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ORIGINAL ARTICLE
Critical Care

Clinical Significance of Low-Triiodothyronine Syndrome in Patients Requiring Non-Surgical Intensive Care

— Triiodothyronine Is a Comprehensive Prognostic Marker for Critical Patients With Cardiovascular Disease —

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Background: Low-triiodothyronine (T_3) syndrome is a known complication in intensive care unit (ICU) patients, but the underlying mechanisms and prognostic impact are unclear.

Methods and Results: This study retrospectively enrolled 2,976 patients who required care in the ICU. Of these patients, 2,425 were euthyroid and were divided into normal (n=1,666; free T_3 [FT_3] ≥1.88 μIU/L) and low-FT_3 (n=759; FT_3 <1.88 μIU/L) groups. Multivariate logistic regression analysis revealed that prognostic nutritional index >46.03 (odds ratio [OR] 2.392; 95% confidence interval [CI] 1.904–3.005), age (per 1-year increase; OR 1.022; 95% CI 1.013–1.031), creatinine (per 0.1-mg/dL increase; OR 1.019; 95% CI 1.014–1.024), and C-reactive protein (per 1-mg/dL increase; OR 1.123; 95% CI 1.095–1.151) were independently associated with low FT_3. Survival rates (within 365 days) were significantly lower in the low-FT_3 group. A multivariate Cox regression model showed that low FT_3 was an independent predictor of 365-day mortality (hazard ratio 1.785; 95% CI 1.387–2.297). Low-T_3 syndrome was significantly more frequent in patients with non-cardiovascular than cardiovascular diseases (73.5% vs. 25.8%). Prognosis was significantly poorer in the low-FT_3 than normal group for patients with cardiovascular disease, particularly those with acute coronary syndrome and acute heart failure.

Conclusions: Low-T_3 syndrome was associated with aging, inflammatory reaction, malnutrition, and renal insufficiency and could lead to adverse outcomes in patients admitted to a non-surgical ICU.

Key Words: Euthyroid sick syndrome; Mortality; Non-thyroidal illness

A low triiodothyronine (T_3) concentration in patients who are euthyroid had been described as low-T_3 syndrome, non-thyroidal illness, or euthyroid sick syndrome. Numerous studies have already addressed this condition, with low-T_3 syndrome being shown to be particularly common in patients requiring admission to an intensive care unit (ICU).[1] A low T_3 concentration was considered to be an adaptive compensatory mechanism and a beneficial response to preserve energy consumption, thus representing adaptive changes by the body to deal with critical situations.

More than 80% of T_3 is converted from T_4 in the periphery by the catalysis of 5'-monodeiodinases in organs such as the liver, kidney, and skeletal muscle.[2] In critical situations, thyroid hormone levels may be changed via these mechanisms rather than the hypothalamic-pituitary-thyroid axis. Therefore, in the critical setting, impaired conversion of thyroxine (T_4) to T_3 because of inactivation of Type I 5'-monodeiodinase in the periphery was believed to be a key mechanism underlying low-T_3 syndrome.[3] Several factors (i.e., malnutrition, pyrexia, sepsis, trauma, surgery, diabetes, cirrhosis, and renal dysfunction) that have been shown to coexist in patients requiring intensive care may easily induce the inactivation of Type I 5'-monodeiodinase. Thus, low-T_3 syndrome was reported to be associated with adverse outcomes in patients with cardiovascular disease

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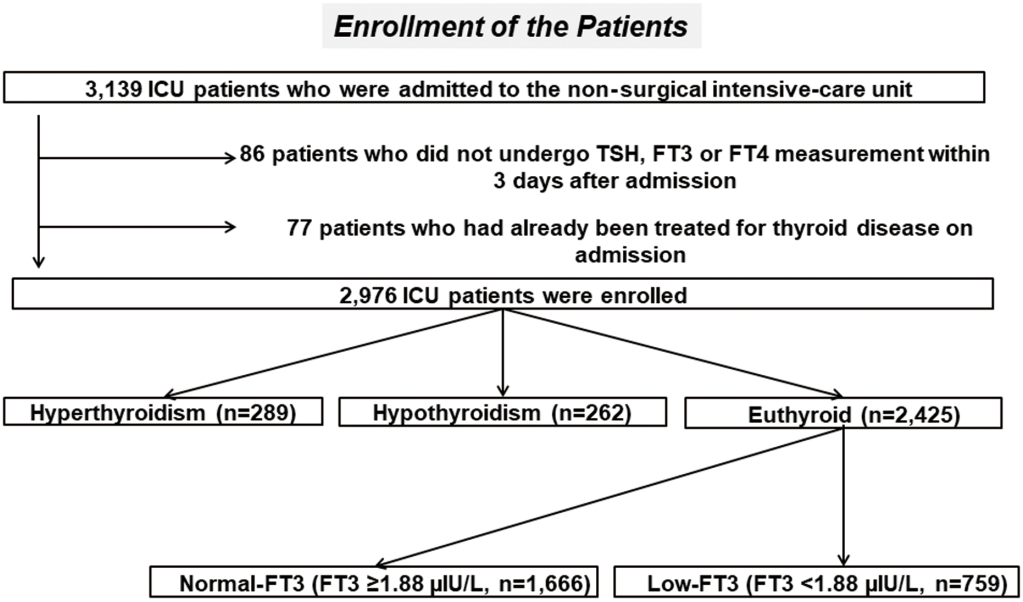

Figure 1. Patient selection process. Between May 2011 and August 2018, 3,139 patients who were admitted to the non-surgical intensive care unit (ICU) at Nippon Medical School Chiba Hokusoh Hospital were screened. Of these, 86 patients who lacked serum thyroid-stimulating hormone (TSH), free triiodothyronine (FT_3), and free thyroxine (FT_4) measurements within 3 days after admission were excluded. The 2,976 patients enrolled in the study were divided into hyperthyroid, hypothyroidism, and euthyroid groups, with the euthyroid patients further divided into those with normal- or low-FT_3.

(i.e., acute myocardial infarction,[4,5] heart failure,[6] and acute aortic dissection[7]), acute respiratory distress syndrome,[8] sepsis,[9] and burns.[10] However, the details of such associations have rarely been reported for non-surgical and/or cardiovascular ICU patients.

The factors associated with and the prognostic impact of low-T_3 syndrome need to be verified in non-surgical and/or cardiovascular ICU patients. Therefore, in the present study we investigated the factors associated with low-T_3 syndrome and the detailed prognostic impact of this syndrome in non-surgical ICU patients.

