Low tri-iodothyronine syndrome improve the risk prediction of mortality in patients with acute heart failure

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Research article

Keywords: acute heart failure, low-T3 syndrome, mortality

Posted Date: October 16th, 2019

DOI: https://doi.org/10.21203/rs.2.16122/v1

Abstract

Background Clinical studies have suggested that low tri-iodothyronine (T3) syndrome negatively affects the clinical outcomes of patients with acute heart failure (AHF). The aim of this prospective cohort study was to evaluate the effect of low T3 syndrome in terms of prognosis and risk predictive potential in AHF.

Methods Low T3 syndrome was defined by a low free T3 level (<3.1 pmol/L) accompanied by a normal thyroid-stimulating hormone level. The association between the free T3 level and mortality and the incremental risk prediction were estimated in adjusted models.

Results In total, 312 patients with AHF for whom detailed thyroid hormone profiles were available were prospectively enrolled. Seventy-two patients exhibited low T3 syndrome. Over a median follow-up period of 35 months, 121 cumulative deaths occurred. Cardiovascular death was observed in 94 patients. After extensive adjustment for confounders, the low T3 syndrome associated hazard ratio (95% confidence interval) was 1.74 (1.16-2.61, P =0.007) for all-cause mortality and 1.90 (1.21-2.98, P =0.005) for cardiovascular mortality. The regression splines suggested a negative linear relationship between the free T3 level and mortality risk. Considering reclassification, adding low T3 syndrome to the fully adjusted model improved the risk prediction for all-cause mortality (Integrated discrimination improvement [IDI] 2.0%, P = 0.030; net reclassification improvement [NRI] 8.9%, P = 0.232) and cardiovascular mortality (IDI = 2.5%, P = 0.030; NRI 21.3%, P = 0.013).

Conclusions Low T3 syndrome reclassified risk prediction for mortality beyond traditional risk factors.

Background

Heart failure is associated with high-level morbidity and mortality [1]. The cardiovascular system, particularly the heart, is a key target of thyroid hormones [2], changes in circulating hormone levels modulate cardiovascular metabolism. Low tri-iodothyronine (T3) syndrome is commonly considered to be an adaptive response to severe functional impairment [3], and has been reported in patients with heart failure. Clinical and experimental studies have shown that T3 plays fundamental roles in the modulation of cardiac contractility, ventricular remodelling and peripheral vascular resistance[4], the reduction in the activity of 5-monodeiodinase (which converts thyroid hormone [T4] to T3) is proportional to the clinical severity of heart disease [5], Changes in T4 levels are associated with significant alterations in heart function.

Low T3 syndrome is not uncommon in patients with heart failure (10.6–34.5% of such patients) [6–8]. Increasing evidence suggests that low T3 syndrome is associated independently with an increased risk of adverse clinical outcomes in patients with acute heart failure (AHF) [6, 8, 9] and chronic heart failure [10]. Although previous studies have demonstrated the independent prognostic impact of low T3 syndrome, there is lack of study adjust for baseline N-terminal pro-brain natriuretic peptide (NT-proBNP) concentrations. Therefore, it remains uncertain whether low T3 syndrome are associated with long-term prognosis in patients with AHF, independently of renal function, NTproBNP levels and other comorbid

conditions [11]. Here, we characterise the effect of low T3 syndrome in terms of prognosis and risk predictive potential in patients with AHF.

Methods

Study design

From April 2012 and August 2016, 482 consecutive patients were hospitalized for AHF in the First Affiliated Hospital of Nanjing Medical University. The inclusion criteria were age ≥18 years and hospitalisation because of AHF. Patients with malignant tumours, those exhibiting cognitive dysfunction or dementia and those with uncontrolled systemic disease or severe mental illness were excluded. In addition, 131 patients were excluded because they were taking amiodarone or antithyroid drugs (*n* = 12) or exhibited clinical hyperthyroidism (*n* = 9), hypothyroidism (*n* = 30), subclinical hyperthyroidism (*n* = 2) or subclinical hypothyroidism (*n* = 78). Our study complies with the Helsinki declaration for investigation in human patients, and the study was registered at http://www.chictr.org/ cn/ (ChiCTR—ONC - 12001944).

