Clinical Investigation

Low T3 Syndrome Is Associated With High Mortality in Hospitalized Patients With Heart Failure

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ABSTRACT

Background: We aimed to clarify the prognosis and pathophysiological parameters of low T3 syndrome in patients with heart failure (HF).

Methods and Results: Hospitalized patients with HF and euthyroidism (n = 911) were divided into 2 groups on the basis of free triiodothyronine (FT3) serum levels: the normal FT3 group (FT3 ≥2.3 pg/mL; n = 590; 64.8%) and the low FT3 group (FT3 <2.3 pg/mL; n = 321; 35.2%). We compared post-discharge cardiac and all-cause mortality by means of Kaplan-Meier analysis and Cox proportional hazard analysis, and the parameters of echocardiography and cardiopulmonary exercise testing by means of Student *t* test. In the follow-up period of median 991 (interquartile range 534-1659) days, there were 193 all-cause deaths, including 88 cardiac deaths. Cardiac and all-cause mortality were higher in the low FT3 group (log-rank $P < .01$). Low FT3 was a predictor of cardiac death (hazard ratio 1.926, 95% confidence interval [CI] 1.268−2.927; $P = .002$) and all-cause death (hazard ratio 2.304, 95% CI 1.736−3.058; $P < .001$). Although left ventricular ejection fraction was similar between the groups, the low FT3 group showed lower peak VO_2 (13.6 ± 4.6 vs 16.6 ± 4.4 mL·kg^{-1}·min,$^{-one}$ $P < .001$) and higher VE/VCO_2 slope (36.5 ± 8.2 vs 33.0 ± 7.5; $P = .001$).

Conclusion: Low T3 syndrome in patients with HF is associated with higher cardiac and all cause-mortality. (*J Cardiac Fail 2019;25:195−203*)

Key Words: Heart failure, low T3 syndrome, nonthyroidal illness syndrome, euthyroid sick syndrome, cardiopulmonary exercise testing, cardiac catheterization, prognosis.

Thyroid hormone abnormalities affect the heart and cardiovascular system.[1,2] It has been recognized that overt hyperthyroidism,[3] subclinical hyperthyroidism,[3,4] and subclinical hypothyroidism[4-6] have an unfavorable prognostic impact in patients with heart failure (HF).

The low concentration of serum triiodothyronine (T3) is driven by the reduction of 5′-monodeiodinase, which is responsible for converting thyroxine (T4) into T3.[7,8] Low T3 syndrome is also known as "nonthyroidal illness syndrome" or "euthyroid sick syndrome," and can occur in patients with several diseases,[8] including HF[9,10] and acute myocardial infarction,[11] and in patients who have undergone cardiopulmonary bypass surgery.[12] Low T3 syndrome has been considered as an adaptive change to deal with such severe conditions.[8] Although only a few studies have shown that low T3 syndrome is associated with adverse prognosis in patients with HF,[13,14] little is known about the associated mechanism of the effect of low T3 syndrome on the prognosis of HF.

Therefore, we aimed to clarify whether low T3 syndrome affects the prognosis of patients with HF and the associated clinical and pathophysiologic parameters (eg, cardiac function, hemodynamic parameters, nutritional status, and exercise capacity).

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Methods

Subjects and Study Protocol

We conducted a prospective observational study of 1,405 consecutive patients with decompensated HF who were admitted to Fukushima Medical University Hospital and discharged from 2010 to 2015. The diagnosis of decompensated HF was made by several cardiologists based on guidelines.[15,16] Blood samples were obtained at hospital discharge. Patients who were prescribed amiodarone, thyroid hormones, and antithyroid drugs and those who had undergone thyroid operation or radiation therapy during follow-up were excluded (n = 305). The patient flow chart is shown in Fig. 1. We first divided the 1100 patients into 5 groups based on the combination of thyroid-stimulating hormone (TSH) and free T4 (FT4) serum levels: euthyroidism (0.4 ≤ TSH ≤4 μIU/L and 0.7 ≤ FT4 ≤ 1.9 ng/dL; n = 911; 82.8%), subclinical hypothyroidism (TSH >4 μIU/L and 0.7 ≤ FT4 ≤ 1.9 ng/dL; n = 132; 12.0%), subclinical hyperthyroidism (TSH <0.4 μIU/L and 0.7 ≤ FT4 ≤ 1.9 ng/dL; n = 45, 4.1%), overt hypothyroidism (TSH >4 μIU/L and FT4 <0.7 ng/dL; n = 0), overt hyperthyroidism (TSH <0.4 μIU/L and FT4 >1.9 ng/dL; n = 2; 0.2%), and unclassified (n = 10; 0.9%). Next, we focused on the euthyroidism group (n = 911), which we further divided into 2 groups based on free T3 (FT3) serum levels: the normal FT3 group (FT3 ≥2.3 pg/mL; n = 590; 64.8%) and the low FT3 group (FT3 <2.3 pg/mL; n = 321, 35.2%). We focused on the normal FT3 and low FT3 groups (Fig. 1) and compared the clinical features and parameters of laboratory data, echocardiography, cardiopulmonary exercise testing (CPX), and cardiac catheterization. The clinical features included age, sex, vital signs, comorbidities, and medications. These assessments were performed within 1 week of hospital discharge.

