Prognostic value of free triiodothyronine in patients with dilated cardiomyopathy

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Abstract

Background: The association between free triiodothyronine (FT3) and long-term prognosis in dilated cardiomyopathy (DCM) patients has not been evaluated. The purpose of this study was to determine whether the level of FT3 could provide prognostic value in patients with DCM.

Methods: Data of consecutive patients diagnosed with DCM were collected from October 2009 to December 2014. FT3 was measured by fluoroimmunoassay. Other biochemical markers, such as free thyroxin (FT4), thyroid-stimulating hormone, red blood cell, hemoglobin, blood urea nitrogen, and serum creatinine, were tested at the same time. Follow-up was performed every 3 months. The primary endpoint was all-cause mortality. Pearson analysis was used to evaluate the correlation of FT3 and other lab metrics with DCM patients' prognosis. The association of long-term mortality in DCM and FT3 was compared using Cox hazards model.

Results: Data of 176 patients diagnosed with DCM were collected. Of them, 24 patients missed FT3 values and six patients were lost to follow-up. Altogether, data of 146 patients were analyzed. During the median follow-up time of 79.9 (53.5–159.6) months, nine patients lost, 61 patients died (non-survival group), and 85 patients survived (survival group). FT3 was significantly lower in non-survival group than that in survival group (3.65 ± 0.83 pmol/L *vs.* 4.36 ± 1.91 pmol/L; $P = 0.003$). FT3 also showed a significantly positive correlation with red blood cell and hemoglobin, negatively correlated with age, blood urea nitrogen and serum creatinine ($P < 0.05$), respectively. Patients in the group of lower FT3 levels (FT3 ≤ 3.49 pmol/L) suffered from a higher risk of all-cause mortality (P for log-rank $= 0.001$). In multivariate Cox regression analysis, FT3 level was significantly associated with all-cause mortality (hazard ratio: 0.70, 95% confidence interval 0.52–0.95, P for trend $= 0.021$).

Conclusion: Low levels of FT3 were associated with increased all-cause mortality in patients with DCM.

Keywords: Dilated cardiomyopathy; Free triiodothyronine; All-cause mortality

Introduction

Dilated cardiomyopathy (DCM) is one of the major causes of heart failure (HF) with a prevalence of approximately 1:2500 and up to 1:250 in the general population.[1,2] It predominantly affects younger adults. DCM is a disorder of the heart muscle characterized mainly by left ventricular dilation and systolic dysfunction in the absence of hypertension, valvular heart diseases, congenital abnormalities, or coronary artery disease (CAD)[2] resulting from the response of the myocardium to genetic and environmental insults.[3] The traditional risk-prediction model is mainly based on parameters related to cardiac function, but its clinical application is still limited.[4,5] Therefore, an accurate risk classification in DCM patients is very important to guide intervention. The cardiovascular system, particularly the heart, is an important target of thyroid hormone (TH) action. Experiments on animals showed that TH has complicated effects on cardiomyocytes, cellular matrix, and cardiac ventricular function.[6-8] Even subtle variations in TH levels can lead to adverse cardiac events.[9,10] The two main iodinated THs are thyroxin (T4) and triiodothyronine (T3). Both of them have biological effects. However, T3 is considered the more potent hormone.[11] Free T3 (FT3), the active form of T3, has many effects on the cardiovascular system, namely, up-regulating cardiac output through positive inotropic effect, reducing systemic vascular resistance through vasodilation, promoting

angiogenesis and improving the function of the endothelium. Reduced levels of FT3 are related to poor hemodynamics and a low serum sodium level, which is also an independent predictor of poor survival.[12,13] In addition, heart diseases may themselves lead to changes in TH concentrations. This is associated with higher morbidity and mortality in the absence of pre-existing thyroid disease.[14] TH has complex effects on the myocardium, its levels act as a promising monitoring index in the risk classification and treatment of DCM.[15,16]

However, the relationship between FT3 and long-term prognosis in DCM patients has not been evaluated. In this study, we aimed to discover the association between FT3 and long-term prognosis in DCM patients.

Methods

Ethical approval

This study was conducted following the *Declaration of Helsinki* and was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (No. 2020-SR-076). Given the retrospective nature of the study, the requirement of written informed consent was waived.