Methods

Subjects

We screened 3,139 patients admitted to the non-surgical ICU of Nippon Medical School Chiba Hokusoh Hospital from the emergency room and the general wards between May 2011 and December 2018. Patients who were readmitted to the non-surgical ICU during the same hospitalization were excluded from the study. Of the 3,139 patients screened, 86 who did not undergo serum thyroid-stimulating hormone (TSH), free T_3 (FT_3) or free T_4 (FT_4) measurements and 77 who had been treated for thyroid disease on admission were excluded. This left 2,976 patients who were enrolled in the present study.

Nippon Medical School Chiba Hokusoh Hospital has 2 ICU departments (surgical or non-surgical), and both are "closed" ICUs, which were treated by the full-time doctor specializing in intensive care medicine. Patients who were admitted to the surgical ICU (i.e., trauma, burn, drowing, and cerebrovascular disease) were excluded from the present study.

Patients with the following diseases were admitted to the non-surgical ICU: acute coronary syndrome (ACS), acute heart failure (AHF), acute aortic disease (acute aortic dissection and acute aneurysmal rupture), pulmonary embolism, arrhythmia (tachycardia [arterial fibrillation/tachycardia/flutter and ventricular fibrillation/tachycardia including cardiac arrest] and bradycardia [sick sinus syndrome and complete atrioventricular block]), sepsis, pericarditis, coronary spasm angina, Takotsubo cardiomyopathy, respiratory emergency disease (exacerbation of chronic obstructive pulmonary disease, bronchial asthma and institutional pneumonia), acute kidney injury, neurogenic emergency disease, gastrointestinal disease, and allergic disease. Patients who had severe symptoms that required a differential diagnosis were also admitted to the non-surgical ICU. Cardiovascular disease was defined as ACS, AHF, acute aortic disease, pulmonary embolism, arrhythmia, pericarditis, coronary spasm angina, and Takotsubo cardiomyopathy, and non-cardiovascular disease was defined as sepsis, respiratory emergency disease, acute kidney injury, neurogenic emergency disease, gastrointestinal disease, allergic disease, and the presence of severe symptoms that required a differential diagnosis.

At Nippon Medical School Chiba Hokusoh Hospital, the cardiovascular care unit was included as a non-surgical ICU. The non-surgical ICU functions as both a cardiac care and a non-cardiac care unit. All physicians in the non-surgical "closed" ICU are cardiologists, and the patients enrolled in this study were admitted to the non-surgical ICU and treated by a cardiologist. Approximately 70% of patients who were admitted to the non-surgical ICU were cardiovascular patients; the remaining patients were non-cardiovascular patients.

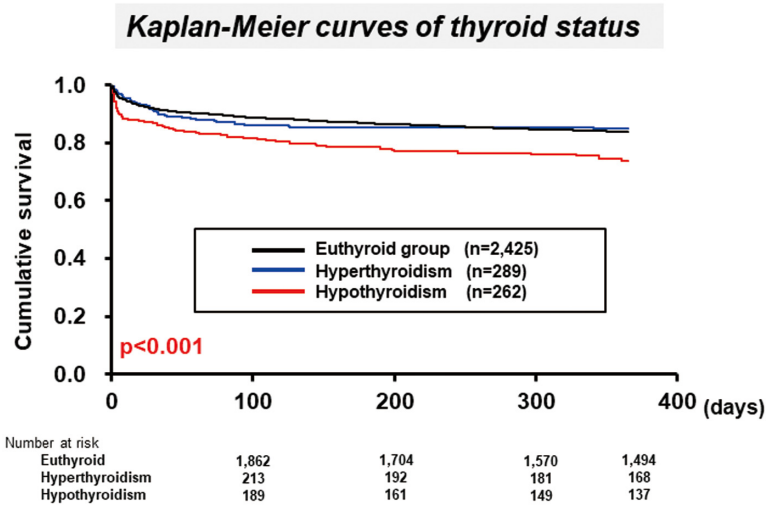

Figure 2. Kaplan-Meier survival curves according to thyroid status. In the all-patient cohort, prognosis, including all-cause death within 365 days, was significantly poorer in the hypothyroid than euthyroid and hyperthyroid groups. T_3, triiodothyronine.

Measurements of Thyroid Function

Blood samples to measure serum TSH, FT_3, and FT_4 were collected from all patients. Measurements were made in most patients on Day 1 (within 30 min after admission; n=2,413 [99.50%]) and Day 2 (n=6; 0.25%), whereas measurements in the remaining patients were made after Day 3 (n=6; 0.25%). Blood samples were centrifuged within 5 min of collection at 1,500 g for 10 min at 4°C and then immediately frozen and stored at −80°C until analysis. Serum TSH, FT_3, and FT_4 levels were measured using an electrochemiluminescence immunoassay (ARCHITECT; Abbott Japan, Chiba, Japan). These immunoassays were performed by clinical laboratory technologists at Nippon Medical School Chiba Hokusoh Hospital. Because the normal ranges of TSH, FT_3, and FT_4 differ between institutes, the normal ranges of serum TSH, FT_3, and FT_4 were defined by our laboratory. Data were retrospectively retrieved from hospital medical records.

Procedure

The presence of both serum TSH <0.5 μIU/L and FT_4 ≤0.70 μIU/L indicated hyperthyroidism, whereas the presence of both serum TSH >4.94 μIU/L and FT_4 ≤1.48 μIU/L indicated hypothyroidism. Based on these definitions, 289 patients were diagnosed with hyperthyroidism and 262 were diagnosed with hypothyroidism using data from the time of admission. Patients were further divided into 2 groups according to serum FT_3 levels: a normal-FT_3 group (n=1,666; FT_3 ≥1.88 μIU/L) and a low-FT_3 group (n=759; FT_3 <1.88 μIU/L; **Figure 1**).

Comparisons were made among euthyroid, hypothyroid, and hyperthyroid patients, as well as between patients in the normal- and low-FT_3 groups, for the following parameters: age, sex, etiology, medical history (diabetes, hypertension, dyslipidemia, and hyperuricemia), vital signs and status (systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, body temperature, body mass index, and left ventricular ejection fraction [LVEF] upon admission), arterial blood gases (pH, PCO_2, PO_2, HCO_3^-, SaO_2, and lactate), laboratory data (white blood cell [WBC] count, hemoglobin, blood urea nitrogen [BUN], creatinine, sodium, potassium, blood glucose, C-reactive protein [CRP], and B-type natriuretic peptide [BNP]), and mechanical support during the ICU stay (non-invasive positive pressure ventilation [NPPV], endotracheal intubation [ETI], intra-aortic balloon pumping,[11] percutaneous cardiopulmonary support [PCPS], and continuous hemodiafiltration [CHDF]). The Acute Physiology and Chronic Health Evaluation (APACHE II) score[12] was also compared among euthyroid, hypothyroid, and hyperthyroid patients, and between patients in the normal- and low-FT_3 groups.