Baseline demographic and clinical data (medical history, physical examination findings, laboratory data, AHF aetiology and complications) were collected within 24 h of admission. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation[12]. The left ventricular ejection fraction (LVEF) was measured by transthoracic echocardiography using the Simpson method. Chronic kidney disease was defined as eGFR <60 mL/(min·1.73 m^2). Hyponatraemia was defined as serum sodium level ≤135 mmol/L. Anaemia was defined as haemoglobin level <130 g/L in males and <120 g/L in females. Hypoalbuminaemia was defined as serum albumin level <34 g/L. All patients were treated in a standard manner. The thyroid function profile was evaluated on admission or the following morning using an automated chemiluminescence immunoassay system (AutoBio 12 Co. Ltd., Zhengzhou, China). The reference intervals used were 3.10–6.80 pmol/L for serum free T3, 12.00–22.00 pmol/L for serum free T4 and 0.27–4.20 mIU/L for thyroid-stimulating hormone (TSH). Low T3 syndrome was diagnosed when the level of free T3 was <3.1 pmol/L, but the TSH level was normal.

The primary endpoint was all-cause mortality, and the secondary endpoint was cardiovascular mortality. Prospective follow-up commenced after the measurement of thyroid function. Mortality was ascertained every 6 months by examination of hospital records or patient contact (directly or by telephone), and verified by viewing death certificates held in the local disease control centre or by contact with family members.

Statistical analysis

Continuous variables are expressed as means and standard deviations (SDs) or as medians with 25^{th} and 75^{th} percentiles, and were compared using the unpaired Student's *t*-test or the Mann–Whitney *U*-test, depending on whether they were normally distributed, as revealed by the Kolmogorov–Smirnov test.

Categorical variables are presented as numbers (%) and were compared using the Pearson χ^2 test. The levels of N-terminal pro-brain natriuretic peptide (NTproBNP) were transformed logarithmically to normalise the distribution. Survival curves were drawn using the Kaplan–Meier method, and survival differences were compared using the log-rank test. Associations of low T3 syndrome with all-cause and cardiovascular mortality during follow-up were assessed using Cox proportional hazard regression analyses with adjustment sets as follows: (i) unadjusted, (ii) age and sex adjusted, (iii) adjusted for age, sex, LnNTproBNP, sodium, hypertension, eGFR, body mass index, diabetes, systolic blood pressure, hemoglobin. Furthermore, to clarify the improvement in risk prediction by low T3 syndrome over established risk factors, integrated discrimination improvement (IDI) and net reclassification improvement (NRI) were calculated. The interactions between low T3 syndrome and other factors (age >65 years, sex, ischaemic heart failure, hypertension, diabetes, chronic kidney disease, LVEF <40%, NTproBNP level >2,231 ng/L, anaemia, hyponatraemia, NYHA score and hypoalbuminemia) were explored using the likelihood ratio test. The linearity of risk was evaluated via restricted cubic spline[13] regression modelling of the association between the free T3 level (a continuous variable) and the risk of all-cause mortality. *P* values <0.05 were considered to be statistically significant. All statistical analyses were performed with the aid of R ver. 3.6.0 and Stata ver. 14 (STATA Corp LP).

Results

Baseline characteristics

Of the 351 patients, 39 (11.1%) were lost to follow-up; we finally analysed 312 patients with AHF of average age 60.4±16.2 years, of whom 69.6% were male. Seventy-two (23.1%) patients exhibited low T3 syndrome, whereas the other 240 (76.9%) were euthyroid. The patients with low T3 syndrome were older, female, smoker, with more heart failure symptoms and poorer nutritional status. They also exhibited a higher NTproBNP level, a more elevated eGFR, a higher EF and a greater prevalence of electrolyte disturbance. The mean±SD free T3 levels in patients with low T3 syndrome and those who were euthyroid were 2.50±0.53 and 4.37±0.71 pmol/L, respectively (*P*<0.001; Table 1).