Hypertension was defined as the recent use of antihypertensive drugs, systolic blood pressure of ≥140 mm Hg, or diastolic blood pressure of ≥90 mm Hg. Diabetes mellitus was defined as the recent use of antidiabetic drugs, a fasting glucose value of ≥126 mg/dL, a casual glucose value of ≥200 mg/dL, and/or Hb_{A1c} (National Glycohemoglobin Standardization Program) ≥6.5%. Dyslipidemia was defined as the recent use of cholesterol-lowering drugs, a triglyceride value of ≥150 mg/dL, a low-density lipoprotein cholesterol value of ≥140 mg/dL, or a high-density lipoprotein cholesterol value of <40 mg/dL. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate of <60 $mL \cdot min^{-1} \cdot 1.73\ cm^{-2}$. Anemia was defined as hemoglobin levels of <12.0 g/dL in women and <13.0 g/dL in men. Atrial fibrillation was identified by means of electrocardiography performed during hospitalization or from medical records. The Geriatric Nutritional Risk Index (GNRI), which is a nutritional index, was calculated as follows: GNRI = 14.89 × serum albumin (g/dL) + 41.7 × %body weight, where %body weight = measured body weight (kg)/(22 × square of height [m]). %body weight = 1 if measured body weight (kg) > (22 × square of height [m]).[17]

The patients were followed until September 2017 for cardiac and all-cause death. We were able to follow all the patients. Cardiac death was classified by independent experienced cardiologists as worsened HF in accordance with the Framingham criteria, ventricular fibrillation documented by electrocardiography or implantable devices, or acute coronary syndrome. Status and dates of death were obtained from the patients' medical records. If these data were unavailable, status was ascertained by a telephone call to the patient's referring hospital physician. Written informed consents were obtained from all of the study subjects. The study protocol was approved by the Ethical Committee of Fukushima Medical University, the investigation conforms with the principles outlined in the Declaration of Helsinki, and reporting of the study conforms to STROBE along with references to STROBE and the broader EQUATOR guidelines.[18]

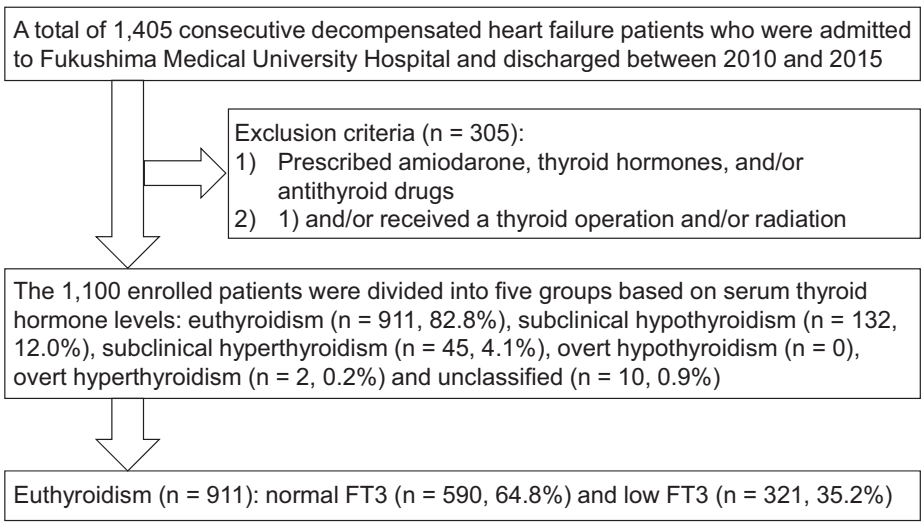

Fig. 1. Patient flow chart. FT3, free triiodothyronine.

Measurement of TSH, FT4, and FT3

Serum TSH, FT4, and FT3 were measured by means of electrochemiluminescence immunoassay (ECLusys TSH, ECLusys FT4, and ECLusys FT3; Roche Diagnostics KK, Tokyo, Japan). These immunoassays were performed by clinical laboratory technologists, who were blind to this investigation, at Fukushima Medical University Hospital.

Echocardiography

Echocardiography was blindly performed by experienced echocardiographers using standard techniques.[19] The left ventricular ejection fraction (LVEF) and right ventricular fractional area change (RV-FAC) were determined. The LVEF was measured from the 4-chamber view by means of the Simpson method. An LVEF ≥50% was defined as heart failure with preserved ejection fraction (HFpEF), an LVEF of 40%−49% as heart failure with mid-range ejection fraction (HFmrEF), and an LVEF of <40% as heart failure with reduced ejection fraction (HFrEF).[15] The RV-FAC, defined as (end-diastolic area − end-systolic area)/end-diastolic area × 100, was used as a measure of right ventricular systolic function. All measurements were performed with the use of ultrasound systems (Acuson Sequoia, Siemens Medical Solutions USA, Mountain View, California).