The nutritional status (Prognostic Nutritional Index [PNI] and Controlling Nutritional Status [CONUT] score) and each constituent factor (albumin, lymphocyte count, and cholesterol) were compared between the normal- and low-FT_3 groups. The PNI was calculated using the following formula

$$\text{PNI} = 10 \times \text{serum albumin (g/dL)} + 0.005 \times \text{lymphocytes (/}\mu\text{L)}$$

with a lower PNI being worse. The median PNI of 43.4 was used to establish cut-off values for the low (<43.4) and high (≥43.4) PNI groups. The CONUT score was calculated using the serum albumin level, lymphocytes, and total cholesterol levels (range 0–12, with a higher being worse). In the CONUT scoring system, point values are assigned to different ranges of laboratory measures as follows:

- Serum albumin ≥3.5 g/dL, 0 points; 3.49–3 g/dL, 2 points; 2.99–2.5 g/dL, 4 points; and <2.5 g/dL, 6 points
- Lymphocytes ≥1,600/μL, 0 points; 1,200–1,599/μL, 1 point; 800–1,199/μL, 2 points; and <800/μL, 3 points
- Total cholesterol ≥180 mg/dL, 0 points; 140–179 mg/dL, 1 point; 100–139 mg/dL, 2 points; and <100 mg/dL, 3 points.

LVEF was calculated using the Teichholz method or Simpson's method at admission (Sonos 5500 [Hewlett Packard, Palo Alto, CA, USA] or Vivid I [GE Yokogawa Medical, Tokyo, Japan]). Because LVEF was measured during the acute phase, it was not adequately evaluated in cases of severe orthopnea. The method for LVEF measurement (Teichholz method or Simpson's method) was decided on a case-by-case basis.

Factors significantly associated with the low-FT_3 group were determined by multivariate logistic regression analysis.

Prognosis of Patients With Normal or Low FT_3

We evaluated the long-term prognosis, including 365-day all-cause mortality, as the primary endpoint. Prognostic value for 365-day mortality was evaluated using a Cox regression hazard model and Kaplan-Meier curves. All-cause mortality was ascertained using information obtained from the medical records at Nippon Medical School Chiba Hokusoh Hospital or using information obtained from other institutes via telephone contact. First, the prognostic value of hypothyroidism, hyperthyroidism, and euthyroidism for predicting 365-day mortality was evaluated using Kaplan-Meier curves. Subsequently, the prognostic value of euthyroidism for predicting 365-day mortality was compared between the normal- and low-FT_3 groups using Kaplan-Meier curves. Based on the results, Cox regression hazard model analysis was performed to obtain hazard ratios (HRs) for 365-day mortality. To evaluate the long-term prognostic impact of FT_3 levels, the following variables were included in a multivariate logistic regression model: sex, age, diabetes, pulse, respiratory rate, body temperature, WBC, BUN, creatinine, alanine aminotransferase, and CRP. Finally, the prognostic value for 365-day mortality was evaluated using a Cox regression hazard model and Kaplan-Meier curves for each disease.

Statistical Analyses

All data were analyzed using SPSS 22.0 (SPSS Japan Institute, Tokyo, Japan). All numerical data are expressed as the median and range or interquartile range (IQR). The Mann-Whitney U test was used for comparisons between the normal- and low-FT_3 groups. The Kruskal-Wallis test was used for comparisons between euthyroid, hypothyroidism and hyperthyroidism groups. The Chi-squared test was used to compare proportions. Two-sided $P<0.05$ was considered significant.

The prognostic value of the low-FT_3 group vs. a reference group of patients with normal FT_3 was assessed using a multivariate Cox proportional hazards regression model.

Table 1. Patient Characteristics According to FT_3 Levels on Admission

	Normal-FT_3 (n=1,666)	Low-FT_3 (n=759)	P value
FT_3 (μIU/L)	≥1.88	<1.88	
Age (years)	68 [59–76]	74 [65–80]	<0.001
Male sex	1,278 (76.7)	509 (67.1)	<0.001
Medical history			
Hypertension (yes)	1,165 (69.9)	551 (72.6)	0.194
Diabetes (yes)	574 (34.5)	319 (42.0)	<0.001
Dyslipidemia (yes)	936 (56.2)	342 (45.1)	<0.001
Etiologies			
Acute coronary syndrome (yes)	931 (55.9)	199 (26.2)	<0.001
STEMI (yes)	551 (33.1)	122 (16.1)	0.633
NSTEMI (yes)	283 (17.0)	51 (6.7)	0.199
UAP (yes)	97 (5.8)	26 (3.4)	0.315
Acute heart failure (yes)	309 (18.5)	218 (28.7)	<0.001
CS1 (yes)	228 (73.8)	124 (56.9)	<0.001
CS2 (yes)	69 (22.3)	55 (25.2)	0.466
CS3 (yes)	12 (3.9)	39 (17.9)	<0.001
Arrhythmia (yes)	110 (6.6)	59 (7.8)	0.303
Acute aortic disease (yes)	82 (4.9)	20 (2.6)	0.009
Pulmonary thromboembolism (yes)	65 (3.9)	15 (2.0)	0.014
Sepsis (yes)	14 (0.8)	106 (14.0)	<0.001
Vital signs and status			
Systolic blood pressure (mmHg)	142 [120–166]	131 [101–157]	<0.001
Diastolic blood pressure (mmHg)	80 [67–98]	71 [56–88]	<0.001
Pulse (beats/min)	83 [67–104]	89 [71–110]	<0.001
Respiratory rate (beats/min)	20 [16–26]	23 [18–30]	<0.001
Body temperature (°C)	36.3 [35.8–36.7]	36.5 [35.9–37.0]	<0.001
Body mass index (%)	23.9 [21.6–26.5]	22.6 [20.3–25.6]	<0.001
LVEF (%)	53 [40–63]	50 [35–62]	0.005
Arterial blood gases			
pH	7.42 [7.37–7.45]	7.40 [7.31–7.45]	<0.001
PCO_2 (mmHg)	38 [34–43]	36 [31–42]	<0.001
PO_2 (mmHg)	116 [83–171]	106 [77–149]	<0.001
HCO_3^- (mmol/L)	23.5 [21.3–25.6]	22.0 [18.4–24.7]	<0.001
SaO_2 (%)	98 [96–99]	98 [95–99]	<0.001
Lactate (mmol/L)	1.5 [1.1–2.6]	1.7 [1.1–3.1]	0.100

(**Table 1** continued the next page.)