Prognostic value of low T3 syndrome

During a median follow-up period of 35 (18–46) months, the numbers of all-cause deaths were 41 for patients with low T3 syndrome and 80 for euthyroid patients (56.9% vs. 33.3%, *P*<0.0001). Cardiovascular death was observed in 34 patients with low T3 syndrome and 61 with euthyroid patients (47.2% vs. 25.4, *P*<0.0001). Kaplan–Meier analysis revealed that low T3 syndrome was associated with significantly increased risk of all-cause mortality and cardiovascular mortality (Figure 1). In further analyses of multivariable-adjusted Cox models, we accounted for risk factors at baseline, including age, sex, hypertension, diabetes, atrial fibrillation, body mass index, NYHA score, LnNTproBNP, eGFR, and anemia; low T3 syndrome was related to all-cause mortality (hazard ratio [HR] 1.74, 95% confidence interval [CI] 1.16–2.61, *P* = 0.007) and cardiovascular mortality (HR 1.90, 95%CI 1.21–2.98, *P* = 0.005) (Table 2).

Restricted cubic spline regression was used to model continuous associations. A significant dose-dependent association was observed between the free T3 level and the risk of all-cause and cardiovascular mortality. The free T3 level exhibited a negative linear relationship with the mortality risk (Figure 2).

Reclassification

Reclassification of AHF patients by adding low T3 syndrome to fully adjusted model according to the occurrence of death during follow-up is summarized in table 3. The IDI after the individual inclusion of low T3 syndrome in the fully adjusted model for all-cause mortality was 2.0% (95% CI 0.1 −7.2; *P* = 0.030), and the NRI was 8.9% (95% CI −0.5–16.2; *P* = 0.232). For prediction of cardiovascular mortality, adding low T3 syndrome to the fully adjusted model increased IDI by 2.5% (95% CI 0.1–7.7, *P* = 0.030) and NRI by 21.3% (95%CI 7.6–50.2, *P* = 0.013).

Subgroup analysis

On subgroup analyses by age, sex, ischaemic heart failure, hypertension, diabetes, chronic kidney disease status, LVEF, NTproBNP level, anaemia and hyponatraemia status, NYHA score and hypoalbuminaemia status, the associations between low T3 syndrome and all-cause mortality were generally similar in all subgroups (Figure 3).

Discussion

We found that low T3 syndrome was common in patients with AHF and was associated with increased all-cause mortality and cardiovascular mortality. A high free T3 level was associated with a lower risk of mortality. We also showed that low T3 syndrome improved risk prediction over clinical risk factors for mortality.

Several studies have shown that low T3 syndrome is associated independently with adverse clinical outcomes in patients with heart failure [6–8,10]. However, definitions of low T3 syndrome and the measurement of thyroid function among different studies varied. Kannan et al.[7] found that an isolated low T3 level was associated with poor clinical outcomes in 1,365 patients with pre-existing heart failure. An isolated low T3 level was also associated with a composite endpoint including death, ventricular assistive device placement and heart transplantation (HR 2.12, 95% CI 1.65–2.72, *P*<0.001). In the cited work, low T3 syndrome was diagnosed when the TSH and free T4 levels were within the reference ranges and the total T3 level was below the reference range. In the cohort study of Sato et al.[8], low T3 syndrome (free T3 <2.3 pg/mL) was associated significantly with higher all cause-mortality in patients with heart failure (unadjusted HR 1.926, 95% CI 1.268–2.927, *P* = 0.002). However, in neither study were Cox regression models adjusted for BNP or NTproBNP levels, usually considered to be the most powerful prognostic factors in patients with heart failure [11]. Our finding that low T3 syndrome is indicative of a

poor prognosis is consistent with those of previous studies exploring the effects of free T3 levels. Associations of low T3 syndrome with all-cause mortality were generally homogeneous across multiple clinically relevant subgroups, including patients divided by age, sex, ischaemic heart failure, hypertension, diabetes, chronic kidney disease status, LVEF, NTproBNP level, anaemia and hyponatraemia status, NYHA score and hypoalbuminaemia status. The differences between our study findings and those of previous works are attributable to the way in which we assessed thyroid function, our definition of low T3 syndrome and the confounders for which we adjusted in regression analyses. However, the evaluation of tissue thyroid hormone status by reference to blood data alone may be unreliable; how thyroid hormones act in target tissues such as the heart is not clear.