Cardiopulmonary Exercise Testing

CPX was encouraged by hospital physicians during hospitalization. Although not all of the participants underwent CPX, we collected the test results of the patients who did. The patients underwent incremental symptom-limited exercise testing before discharge with the use of an upright cycle ergometer with a ramp protocol (Strength Ergo 8; Fukuda Denshi Co, Tokyo, Japan). Breath-by-breath oxygen consumption (VO_2), carbon dioxide production (VCO_2), and minute ventilation (VE) were measured during exercise with the use of an AE-300S respiratory monitor (Minato Medical Science, Osaka, Japan).[5,20] Peak VO_2 was measured as an average of the last 30 seconds of exercise. Ventilatory response to exercise (slope of the relationship between ventilation and carbon dioxide production; VE/VCO_2 slope) was calculated as the regression slope relating VE to CO_2 from the start of exercise until the respiratory compensation point (the time at which ventilation is stimulated by CO_2 output and end-tidal CO_2 tension begins to decrease).[5,20] The ventilatory anaerobic threshold was calculated by means of the V-slope method. Peak VO_2 and VE/VCO_2 slope were examined and compared as exercise capacity.

Cardiac Catheterization and Hemodynamic Measurements

Cardiac catheterization was encouraged by hospital physicians during hospitalization to diagnose the etiology and severity of HF. The judgement of whether to carry out cardiac catheterization was left to the attending physicians. All right-heart catheterizations were performed with the patients in a stable condition, in a resting supine position under fluoroscopic guidance, at room temperature >30 minutes after catheter placement. The cardiac catheterization investigated generally measured parameters such as pulmonary artery pressure, pulmonary artery wedge pressure, right atrial pressure, cardiac output, and cardiac index. Cardiac output was calculated based on the thermodilution method. Cardiac index was calculated as cardiac output (L/min)/basal body area (m^2). All measurements were performed with the use of a 7-F Swan-Ganz catheter (Edwards Lifesciences, Irvine, California) and a hemodynamic recording system (Mac-Lab, GE Healthcare Japan Corp, Tokyo, Japan).

Statistical Analysis

Parametric variables are presented as mean ± SD, nonparametric variables (eg, B-type natriuretic peptide [BNP] and C-reactive protein) as median (interquartile range), and categoric variables as n (%). Parametric variables were compared by means of Student *t* test, nonparametric variables by means of Mann-Whitney *U* test, and categoric variables by means of chi-square test. Pearson and the Spearman correlation analyses were used to evaluate the correlations between serum FT3 levels and other parameters of laboratory data, echocardiography, CPX, and cardiac catheterization. Kaplan-Meier analysis was used for presenting cardiac death and all-cause death, and log-rank test was used for initial comparisons. The proportional hazards assumption for the model was checked by examining log minus-log transformed data. The curves helped in identifying the nonproportionality patterns in hazard function such as convergence (the difference in risk between the 2 groups decreases with time), divergence, or crossing of the curves. The Cox proportional hazard analyses were used to evaluate low FT3 (categoric variable) as a predictor of cardiac and all-cause death. In addition, we conducted the subgroup analyses to assess the potential heterogeneity of associations between low FT3 (categoric variable) and cardiac death and all-cause death. Interactions between low FT3 and clinically relevant variables were estimated by means of Cox proportional hazards analysis. A *P* value of <.05 was considered to be statistically significant for all comparisons. These analyses were performed with the use of statistical software packages SPSS v24.0 (IBM, Armonk, New York) and EZR v1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Results

Of the 911 hospitalized patients with HF and euthyroidism, 321 (35.2%) belonged to the low FT3 group (Fig. 1). Comparisons of clinical characteristics are presented in Table 1. Compared with the normal FT3 group, the low FT3 group was had higher age, systolic blood pressure, heart rate, and prevalence of ischemic etiology and lower

Table 1. Comparisons of Clinical Characteristics (n = 911)