	Normal-FT_3 (n=1,666)	Low-FT_3 (n=759)	P value
Laboratory data			
TSH	1.57 [1.01–2.42]	1.66 [1.00–2.60]	0.115
FT_3 (μIU/L)	2.41 [2.14–2.69]	1.52 [1.28–1.72]	<0.001
FT_4 (μIU/L)	1.03 [0.93–1.13]	0.98 [0.84–1.12]	<0.001
WBC (U/L)	9,070 [7,018–11,520]	9,800 [7,250–13,065]	<0.001
Hemoglobin (g/dL)	13.8 [12.4–15.1]	11.6 [10.0–13.5]	<0.001
BUN (mg/dL)	17.0 [13.6–21.9]	28.8 [18.5–50.7]	<0.001
Creatinine (mg/dL)	0.88 [0.71–1.14]	1.31 [1.85–2.87]	<0.001
Sodium (mmol/L)	140 [138–142]	139 [136–141]	<0.001
Potassium (mmol/L)	4.1 [3.8–4.4]	4.3 [3.8–4.9]	<0.001
Blood glucose (mg/dL)	153 [119–220]	150 [117–213]	0.181
CRP (mg/dL)	0.19 [0.07–0.70]	1.63 [0.27–7.89]	<0.001
BNP (pg/mL)	94 [27–368]	442 [114–1,132]	<0.001
Nutritional status			
PNI	48.1 [43.1–53.6]	39.0 [33.0–45.3]	<0.001
CONUT score	1 [0–3]	4 [2–7]	<0.001
Albumin (g/dL)	3.9 [3.6–4.1]	3.3 [2.9–3.8]	<0.001
Lymphocyte count (/μL)	1,819 [1,265–2,698]	1,093 [592–1,704]	<0.001
Total cholesterol (mg/dL)	181 [155–209]	154 [123–187]	<0.001
Scoring			
APACHE II (points)	9 [6–13]	14 [9–18]	<0.001
Mechanical support during the ICU stay			
NPPV (yes)	336 (20.2)	231 (30.4)	<0.001
ETI (yes)	217 (13.0)	184 (24.2)	<0.001
Pacing (yes)	88 (5.3)	50 (6.6)	0.219
IABP (yes)	247 (14.8)	89 (11.7)	0.043
PCPS (yes)	64 (3.8)	33 (4.3)	0.577
CHDF (yes)	103 (6.2)	199 (26.2)	<0.001
Short-term prognosis			
In-hospital mortality (yes)	112 (6.7)	131 (17.3)	<0.001

Unless indicated otherwise, data are given as the median [interquartile range] or n (%). P values between 2 groups were calculated using the Mann-Whitney U test or the bivariate test. APACHE II, Acute Physiology and Chronic Health Evaluation II; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CHDF, continuous hemodiafiltration; CS, clinical scenarios; CONUT, Controlling Nutritional Status; CRP, C-reactive protein; ETI, endotracheal intubation; FT_3, free triiodothyronine; FT_4, free thyroxine; IABP, intra-aortic balloon pumping; ICU, intensive care unit; LVEF, left ventricular ejection fraction measured on echocardiography; NPPV, non-invasive positive pressure ventilation; NSTEMI, non-ST segment elevation myocardial infarction; PCPS, percutaneous cardiopulmonary support; PNI, Prognostic Nutritional Index; STEMI, ST-elevation myocardial infarction; TSH, thyroid-stimulating hormone; UAP, unstable angina pectoris; WBC, white blood cells.

Multivariate Cox regression analysis was used to determine the HR for 365-day mortality. Cumulative survival rates for each of the diseases were analyzed using Kaplan-Meier curves, and a log-rank test was used to calculate the statistical significance of differences.

All clinically relevant factors affecting the low-FT_3 group, including the age (per 1-year increase), PNI (per 1-point decrease), sex (male), diabetes (yes), pulse (per 10-beats/min increase), respiratory rate (per 1-beat/min increase), creatinine (per 0.1-mg/dL increase), sodium (1.0-mmol/L increase), potassium (1.0-mmol/L increase), CRP (per 1.0-mg/dL increase), and LVEF (per 10% increase), were included in the multivariate logistic regression model. The multivariate logistic regression analysis was performed using simultaneous forced entry.

Ethical Considerations

The Research Ethics Committee of Nippon Medical School Chiba Hokusoh Hospital approved the study protocol. The need for written informed consent was waived by the Ethics Committee because of the study's retrospective design. The content of the present study was described in a poster displayed at Nippon Medical School Chiba Hokusoh Hospital and shared on the institute's homepage, where it could be easily seen by anyone, in accordance with the advice of the ethics committee. The study procedures were performed in accordance with the Declaration of Helsinki.

Results

Patient Characteristics and Factors Associated With Low-T_3 Syndrome

The median age of euthyroid patients was 69 years, and the euthyroid patient cohort consisted of 1,787 (73.7%) male patients. In all, 1,130 (46.5%) patients had ACS, 527 (21.7%) had AHF, 102 (4.2%) had acute aortic disease, 80 (3.2%) had pulmonary embolism, 120 (4.9%) had sepsis 169 (7.0%) had arrhythmia, and 297 (12.2%) had other diseases.

The characteristics of patients in the euthyroid, hypothyroid, and hyperthyroid groups are presented in the **Supplementary Table**. The proportion of female subjects

Table 2. Multivariate Logistic Model of Factors Associated With Low Triiodothyronine Syndrome

Influencing factor	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
PNI (per 1-point decrease)	1.121 (1.107–1.135)	<0.001	1.075 (1.062–1.089)	<0.001
Age (per-1 year increase)	1.034 (1.027–1.042)	<0.001	1.022 (1.013–1.031)	<0.001
Male sex	1.618 (1.339–1.953)	<0.001	1.522 (1.209–1.916)	<0.001
Diabetes (yes)	1.379 (1.157–1.645)	<0.001	1.087 (0.874–1.536)	0.452
Pulse (per 10-beats/min increase)	1.033 (1.006–1.061)	0.015	0.996 (0.961–1.032)	0.823
Respiratory rate (per 1-beat/min increase)	1.018 (1.008–1.028)	<0.001	1.003 (0.990–1.016)	0.668
Creatinine (per 0.1-mg/dL increase)	1.029 (1.024–1.034)	<0.001	1.019 (1.014–1.024)	<0.001
Sodium (per 1.0-mmol/L increase)	0.914 (0.895–0.933)	<0.001	0.972 (0.949–0.995)	0.017
Potassium (per 1.0-mmol/L increase)	1.605 (1.440–1.788)	<0.001	1.106 (0.963–1.270)	0.152
CRP (per 1.0-mg/dL increase)	1.170 (1.144–1.196)	<0.001	1.107 (1.081–1.133)	<0.001
LVEF (per 10% increase)	0.926 (0.883–0.972)	0.002	0.946 (0.892–1.003)	0.065

CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

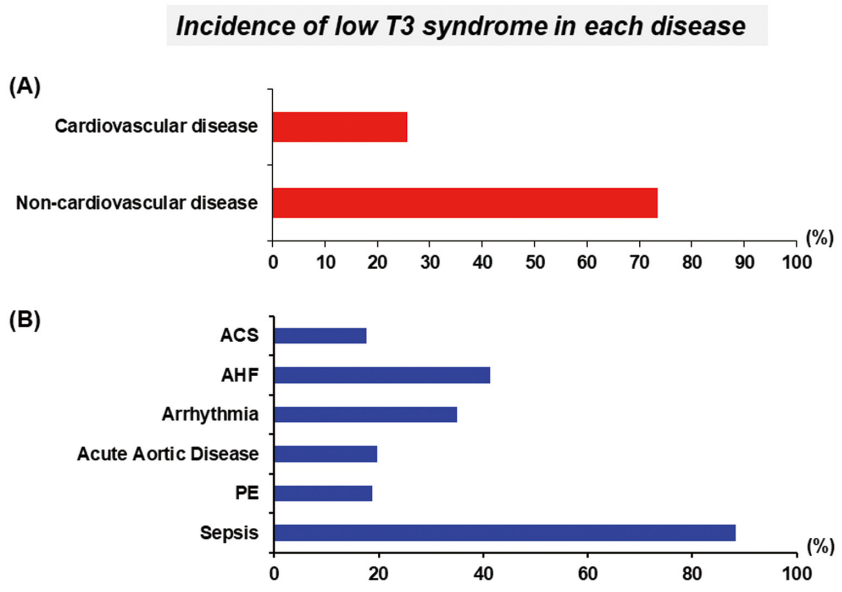

Figure 3. Incidence of low-triiodothyronine (T_3) syndrome according to disease. (**A**) Low-T_3 syndrome was present in 73.5% of patients with non-cardiovascular disease and in 25.8% of those with cardiovascular disease. (**B**) Low-T_3 syndrome was significantly more frequent in patients with sepsis (88.3%) and acute heart failure (AHF; 41.4%) than in those with acute coronary syndrome (ACS; 17.6%), acute aortic disease (19.6%), and pulmonary embolism (18.8%).

was significantly higher and age was significantly older in the hypothyroid compared with euthyroid group (P<0.001 for both). LVEF was significantly (P<0.001) lower in the hypothyroid compared with euthyroid group. Serum creatinine, BUN, and BNP concentrations were significantly higher in the hypothyroid compared with euthyroid group (all P<0.001), and APACHE II scores were significantly higher in the hypothyroid than euthyroid group (P<0.001). Furthermore, the Kaplan-Meier survival curves revealed that prognosis, including all-cause death, was significantly poorer in the hypothyroid compared with euthyroid group (P<0.001; **Figure 2**). These results suggest that the hypothyroid group included critical patients in all cohorts.

Patient characteristics according to serum FT_3 levels (normal or low) on admission are presented in **Table 1**. The proportion of male subjects was significantly (P<0.001) higher in the low-FT_3 than normal-FT_3 group. Systolic blood pressure and LVEF were significantly lower (P<0.001 for both) and heart rate was significantly higher in the low-FT_3 than normal-FT_3 group. Serum creatinine, BUN, potassium, CRP, and BNP concentrations, as well as APACHE II scores, were significantly higher in the low-FT_3 than normal-FT_3 group (all P<0.001). Furthermore, mechanical support (including NPPV, ETI, and CHDF) during the ICU stay was significantly more likely to be required in the low-FT_3 than normal-FT_3 group (P<0.001). Interestingly, the PNI, the CONUT score, and its constituent factors (i.e., albumin, lymphocyte count, and total cholesterol) were significantly worse in the low-FT_3 than normal-FT_3 group (all P<0.001). These results suggest that the low-FT_3 group included a greater proportion of critical patients than the normal-FT_3 cohort.

Multivariate logistic regression analysis revealed that the PNI (per 1-point decrease; odds ratio [OR] 1.075; 95% confidence interval [CI] 1.062–1.089; P<0.001), age (per 1-year increase; OR 1.022; 95% CI 1.013–1.031; P<0.001), male sex (OR 1.522; 95% CI 1.209–1.916; P<0.001), creatinine (per 0.1-mg/dL increase; OR 1.019; 95% CI 1.014–1.024; P<0.001), and CRP (per-1.0 mg/dL increase; OR 1.107; 95% CI 1.081–1.133; P<0.001) were independently

