Interest

The authors declare no conflict of interest.

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