Characteristic	Normal FT3 (n = 590)	Low FT3 (n = 321)	*P* Value
Demographic data			
Age (y)	64.4 ± 14.4	72.9 ± 13.1	<.001
Male sex	370 (62.7)	171 (53.3)	.006
Body mass index (kg/m^2)	23.8 ± 4.1	22.9 ± 4.2	.001
Systolic BP (mm Hg)	130.1 ± 29.5	138.4 ± 37.5	.001
Diastolic BP (mm Hg)	75.0 ± 20.7	76.5 ± 23.9	.311
Heart rate (beats/min)	78.7 ± 21.6	86.6 ± 27.3	<.001
NYHA III or IV	13 (2.2)	11 (3.4)	.271
Ischemic etiology	149 (25.3)	105 (32.7)	.017
LVEF			.061
Reduced	198 (33.6)	119 (37.1)	
Mid-range	45 (7.6)	36 (11.2)	
Preserved	347 (58.8)	166 (51.7)	
Comorbidities			
Hypertension	448 (75.9)	263 (81.9)	.037
Diabetes mellitus	212 (35.9)	156 (48.6)	<.001
Dyslipidemia	473 (80.2)	252 (78.5)	.552
CKD	275 (46.6)	205 (63.9)	<.001
Anemia	238 (40.3)	227 (70.7)	<.001
Atrial fibrillation	202 (34.2)	115 (35.8)	.631
Medications			
RAS inhibitors	429 (72.7)	243 (75.7)	.327
Beta-blockers	447 (75.8)	233 (72.6)	.292
Diuretics	319 (54.1)	220 (68.5)	<.001
Inotropic agents	36 (6.1)	40 (12.5)	.001

Values are presented as mean ± SD or n (%). FT3, free triiodothyronine; BP, blood pressure; NYHA, New York Heart Association functional class; LVEF, left ventricular ejection fraction; CKD, chronic kidney disease; RAS, renin-angiotensin system.

Table 2. Comparisons of Laboratory Data, Echocardiography, CPX, and Cardiac Catheterization

Variable	Normal FT3 (n = 590)	Low FT3 (n = 321)	*P* Value
Laboratory data			
TSH (IU/mL)	1.75 ± 0.87	1.75 ± 0.93	.981
FT4 (ng/dL)	1.3 ± 0.2	1.2 ± 0.2	<.001
FT3 (pg/mL)	2.9 ± 0.4	1.9 ± 0.3	<.001
BNP (pg/mL)	181.0 (62.6−459.3)	411.8 (152.8−949.1)	<.001
Troponin I (ng/mL)	0.04 (0.02−0.08)	0.10 (0.04−1.48)	<.001
Total protein (g/dL)	7.1 ± 0.7	6.6 ± 0.8	<.001
Albumin (g/dL)	4.0 ± 0.5	3.4 ± 06	<.001
AST (IU/L)	23.0 (19.0−32.0)	29.0 (21.0−51.0)	<.001
ALT (IU/L)	19.0 (14.0−30.5)	20.0 (13.0−36.0)	.631
ALP (IU/L)	246.1 ± 108.1	292.3 ± 159.0	.003
GGT (IU/L)	34.0 (21.0−59.0)	33.0 (20.0−66.5)	.981
Creatinine (mg/dL)	1.10 ± 1.08	1.55 ± 1.71	<.001
Sodium (mEq/L)	139.6 ± 2.9	138.3 ± 4.4	<.001
CRP (mg/dL)	0.11 (0.05−0.39)	0.58 (0.10−2.72)	<.001
GNRI	99.3 ± 8.4	90.0 ± 9.7	<.001
Echocardiography			
LVEF (%)	53.1 ± 15.5	50.8 ± 14.9	.057
RV-FAC (%)	42.1 ± 14.2	43.1 ± 15.3	.549
CPX	(n = 233)	(n = 70)	
Peak VO_2 ($mL \cdot kg^{-1} \cdot min^{-1}$)	16.6 ± 4.4	13.6 ± 4.6	<.001
VE/VCO_2 slope	33.0 ± 7.5	36.5 ± 8.2	.001
Cardiac catheterization	(n = 404)	(n = 179)	
Systolic PAP (mm Hg)	37.3 ± 18.5	34.9 ± 14.1	.079
Diastolic PAP (mm Hg)	16.2 ± 10.2	16.4 ± 9.7	.874
Mean PAP (mm Hg)	24.1 ± 12.6	23.0 ± 9.9	.236
PAWP (mm Hg)	13.7 ± 7.7	14.6 ± 8.1	.189
Mean RAP (mm Hg)	6.9 ± 4.2	8.6 ± 6.0	.001
Cardiac output (L/min)	4.4 ± 1.5	4.2 ± 1.2	.285
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	2.7 ± 0.8	2.7 ± 0.8	.541

Data are presented as mean ± SD or median (interquartile range). CPX, cardiopulmonary exercise testing; FT3, free triiodothyronine; TSH, thyroid-stimulating hormone; FT4, free thyroxine; BNP, B-type natriuretic peptide; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; CRP, C-reactive protein; GNRI, Geriatric Nutritional Risk Index; LVEF, left ventricular ejection fraction; RV-FAC, right ventricular fractional area change; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; RAP, right atrial pressure.