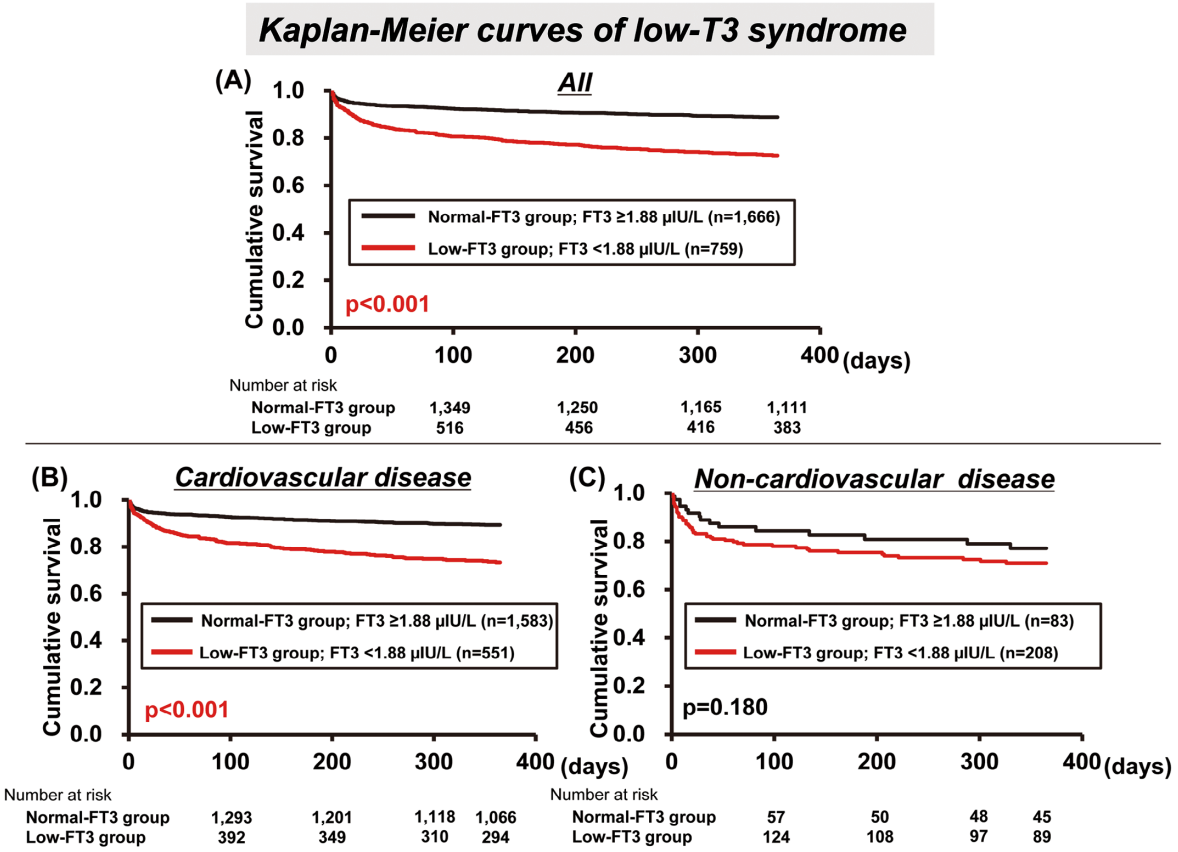

Figure 4. Kaplan-Meier survival curves for low-triiodothyronine (T_3) syndrome. (**A**,**B**) In the all-patient cohort (**A**) and in patients with cardiovascular disease (**B**), prognosis, including all-cause death within 365 days, was significantly poorer in the low-FT_3 than normal-FT_3 group. (**C**) In patients with non-cardiovascular disease, prognosis, including all-cause death within 365 days, did not differ significantly different between the low- and normal-FT_3 groups.

Table 3. Multivariate Cox Regression Model of Clinical Findings Associated With 365-Day Cumulative Mortality in Patients With Low Triiodothyronine (FT_3 <1.88 μIU/L)

365-day mortality	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
All	2.652 (2.154–3.263)	<0.001	1.785 (1.387–2.297)	<0.001
Cardiovascular disease	2.689 (2.134–3.388)	<0.001	1.774 (1.329–2.289)	<0.001
Non-cardiovascular disease	2.380 (0.778–2.449)	0.271	0.952 (0.484–1.874)	0.888

Adjusting factors: male sex, age (per 1-year increase), diabetes (yes), pulse (per 10-beats/min increase), respiratory rate (per 1-beat/min increase), body temperature (per 1°C increase), WBC count (per 1,000-U/L increase), BUN (per 10-mg/dL increase), creatinine (per 0.1-mg/dL increase), alanine aminotransferase (per 1.0-mg/dL increase), and CRP (per 1.0-mg/dL increase). HR, hazard ratio. Other abbreviations as in Tables 1,2.

associated with low-T_3 syndrome (**Table 2**), suggesting that the likelihood of low-T_3 syndrome at admission was associated with age, sex, and the presence of malnutrition, renal dysfunction, and inflammation in patients who required admission to the non-surgical ICU.

Incidence and Prognostic Value of Low-T_3 Syndrome

Low-T_3 syndrome was significantly more frequent in patients with non-cardiovascular than cardiovascular disease (73.5% vs. 25.8%, respectively). Low-T_3 syndrome was most frequent in patients with sepsis within the non-cardiovascular cohort and in those with AHF (41.6%) within the cardiovascular cohort (**Figure 3**).

The median duration of follow-up for long-term prognosis was 365 days in the overall population. All-cause death occurred in 360 (14.8%) patients within 365 days. The Kaplan-Meier survival curves, including for all-cause death, for the serum FT_3 groups are shown in **Figure 4**. The 365-day survival rates in the normal-T_3 and low-T_3 groups were 89.7% and 75.4%, respectively. The survival rate of the low-FT_3 group in the all-patients cohort was significantly lower than that of the normal-FT_3 group (P<0.001;

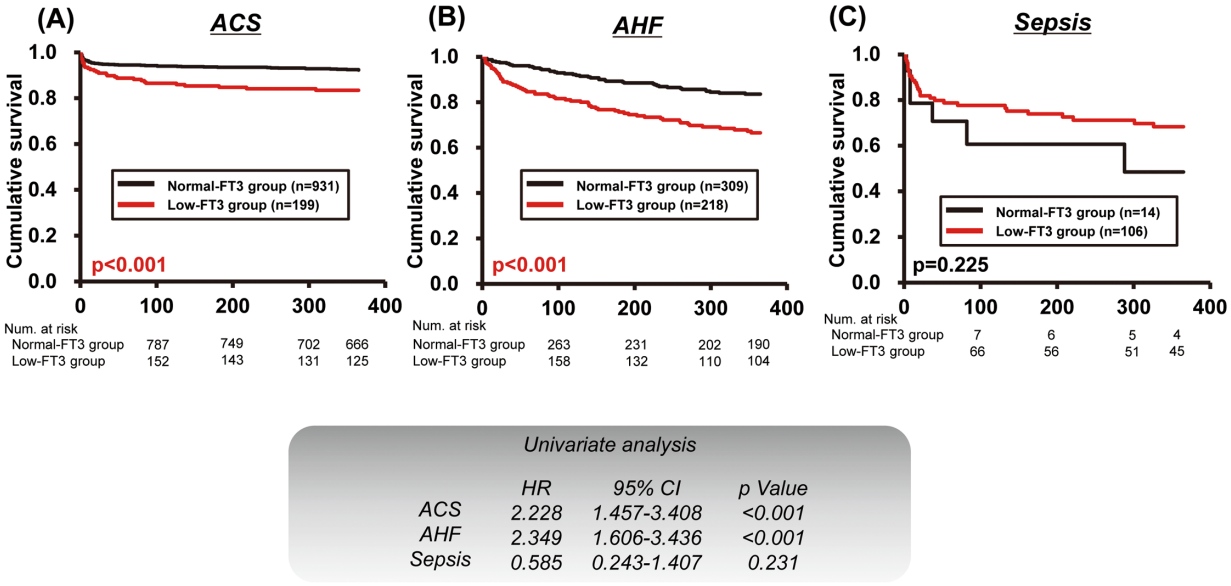

Figure 5. Kaplan-Meier survival curves for low-triiodothyronine (T_3) syndrome according to disease. (**A**,**B**) In patients with acute coronary syndrome (ACS; **A**) and acute heart failure (AHF; **B**), prognosis, including all-cause death within 365 days, was significantly poorer in the low-FT_3 than normal-FT_3 group. (**C**) In patients with sepsis, prognosis, including all-cause death within 365 days, did not differ significantly between the low- and normal-FT_3 groups. HR, hazards ratio; CI, confidence interval.