Our findings provide further evidence of a consistent, dose-dependent association between the free T3 level and mortality of patients with AHF. Low T3 syndrome improved risk prediction, especially for cardiovascular mortality, beyond traditional clinical risk factors in AHF.

The mechanism by which low T3 levels cause adverse clinical outcomes may include effects on cardiac contractility, pathological cardiac remodelling and the development of peripheral vascular resistance [4, 14]. Thyroid hormones critically regulate cardiac contractility by upregulating the expression of genes encoding sodium/potassium-transporting ATPases, thereby increasing expression of the myosin heavy chain (MHC) α gene and decreasing that of the MHC β gene, resulting in faster contraction [15, 16]. Thyroid hormones also reduce cardiac fibrosis by down-regulating the expression of collagen-encoding genes and inducing metalloproteinase expression; the hormones act in an inotropic manner to upregulate the expression of β1-adrenergic receptors and modulate the activities of ionic channels [17, 18]. Cardiac remodelling is a critical step during the progression of heart failure. Accumulating experimental evidence indicates that matrix metalloproteinases play important roles in the pathogenesis and progression of left ventricular dysfunction [19]. Hyroid hormones seem to significantly regulate metalloproteinase expression [20], and to reduce peripheral arterial resistance by acting directly on vascular smooth muscle cells to lower the mean arterial pressure. When this reduction is sensed by the kidney, the renin–angiotensin–aldosterone system is activated to increase renal sodium absorption [21].

Given the roles played by thyroid hormones in cardiovascular regulation, might such hormones be useful in the treatment of heart failure? Such treatment (possibly using hormonal analogues) poses certain challenges; the available data are limited. Morkin et al. [22] demonstrated that 3,5-diiodothyropropionic acid (a T4 analogue) was tolerated well and improved cardiac performance. In patients with heart failure who received 4 weeks of therapy, the cardiac index and exercise capacity increased and the systemic vascular resistance index decreased. However, in a subsequent phase II multicentre randomised placebo-controlled study, the agent afforded no symptomatic benefit in patients with congestive heart failure [23]. In another randomised placebo-controlled study of patients with ischaemic and non-ischaemic dilated cardiomyopathy, T3 replacement therapy significantly improved ventricular performance; the heart rate and NTproBNP level decreased significantly [24]. However, none of the cited works [22–24] assessed mortality or hospital re-admission; the assumption that increases in the cardiac index and exercise capacity reflect a clinical benefit needs to be proven.

Our study has certain limitations. First, it had a single-centre observational design, and residual or unmeasured factors may have confounded the association between low T3 syndrome and mortality. However, we performed subgroup analyses to increase confidence in the internal validity of our results. Second, thyroid hormone function was measured only once; we did not measure changes in T3 levels over time. Future studies should explore whether dynamic changes in the free T3 level correlate with adverse clinical outcomes.

Conclusion

Low T3 syndrome is an independent prognostic factor predicting higher all-cause and cardiovascular mortality in patients with acute heart failure. The free T3 level is linearly, and negatively, associated with such risk. Low T3 syndrome is a clinically significant risk stratification factor in patients with acute heart failure.

Abbreviations

T3: tri-iodothyronine; AHF: acute heart failure; IDI: integrated discrimination improvement; NRI: net reclassification improvement; T4: tetra-iodothyronine; NT-proBNP: N-terminal pro-brain natriuretic peptide; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; TSH: thyroid-stimulating hormone; SD: standard deviation; HR: hazard ratio; CI: confidence interval; MHC: myosin heavy chain; NYHA: New York Heart Association functional class; ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blocker.