prevalence of male sex and body mass index. The LVEF did not significantly differ between the 2 groups. The low FT3 group had a higher prevalence of comorbidities, such as hypertension, diabetes mellitus, CKD, and anemia. Diuretics and inotropic agents were prescribed more frequently in the low FT3 group. In the laboratory data (Table 2), levels of TSH and FT4 were within normal range, but the latter was significantly lower in the low FT3 group. BNP, troponin I, aspartate transaminase, alkaline phosphatase, creatinine, and C-reactive protein were higher, whereas total protein, albumin, sodium, and GNRI were lower in the low FT3 group than in the normal FT3 group. Echocardiographic parameters showed no significant differences in cardiac contractility between the 2 groups (Table 2). Not all of the patients underwent CPX and cardiac catheterization for various reasons (eg, rejection of the patients, medical reasons, etc). Among the 303 patients (33.3%) who underwent CPX (Table 2), the low FT3 group showed lower peak VO_2 and higher VE/VCO_2 slope. Among the 583 patients (64.0%) who underwent cardiac catheterization, there were no significant differences between the 2 groups except for higher mean right atrial pressure in the low FT3 group (Table 2). In addition, the correlations between serum FT3 levels and other parameters of laboratory data, echocardiography, CPX, and cardiac catheterization are presented in Table 3. There were significant correlations between serum FT3 levels and FT4, BNP, troponin I, total protein, albumin, aspartate transaminase, alkaline phosphatase, creatinine, sodium, C-reactive protein, GNRI, peak VO_2, VE/VCO_2 slope, and mean right atrial pressure.

In the follow-up period of median 991 (interquartile range 534−1659) days, there were 193 all-cause deaths, including 88 cardiac deaths. In the Kaplan-Meier analysis (Fig. 2), cardiac and all-cause mortality were significantly higher in the low FT3 group (cardiac mortality: log-rank $P = .002$; all-cause mortality: log-rank $P < .001$). In the univariable Cox proportional hazards analysis (Tables 4 and 5), low FT3 (categoric variable) was associated with cardiac and all-cause death: cardiac death hazard ratio (HR) 1.926, 95% confidence interval (CI) 1.268−2.927 ($P = .002$); all-cause death HR 2.304, 95% CI 1.736−3.058 ($P < .001$). Next, we performed subgroup analyses considering clinical

Table 3. Correlation Analysis With Serum FT3 Levels

Variable	*r*	*P* Value
Laboratory data (n = 911)		
TSH	−0.026	.433
FT4	0.279	<.001
BNP) §	−0.364	<.001
Troponin I §	−0.345	<.001
Total protein	0.330	<.001
Albumin	0.548	<.001
AST*	−0.166	<.001
ALT*	0.047	.175
ALP	−0.153	.002
GGT*	0.007	.855
Creatinine	−0.184	<.001
Sodium	0.157	<.001
CRP*	−0.347	<.001
GNRI	0.530	<.001
Echocardiography (n = 911)		
LVEF	0.062	.092
RV-FAC	−0.014	.773
CPX (n = 303)		
Peak VO_2	0.364	<.001
VE/VO_2 slope	−0.191	.001
Cardiac catheterization (n = 583)		
Systolic PAP	0.053	.205
Diastolic PAP	0.040	.333
Mean PAP	0.037	.367
PAWP	−0.081	.051
Mean RAP	−0.126	.003
Cardiac output	0.074	.074
Cardiac index	−0.018	.663

Pearson and the Spearman correlation analyses were used for parametric and nonparametric (*) variables, respectively. Abbreviations as in Table 2.

confounding factors, including demographic data, comorbidities, medications, BNP level, and renal function. In the subgroup analysis regarding cardiac death (Table 4), there were no interactions except for an interaction between low FT3 and diabetes mellitus. In the subgroup analysis regarding all-cause death (Table 5), the use of inotropic agents showed a significant interaction with low FT3.

Discussions

Patients with HF and low T3 syndrome accounted for 35.2% of the patients with HF and euthyroidism in the present study. To the best of our knowledge, this study is the first to report that patients with HF and low T3 syndrome experience an adverse prognosis accompanied by cardiac overload and myocardial damage (demonstrated by higher levels of BNP and troponin I), high central venous pressure (higher mean right atrial pressure), liver congestion (higher aspartate transaminase and alkaline phosphatase), lower nutritional status (lower body mass index, total protein, albumin, and GNRI), and impaired exercise capacity (lower peak VO_2 and higher VE/VCO_2 slope), but not accompanied by differences in cardiac systolic function.

Low T3 Syndrome and Both Cardiac Function and Comorbidities

In general, T3 increases heart rate and left ventricular contractility and decreases systemic vascular resistance and exercise capacity.[1,21,22] In the present study, LVEF did not differ between the low FT3 and normal FT3 groups, whereas heart rate was higher and peak VO_2 lower in the low FT3 group. In contrast, comorbidities (eg, CKD), which have been regarded as adverse predictors of prognosis in patients with HF,[15,16] were observed more frequently in the low FT3 group than in the normal FT3 group. In patients with severe illness, including acute myocardial infarction[11] and HF,[10] the conversion of FT4 into FT3, which is the biologically active form, through 5′-monodeiodinase in peripheral tissues is reduced.[7,8] The 5′-monodeiodinase family