Figure 4A). In the low-FT_3 group, 187 patients died within 365 days, 111 (59.4%) due to cardiovascular disease and 73 (39.0%) due to non-cardiovascular disease; the cause of death was unknown for 3 patients. The cardiovascular diseases in these cases were HF (n=55), cardiac death (n=31), cerebral disease (n=8), sudden death (n=10), aortic disease (n=4), and pulmonary embolism (n=3). The non-cardiovascular diseases were malignancy (n=18), infectious disease (n=30), and other (e.g., kidney and lung disease, n=25). Interestingly, the prognosis was significantly worse in the low-T_3 than normal-T_3 group in the cardiovascular (P<0.001) but not non-cardiovascular (P=0.255) cohort (**Figure 4B**,**C**). Factors predicting 365-day mortality were assessed by multivariate Cox logistic regression analysis (**Table 3**). Multivariate logistic analysis indicated that low FT_3 was an independent predictor of 365-day mortality in all patients (HR 1.785; 95% CI 1.387–2.297; P<0.001) and in cardiovascular patients (HR 1.774; 95% CI 1.329–2.289; P<0.001), but not in non-cardiovascular patients (HR 0.952; 95% CI 0.484–1.874; P=0.888).

In terms of prognostic impact, ACS (HR 2.228; 95% CI 1.457–3.408; P<0.001) and AHF (HR 2.349; 95% CI 1.606–3.436; P<0.001) were significant predictors of 365-day mortality, but sepsis was not (HR 0.585; 95% CI 0.243–1.407; P=0.231; **Figure 5**).

Discussion

Factors Associated With Low-T_3 Syndrome

Low-T_3 syndrome was independently associated with male sex, old age, renal insufficiency, inflammatory reaction, and malnutrition in patients admitted to the non-surgical ICU. Low-T_3 syndrome was more likely to be a complication in patients with non-cardiovascular disease than in those with cardiovascular disease. AHF and sepsis were representative diseases that were complicated with low-T_3 syndrome at admission in each the cardiovascular and non-cardiovascular cohorts.

Inflammation is well known to induce low-T_3 syndrome, as has been discussed in many papers.[13–15] In the setting of infectious or inflammatory diseases, T_3 synthesis has been shown to be inhibited by free fatty acids or cytokines.[13] Interferon-α can also cause disturbances in thyroid hormone metabolism.[14] Inflammatory cytokines have been reported to decrease 5'-monodeiodinase activity.[15] Because inflammatory conditions lead to low-T_3 syndrome via these complex mechanisms, it makes sense that sepsis was the most common disease found to be a complication among patients with low-T_3 syndrome treated in the ICU. In the present study, approximately 90% of patients had low-T_3 syndrome at admission.

Another finding associated with low-T_3 syndrome is malnutrition. Starvation in both clinical and experimental settings has been suggested as a mechanism associated with low-T_3 syndrome.[16] In both humans and experimental animal models, nutritional deprivation is associated with reductions in circulating T_3 concentrations, T_3 production, and Type I 5'-deiodinase activity. Under fasting conditions, thyroid hormone regulation of 5'-deiodinase is principally at the pretranslational mRNA level.[16] 5'-Deiodinase

mRNA levels and activity are decreased relatively late after nutritional deprivation, suggesting that changes in serum and tissue T_3 concentrations are noted secondary to the decrease in 5'-deiodinase mRNA under such conditions. These results suggest that the nutritional status before admission is associated with the presence of low-T_3 syndrome at the time of admission. Because low-T_3 syndrome at admission reflects malnutrition before admission, it may be associated with an adverse outcome.

Renal dysfunction was also suggested as a factor inducing low-T_3 syndrome in the present study. There has been considerable research on low-T_3 syndrome in patients with chronic kidney disease.[17] Most T_3 is converted from T_4 in the periphery by catalysis by 5'-monodeiodinases in various organs, including the kidney.[2] Under critical conditions, these mechanisms may lead to changes in thyroid hormone concentrations, rather than the hypothalamic-pituitary-thyroid axis. Renal insufficiency (i.e., chronic kidney disease and acute kidney injury) coexisting in patients requiring intensive care may easily induce the inactivation of Type I 5'-monodeiodinase. Impairment of the conversion of T_4 to T_3 by inactivation of Type I 5'-monodeiodinase in the kidney has been suggested as a mechanism underlying low-T_3 syndrome.[3]

Aging and male sex were also suggested to be associated with low-T_3 syndrome. Although low T_3 syndrome is known to be very common in the hospitalized older population,[18] sex differences have not been commonly described as an epidemiological factor in previous reports. Hypothyroidism mainly develops in older women and is associated with disease specificity (i.e., autoimmune disease). The mechanisms underlying low-T_3 syndrome differ markedly from those underlying hyper- and/or hypothyroidism; therefore, the epidemiology of low-T_3 syndrome may differ from that of general thyroid disease. Although there may be pronounced downregulation of the thyroid axis in elderly patients, the mechanisms directly responsible for inducing low-T_3 syndrome in older and male patients have not yet been described. Therefore, aging and male sex may not induce low-T_3 syndrome, but rather accompany it.

Japan's population is aging faster than the populations of Western countries, and life expectancy in Japan is increasing year by year. Critically ill patients requiring intensive care are also growing older. The general male population is more likely to require intensive care than the female population, which may be associated with socially vulnerability. Elderly socially vulnerable patients, especially men, may not be adept at managing their psychological stress, medication adherence, and nutritional status by themselves. Although women can maintain control of their life environments even if they become socially poor (i.e., having no partner or children, or living alone) in later life, men may not be as self-sufficient under conditions of social vulnerability. Such epidemiological specificities of the present cohort, wherein older man can easily become critically ill, may have affected our findings of older age and male sex being associated with low-T_3 syndrome.