Declarations

Ethics approval and consent to participate

Our study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University, and all patients gave written informed consent.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by the Twelve-Fifth National Key Technology R&D Program (2011BAI11B08).

Authors' contributions

JZ and SGL contributed equally to this work and should be considered co-first authors. JZ, SGL and XLL designed the study. LC, XYL and RRG analyzed and interpreted the patient data. SGL, YLZ, HFZ and WMY wrote the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version.

Acknowledgement

The authors wish to thank all the patients who made this study possible.

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Tables

Table 1. Clinical characteristics of acute heart failure patients with or without low T3 syndrome.

	Euthyroid (n=240)	Low T3 syndrome (n=72)	*P* value
Age(y)	58.8 (16.4)	65.9 (14.0)	0.001
Male	175 (72.9%)	42 (58.3%)	0.018
Hypertension	137 (57.1%)	42 (58.3%)	0.851
Diabetes	58 (24.2%)	21 (29.2%)	0.392
Atrial fibrillation	69(28.8%)	26(36.1%)	0.234
Ischemic heart failure	61 (25.4%)	21 (29.2%)	0.526
Smoke	114 (47.5%)	23 (31.9%)	0.02
NYHA			<0.001
II	55 (22.9%)	5 (6.9%)	
III	132 (55.0%)	29 (40.3%)	
IV	53 (22.1%)	38 (52.8%)	
Heart rate(beats/min)	85.6 (19.3)	88.3 (20.3)	0.299
Systolic blood pressure (mmHg)	129 (22.0)	128 (27.1)	0.866
Diastolic blood pressure (mmHg)	80.2 (15.7)	78.8 (18.8)	0.537
Potassium (mmol/L)	3.98 (0.48)	4.09 (0.63)	0.125
Sodium (mmol/L)	140 (3.44)	138 (4.20)	<0.001
Calcium (mmol/L)	4.02 (27.3)	2.18 (0.156)	0.568
Albumin (g/L)	37.7 (4.48)	33.9 (5.01)	<0.001
Blood urea nitrogen (mmol/L)	7.84 (4.04)	10.4 (6.21)	<0.001
Creatinine (μmoI/L)	97.1 (55.8)	117 (66.6)	0.013
eGFR (mL/(min·1.73 m^2))	76.0 (26.3)	61.7 (25.8)	0.001
Uric acid, mg/dL	469 (147)	504 (168)	0.087
Hemoglobin (g/L)	137 (20.1)	129 (25.6)	0.006
FT3 (pmol/L)	4.37 (0.71)	2.50 (0.53)	<0.001
FT4 (pmol/L)	18.6 (3.33)	19.2 (13.3)	0.504
TSH (mIU/L)	2.35 (1.01)	1.80 (0.95)	<0.001
NTproBNP (ng/L)	1974 [1134, 5113]	2936 [1554, 6133]	0.003
LVEF, %	40.0 (13.9)	44.7 (14.7)	0.014
Body mass index (kg/M2)	24.2 (4.17)	24.5 (4.36)	0.569
loop diuretic	100%	100%	1.000
Antisterone	217 (90.4%)	62 (86.1%)	0.353
ACEI/ARB	196 (81.7%)	53 (73.6%)	0.159
Beta-blocker	192 (80.0%)	63 (87.5%)	0.130
Aspirin	97 (40.4%)	30 (41.7%)	0.850
All-cause mortality	80(33.3%)	41(56.9%)	<0.001
Cardiovascular mortality	60(25.4%)	34(47.2%)	<0.001

Data are presented as mean (SD) or median (interquartile range), or n (%). eGFR, estimated glomerular filtration rate; FT3, free tri-iodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; NTproBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association functional class; LVEF, left ventricular ejection fraction; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker.

Table 2. Predictive value of low T3 syndrome.