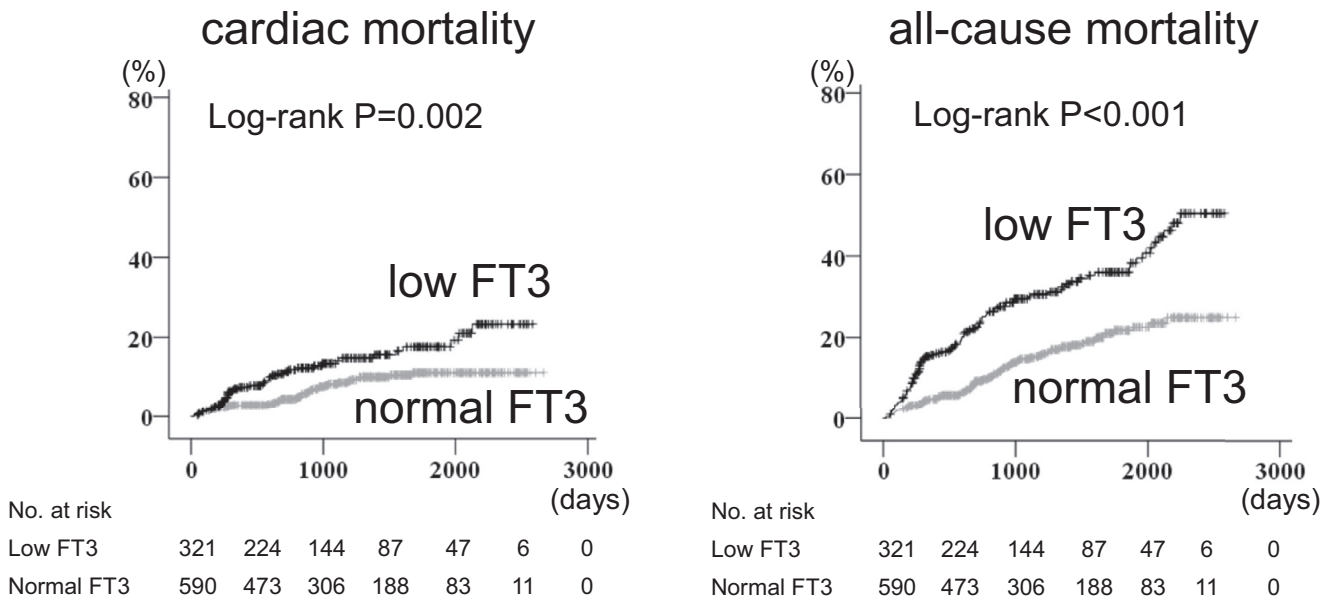

Fig. 2. Kaplan-Meier analysis for cardiac and all-cause mortality in the normal FT3 and low FT3 groups. Event rates was analyzed by means of a log-rank test. FT3, free triiodothyronine.

Table 4. Cox Proportional Hazards Analysis for Cardiac Death and Subgroup Analysis: Impact of Low FT3 (Categoric Variable)

Factor	Subgroup	n	HR	95% CI	*P* value	Interaction *P* Value
Total	–	911	1.926	1.268−2.927	.002	–
Age	≥70 y	461	2.212	1.253−3.903	.006	.366
	<70 y	450	1.408	0.695−2.851	.342	
Sex	Male	541	2.055	1.219−3.463	.007	.876
	Female	370	1.933	0.953−3.922	.068	
Body mass index	≥23.1 kg/m^2	442	1.242	0.577−2.672	.580	.260
	<23.1 kg/m^2	446	2.136	1.250−3.648	.005	
Systolic BP	≥127.0 mm Hg	456	1.550	0.858−2.802	.146	.279
	<127.0 mm Hg	455	2.412	1.335−4.357	.004	
Heart rate	≥78.0 beats/min	467	1.727	1.007−2.962	.047	.759
	<78.0 beats/min	444	2.026	1.037−3.958	.039	
Ischemic etiology	Yes	254	1.734	0.802−3.746	.162	.770
	No	657	1.979	1.202−3.258	.007	
LVEF	Reduced	317	1.838	1.054−3.204	.032	.823
	Mid-range	81	1.512	0.456−5.016	.499	
	Preserved	513	2.045	0.961−4.352	.063	
Hypertension	Yes	711	1.898	1.180−3.054	.008	.831
	No	200	2.089	0.865−5.046	.102	
Diabetes mellitus	Yes	368	1.135	0.616−2.093	.684	.023
	No	543	2.977	1.666−5.320	<.001	
Dyslipidemia	Yes	725	1.733	1.083−2.775	.022	.362
	No	186	2.828	1.096−7.296	.032	
CKD	Yes	480	1.778	1.095−2.888	.020	.661
	No	431	1.422	0.579−3.495	.442	
Anemia	Yes	465	1.566	0.940−2.611	.085	.682
	No	446	1.866	0.844−4.126	.123	
Atrial fibrillation	Yes	317	1.896	1.001−3.594	.050	.988
	No	594	1.883	1.081−3.280	.025	
Use of RAS inhibitors	Yes	672	1.820	1.106−2.995	.019	.619
	No	239	2.269	1.051−4.899	.037	
Use of beta-blockers	Yes	680	2.038	1.271−3.268	.003	.635
	No	231	1.619	0.658−3.987	.294	
Use of diuretics	Yes	539	1.842	1.143−2.966	.012	.743
	No	372	1.575	0.628−3.950	.332	
Use of inotropic agents	Yes	76	1.036	0.446−2.404	.935	.246
	No	835	1.923	1.186−3.120	.008	
BNP	≥225.5 pg/l	384	1.415	0.833−2.404	.199	.368
	<225.5 pg/mL	383	2.577	0.818−8.123	.106	
Creatinine	≥0.91 mg/dL	425	1.944	1.150−3.286	.013	.947
	<0.91 mg/dL	420	1.844	0.776−4.383	.166	