Because AHF was clearly associated with aging, renal insufficiency, malnutrition, and inflammation, the proportion of patients with low-T_3 syndrome was relatively high in the total AHF cohort (41.5%). Low-T_3 syndrome has been reported to be present in approximately 30–40% of AHF patients,[19,20] which is consistent with the data in the present study.

Prognostic Impact of Low-T_3 Syndrome

A prognostic impact of low-T_3 syndrome was observed in patients with cardiovascular disease, particularly those with ACS and AHF. Some consideration may be required regarding these findings.

As mentioned above, sepsis was the most frequent condition among low-T_3 syndrome patients requiring intensive care; thus, most sepsis patients had low-T_3 syndrome as a complication at admission. This study was unable to suggest the prognostic impact of low-T_3 syndrome in patients with sepsis, and this may be because of the prevalence of sepsis. Patients with sepsis of varying degrees of severity (i.e., ranging from mild to severe/critical status) had low-T_3 syndrome as a complication because sepsis is a representative disease caused by infection. Therefore, low-T_3 syndrome may not necessarily lead to adverse outcomes in sepsis patients. Because direct mechanisms that were not associated with the prognosis of sepsis patients were not identified by our analysis, further studies may be required.

In present study, the causes of death among patients with low-T_3 syndrome were heterogeneous. This was especially true with a longer follow-up time. Non-cardiovascular patients who require intensive care and AHF patients usually have various comorbidities (e.g., malignant disease, chronic kidney injury, chronic obstructive pulmonary disease, and diabetes) at the time of admission. These different types of disorders may effect the long-term prognosis of these patients. Meanwhile, cardiovascular patients (e.g., ACS, acute aortic disease, pulmonary embolism, and arrhythmia) were suddenly admitted to the ICU without comorbidities. These patients would be more likely to die of cardiovascular disease during a short-term follow-up; thus; cardiovascular deaths accounted for approximately 60% of all deaths among patients with low-T_3 syndrome. It has also been reported that low-T_3 syndrome is an independent prognostic factor in cardiovascular patients and that it is associated with an increased risk of cardiac mortality and major adverse cardiovascular events.[21] From these perspectives, we hypothesized that the effect of low T_3-sydnrome on mortality was due to damage to the cardiovascular system in patients with cardiovascular disease who require intensive care. Further studies are required to investigate the effects of different causes of death on the risk of mortality in low-T_3 syndrome.

The present study revealed that malnutrition and renal function were other important factors inducing low-T_3 syndrome. These factors have been suggested to be independent predictors of adverse outcomes in patients with ACS and AHF in various reports.[22–24] The prognostic impact of low-T_3 syndrome in ACS and AHF may be related to malnutrition and renal function. The prevalence of low-T_3 syndrome in ACS and AHF patients is not very high compared with the prevalence of low-T_3 syndrome in sepsis patients.[19,20,25,26] Only severely ill patients had low-T_3 syndrome as a complication. Thus, low-T_3 syndrome was a complication in patients with severe ACS (e.g., those with Killip II/IV status and/or those with high creatine kinase/troponin T_4 values[26]) and severe AHF, such as clinical scenarios 3 as shown in previous study.[6] Because the number of patients with ACS and AHF is increasing year by year in the aging Japanese society,[27,28] a comprehensive biomarker that is associated with long-term prognosis would be useful in future intensive care for cardiovascular disease. Low-T_3 syndrome may be a comprehensive marker in patients who require intensive care.

The findings of the present study may suggest a treatment strategy for low-T_3 syndrome. Whether low-T_3 syndrome itself is directly linked to an adverse outcome remains unclear. De Groot suggested that if low-T_3 syndrome were considered a "functional" central hypothyroidism, hormone replacement would be appropriate in severe cases.[29] However, no definitive prospective studies have yet been conducted to determine whether treatment for low-T_3 syndrome would be beneficial in the long term for intensive care patients.[30] From our perspective, low-T_3 syndrome developed due to the primary disease (e.g., malnutrition, inflammation, and renal insufficiency). Because the factors that induce this condition are an important issue for adverse outcomes of low-T_3 syndrome, it is important to treat the primary disease (e.g., malnutrition, inflammation, and renal insufficiency) as early as possible, rather than to administer thyroid hormone replacement therapy. The presence of low-T_3 syndrome may be useful for decision making regarding the treatment strategy in intensive care.

Study Limitations

Several limitations associated with the present study warrant mention. First, the study was performed at a single center and was not a prospective randomized control trial. It is therefore possible that unmeasured variables affected the results. Furthermore, the difficulty in standardizing care for each patient may have influenced the major findings of this study. Second, because this was retrospective study, we could not obtain echocardiography data (e.g., left ventricular dimension and volumes) for all patients. LVEF was calculated using different methods (Teichholz or Simpson's method) because it was measured during the acute phase. There are big differences between the Teichholz and Simpson's method; thus, the calculated LVEF may not accurately reveal left ventricular function. This issue is one of the major limitations of present study. Third, this was a retrospective study and, although we were able to evaluate the TSH, FT_3, and FT_4 concentrations within 30 min after admission in most patients (99.5%), the remaining patients (0.5%) were evaluated 1 day after admission. Fourth, data on serum albumin levels or the lymphocyte count on admission were lacking for 39 (1.6%) patients and were obtained 1 day after admission for 136 (5.6%) patients. Fifth, there were differences in patient characteristics between the normal-T_3 and low-T_3 groups. Therefore, it is strictly difficult to exclude residual confounding factors, even after adjustment. It may be natural for patients with a worse condition to have a poor outcome. Furthermore, the only endpoint in the present study was all-cause death. Another endpoint (e.g., readmission due to cardiovascular events) may be required. Finally, we did not present time-dependent changes in thyroid hormones throughout treatment. This is essential for establishing low-T_3 syndrome as a comprehensive biomarker that is affected by emergency stress. Further studies are required.

Conclusions

In conclusion, patients with low-T_3 syndrome experienced adverse outcomes, including all-cause death, in the non-surgical ICU cohort with cardiovascular disease. Aging, male sex, inflammation, renal insufficiency, and malnutrition were independently associated with low-T_3 syndrome in critical patients in the non-surgical ICU. The T_3 level at admission may be a comprehensive prognostic marker of these factors in critically ill cardiovascular disease patients.

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Disclosures

The authors declare no conflicts of interest related to the present study.

IRB Information

This study was approved by the Ethics Committee of Nippon Medical School Chiba Hokusoh Hospital (Reference no. 841).

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Supplementary Files

Please find supplementary file(s);
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