Model	Low T3 syndrome (all-cause mortality)		Low T3 syndrome (cardiovascular mortality)	
	HR(95%CI)	*P* value	HR(95%CI)	*P* value
Unadjusted	2.16(1.48-3.15)	<0.001	2.29(1.51-3.49)	<0.001
Age and sex adjusted	1.80(1.23-2.63)	0.003	1.95(1.28-2.99)	0.002
Fully adjusted*	1.74(1.16-2.61)	0.007	1.90(1.21-2.98)	0.005

HR, hazard ratio; 95% CI, 95% confidence interval;

*Fully adjusted: age, sex, hypertension, diabetes, body mass index, NYHA, atrial fibrillation, LnNTproBNP, eGFR, anemia.

Table 3. Improvement of risk prediction by adding low T3 syndrome to fully adjusted model.

Endpoints level	Integrated discrimination improvement			Net reclassification improvement		
	IDI (%)	CI (95%)	*P*	NRI (%)	CI (95%)	*P*
All-cause mortality	2.0	0.1-7.2	0.030	8.9	-0.5-16.2	0.232
CV mortality	2.5	0.1-7.7	0.030	21.3	7.6-50.2	0.013

IDI, integrated discrimination improvement; NRI, net reclassification improvement; CI, confidence interval; CV, cardiovascular.