HR, hazard ratio; CI, confidence interval; other abbreviations as in Tables 1 and 2.

has mainly 2 types. Type I 5′-monodeiodinase is distributed widely within the human body, and is especially enriched in the kidneys[23] and the liver.[24] Thus, liver and/or kidney function impairment may lead to low T3 syndrome. In the present study, the prevalence of CKD, creatinine serum levels, central venous pressure (mean right atrial pressure), and several liver enzymes (aspartate transaminase, alkaline phosphatase) were higher and nutritional status (body mass index, total protein, albumin, and GNRI) lower in the low FT3 group than in the normal FT3 group. Several studies have reported the association between low T3 syndrome and starvation.[25-27] In addition, in patients with HF, gastrointestinal congestion leads to appetite loss and proinflammatory activation and results in cardiac cachexia.[28] In the present study, mean right atrial pressure of the low FT3 group was >8 mm Hg, which was considered to be associated with malnutrition and cardiac cachexia.[28,29] These results suggest that congestive hepatopathy may exist and may lead to malnutrition, which is also partly associated with the development of low T3 syndrome.[25-27]

Exercise Capacity and Prognosis

Type II 5′ monodeiodinase is expressed in the brain, placenta, heart, and skeletal muscles.[30] Considering the higher prevalence of ischemic etiology and higher troponin I levels in the low FT3 group, further study on cardiac type II 5′-monodeiodinase and low T3 syndrome is necessary because it is still unclear as to whether or not cardiomyocyte damage changes type II 5′-monodeiodinase activity in the human body. Moreover, the effect of type II 5′-monodeiodinase in skeletal muscle should be investigated because skeletal muscle abnormalities limit exercise capacity rather than central circulation.[31,32] In the present study, patients in the low FT3 group showed lower exercise capacity than patients in the normal FT3 group. Peak VO_2 in patients in the low FT3 group was <14 mL·kg^{-1}·min^{-1}, which is considered as one of the indications for heart transplantation.[33] The VE/VCO_2 slope in the low FT3 group was >34, which is an indicator for higher cardiac event rate.[34] Malnutrition may explain the relationship between low T3 syndrome and

Table 5. Cox Proportional Hazards Analysis for All-Cause Death and subgroup Analysis: Impact of Low FT3 (Categoric Variable)

Factor	Subgroup	n	HR	95% CI	P value	Interaction P value
Total	–	911	2.304	1.736−3.058	<.001	–
Age	≥70 y	461	2.111	1.483−3.003	<.001	.701
	<70 y	450	1.855	1.102−3.123	.020	
Sex	Male	541	2.712	1.897−3.878	<.001	.213
	Female	370	1.905	1.198−3.029	.006	
Body mass index	≥23.1 kg/m^2	442	2.410	1.502−3.867	<.001	.602
	<23.1 kg/m^2	446	2.076	1.422−3.030	<.001	
Systolic BP	≥127.0 mm Hg	456	2.357	1.584−3.507	<.001	.912
	<127.0 mm Hg	455	2.249	1.496−3.379	<.001	
Heart rate	≥78.0 beats/min	467	2.161	1.496−3.120	<.001	.875
	<78.0 beats/min	444	2.281	1.452−3.582	<.001	
Ischemic etiology	Yes	254	2.013	1.189−3.408	.009	.597
	No	657	2.405	1.719−3.365	<.001	
LVEF	Reduced	317	1.938	1.272−2.953	.002	.493
	Mid-range	81	3.354	1.302−8.637	.012	
	Preserved	513	2.388	1.556−3.666	<.001	
Hypertension	Yes	711	2.214	1.622−3.021	<.001	.592
	No	200	2.709	1.367−5.371	.004	
Diabetes mellitus	Yes	368	1.839	1.217−2.780	.004	.183
	No	543	2.729	1.850−4.026	<.001	
Dyslipidemia	Yes	725	2.329	1.688−3.214	<.001	.858
	No	186	2.204	1.216−3.992	.009	
CKD	Yes	480	2.015	1.423−2.852	<.001	.645
	No	431	2.356	1.425−3.896	.001	
Anemia	Yes	465	1.825	1.303−2.556	<.001	.801
	No	446	1.981	1.106−3.547	.021	
Atrial fibrillation	Yes	317	2.905	1.895−4.456	<.001	.129
	No	594	1.839	1.251−2.704	.002	
Use of RAS inhibitors	Yes	672	2.303	1.655−3.204	<.001	.923
	No	239	2.351	1.356−4.074	.002	
Use of beta-blockers	Yes	680	2.342	1.666−3.293	<.001	.780
	No	231	2.101	1.262−3.500	.004	
Use of diuretics	Yes	539	2.086	1.499−2.902	<.001	.635
	No	372	2.435	1.395−4.250	.002	
Use of inotropic agents	Yes	76	1.054	0.541−2.054	.877	.027
	No	835	2.462	1.801−3.366	<.001	
BNP	≥225.5 pg/mL	384	1.896	1.313−2.737	.001	.215
	<225.5 pg/mL	383	3.132	1.563−6.277	.001	
Creatinine	≥0.91 mg/dL	425	2.153	1.485−3.121	<.001	.743
	<0.91 mg/dL	420	2.393	1.436−3.989	.001	