Figures

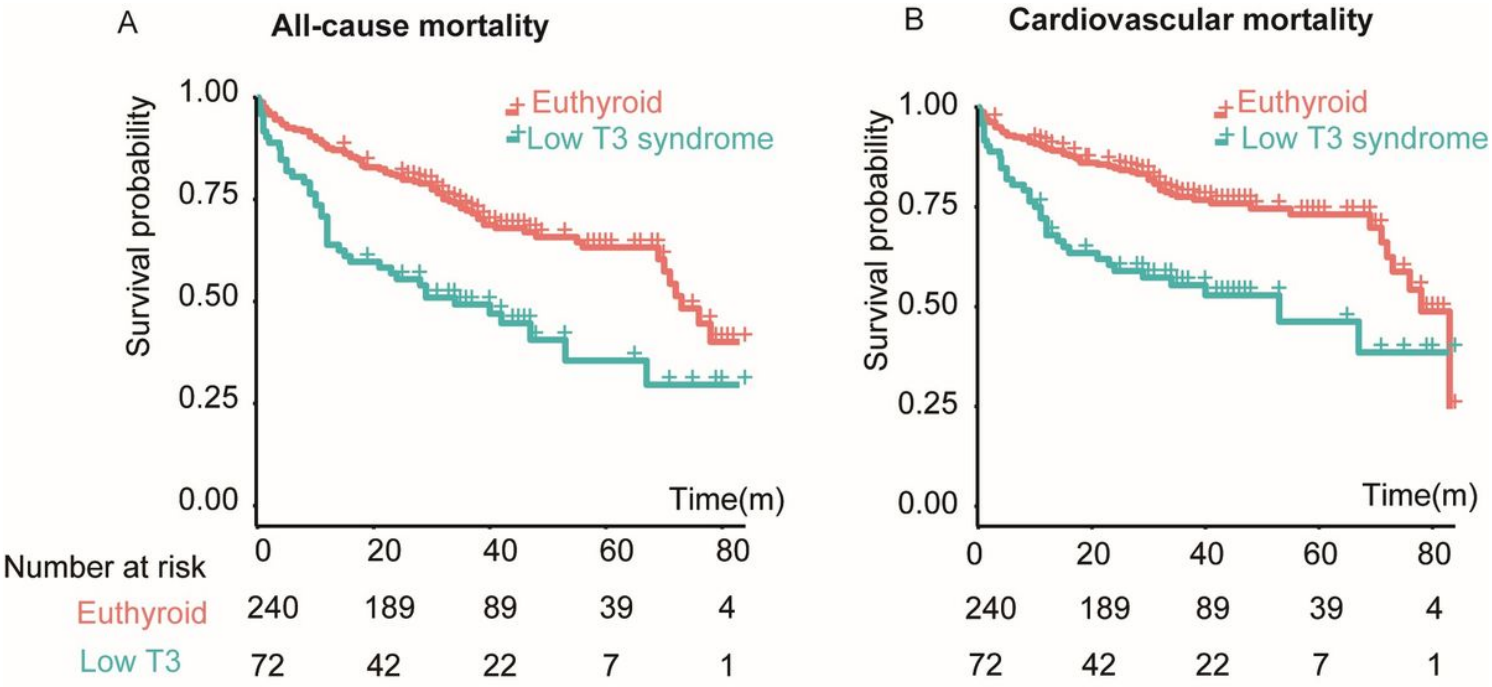

Figure 1

Kaplan–Meier survival curve for all-cause and cardiovascular mortality in patients with euthyroidism and low T3 syndrome.

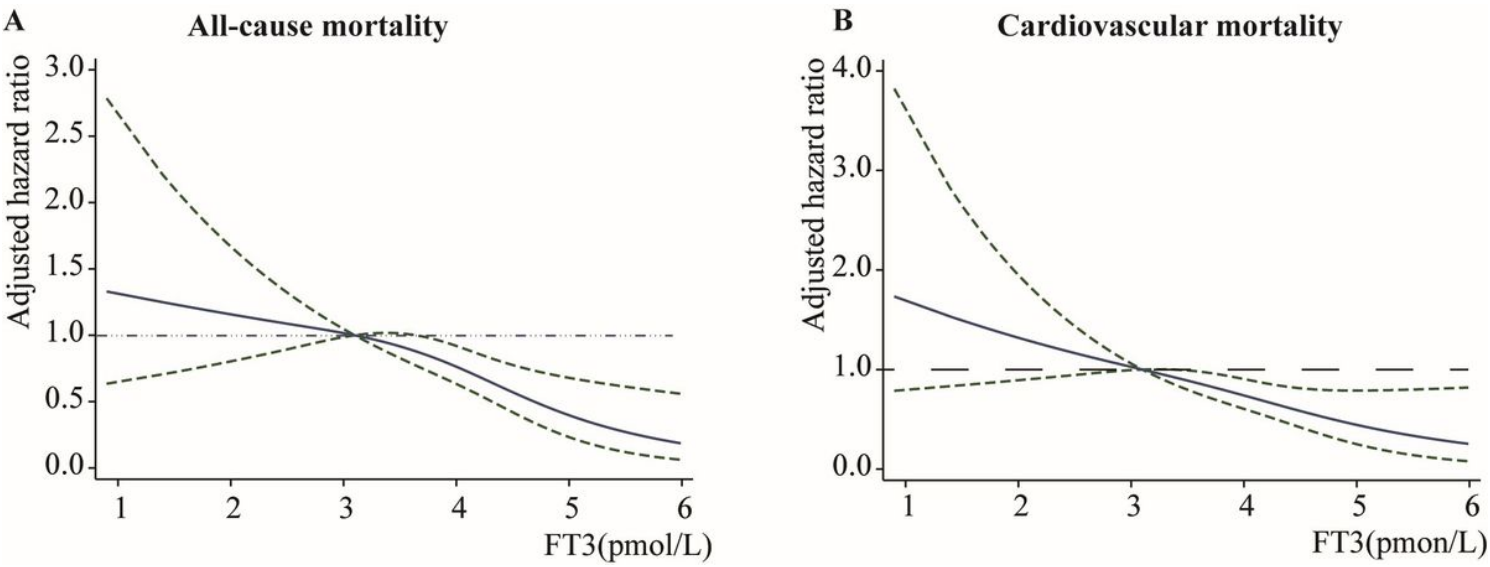

Figure 2

Continuous association between free T3 levels and risk of all-cause and cardiovascular mortality. Dashed lines are 95% confidence intervals. Hazard ratios were estimated using cox regression modeling, adjusting for age, lnNTproBNP, sex, eGFR, hypertension, diabetes, body mass index, NYHA, sodium, anemia.

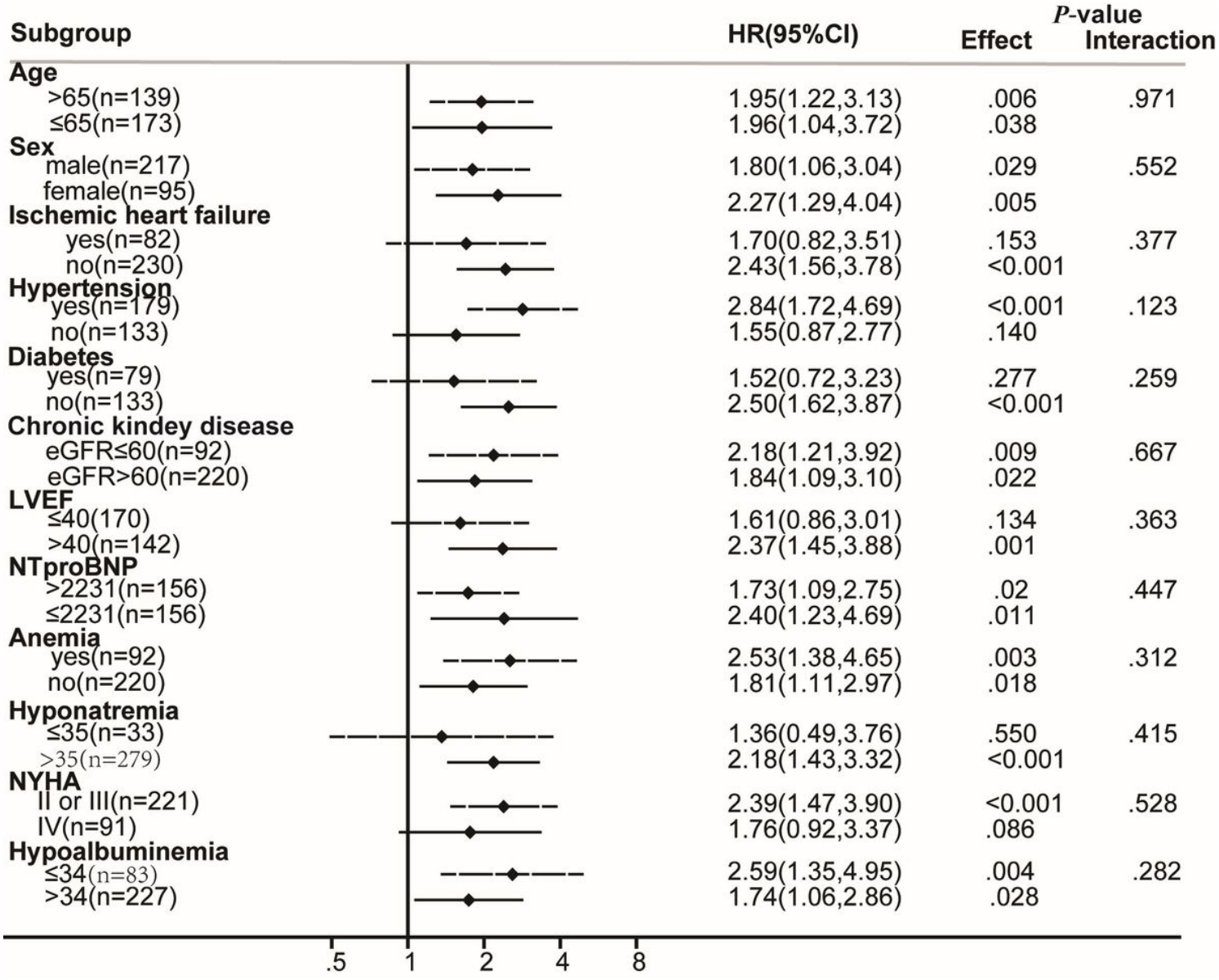

Figure 3

Association of low T3 syndrome and all-cause mortality in subgroups of AHF patients.