Abbreviations as in Tables 1, 2, and 4.

impaired exercise capacity.[35] Nevertheless, the association between type II 5′-monodeiodinase and exercise capacity in patients with HF remains unknown.

Prognostic Impact and Management of Low T3 Syndrome in Patients With HF

Despite the recommendation of thyroid function tests in patients with newly diagnosed HF,[15] the management of low T3 syndrome has not been well discussed.[36] Low T3 syndrome has been considered as an "adaptive" response by the body to spare energy in patients with severe illness.[37,38] Only a few studies have shown that low T3 syndrome is associated with adverse prognosis in patients with HF.[13,14] In patients with cardiac disease, the presence of low T3 syndrome is reported to be associated with higher mortality,[14] increased length of hospitalization,[13] and a higher rate of intensive care unit admission.[13] In the present study, patients with HF and low FT3 showed higher cardiac mortality and all-cause mortality with a few interactions. In terms of cardiac mortality, diabetes mellitus showed an interaction with low FT3. According to results of nonhuman animal examinations, there is a possibility that cardiac tissue content of thyroid hormone differs from serum thyroid hormone levels in diabetic patients.[39] This hypothesis can be a plausible explanation for the present result that the classification based on the FT3 serum levels showed no association with cardiac death in patients with diabetes mellitus. Regarding all-cause mortality, there was an interaction between the use of inotropic agents and low FT3. Inotropic agents are reported to affect the conversion of T4 into T3.[40] Considering its pathogenesis as described above, low T3 is probably a "marker" for more severe illness. However, it has been reported that lower serum FT3 levels themselves potentially worsen the cardiac function.[1,2,14,41] In addition, there have been pros and cons regarding the benefit of hormone replacement therapy.[41-43] Therefore, there is still room to debate whether low T3 is a "cause" of poor prognosis to form a vicious cycle or not.

Study Strengths and Limitations

There are several strengths to the present study. This is the first study to show the association of low T3 syndrome

with adverse prognosis in patients with HF, taking into consideration a multifaceted background including echocardiographic data, exercise capacity, and hemodynamic parameters within a given population. The study also included more subjects than previous studies and follow-up was possible on all the patients.

This study also has several limitations. First, as a prospective cohort study of a single center with a relatively small number of patients, the results may not be representative of the general HF population. Second, because the study included variables during hospitalization for decompensated heart failure, without taking into consideration changes in medical parameters and post-discharge treatment, we should pay attention to extrapolating our findings to patients with stable chronic heart failure. Third, although we encouraged CPX and cardiac catheterizations, not all patients with HF underwent CPX and cardiac catheterization for several reasons (eg, age, probability of heart transplantation, adherence, etc). Therefore, there might be a potential selection bias in these measurements. However, our study was meaningful in that we collected the results of all patients who underwent those examinations and found that in the patients with HF who were evaluated for exercise capacity or detailed cardiac function, those with low T3 syndrome had poor exercise capacity and higher right atrial pressure. Fourth, because this was a cross-sectional and prospective observational study without intervention for low T3 syndrome, the causal relationships and mechanisms of low T3 on impaired exercise capacity, higher central venous pressure, and worse prognosis could not be fully explained. Finally, we excluded patients who were prescribed amiodarone and thyroid treatment to exclude the impact of treatment on thyroid function tests in this study. Therefore, the impact of thyroid treatment on clinical findings was not presented in this study. For these reasons, the present results should be viewed as preliminary, and further studies with a larger population are needed.

Conclusion

The presence of low T3 syndrome in patients with HF is associated with higher cardiac and all cause-mortality, accompanied by cardiac overload and damage, high central venous pressure, liver congestion, lower nutritional status, and impaired exercise capacity.

Disclosures

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Supplementary Data

Supplementary data related to this article can be found at doi:10.1016/j.cardfail.2019.01.007.

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