Study population

Data of consecutive DCM patients were collected in this study at the First Affiliated Hospital of Nanjing Medical University from October 2009 to December 2014. DCM diagnosis was based on (1) left ventricular end-diastolic dimension (LVEDd) > 5.5 cm in male and LVEDd > 5.0 cm in female, or LVEDd greater than 117% (>2 standard deviation [SD] of the predicted value of 112% corrected for age and body surface area); (2) left ventricular fractional shortening less than 25% (>2SD) and/or left ventricular ejection fraction less than 45% (>2SD); and (3) excluding any known cause of myocardial disease.[17-20] Patients with subclinical hypothyroidism (normal FT3 and free T4 [FT4], thyroid-stimulating hormone [TSH] increased), subclinical hyperthyroidism (normal FT3 and FT4, TSH decreased), hypothyroidism, and hyperthyroidism were excluded. Patients receiving thyroxine, antithyroid drugs, amiodarone, or corticosteroids were excluded. Children <18 years old and alcohol abusers were not included.

Measurement of thyroid function and other biochemical indexes

Thyroid status was evaluated using 12-h fasting TSH, FT3, FT4 levels. Plasma TSH was measured with an electro-chemiluminescence immunoassay. FT3 and FT4 were measured by time-resolved fluoroimmunoassay. The distribution trend of poor long-term prognosis in DCM patients was explored across FT3 quartiles. Other biochemical markers such as lower red blood cell (RBC) and hemoglobin (HGB), and higher serum creatinine (Cr), blood urea nitrogen (BUN), and high-density lipoprotein cholesterol (HDL-C) were tested at the same time with thyroid function.

Follow-up and endpoints

Patients were followed up at the clinical department or hospitalization every 3 months in this study. Follow-up information and death events were recorded. The primary endpoint was all-cause mortality. According to the primary outcome, patients were divided into two groups: the survival group and the non-survival group. Recorded death refers to the death of the patient during follow-up, which is verified with telephone interview and review of the patient's medical record on readmission.

Statistical analysis

Continuous variables with a normal distribution were expressed as mean ± SD. Continuous non-normal distributed variables were expressed as medians and interquartile range (IQR). Comparisons between two groups were made using two-tailed unpaired Student t test. Comparisons among three or more groups were carried out using one-way analysis of variance, and inter-group differences were analyzed using two-way analysis of variance. Categorical variables were presented as frequencies or percentages and were compared with the Chi-squared or Fisher exact test when appropriate. Univariate and multivariate Cox proportional hazards models were used to estimate the hazard ratio with 95% confidence intervals (CIs). Kaplan-Meier analysis was used to study cumulative survival of different groups. The statistical analysis was done using the statistical packages R (The R Foundation; http://www.r-project.org; version 3.4.3). A value of $P < 0.05$ was considered statistically significant.

Results

From October 2009 to December 2014, a total of 176 consecutive patients with DCM were admitted to the First Affiliated Hospital of Nanjing Medical University. Among them, 24 patients missed FT3 values and six patients were lost to follow-up, and finally data of 146 subjects were analyzed in this study. The median follow-up was 79.9 (53.5–159.6) months. Sixty-one patients died (non-survival group) and 85 patients survived (survival group). Patients in the non-survival group were older than the survival group (61.64 ± 12.63 *vs.* 52.85 ± 16.35 years old, $P < 0.001$). They also had lower diastolic blood pressure (DBP) ($P = 0.004$). No significant differences of sex ($P = 0.71$), smoking ($P = 0.21$), drinking status ($P = 0.10$), comorbidities ($P > 0.05$), LVDd ($P = 0.57$), and left ventricular ejection fraction ($P = 0.25$) between two groups [Table 1]. Lower RBC counts ($P = 0.01$) and HGB ($P = 0.03$), and higher serum Cr ($P = 0.001$), BUN ($P = 0.001$), and HDL-C ($P = 0.01$) levels in non-survival group. There were no significant differences in medications and device treatment between the two groups ($P > 0.05$) [Table 2].

Patients in non-survival group had a lower FT3 and higher TSH levels than the survival group ($P = 0.0007$ and $P = 0.0003$) [Figure 1A and 1C]. FT4 levels were also lower in non-survival group than those in the survival group, but the difference was not statistically significant ($P > 0.05$) [Figure 1B]. In correlation analysis, FT3 showed significantly positive correlation with RBC ($r = 0.22$, $P < 0.01$ and HGB ($r = 0.21$,

Table 1: Baseline characteristics of survival and non-survival patients with dilated cardiomyopathy.

Items	Survival ($n = 85$)	Non-survival ($n = 61$)	Statistics	*P* values
Demographics				
Age (years)	52.85 ± 16.35	61.64 ± 12.63	3.663[*]	<0.001
Male, *n* (%)	69 (81.2)	48 (78.7)	0.138[†]	0.710
SBP (mmHg)	119.95 ± 16.89	114.43 ± 18.73	−1.853[*]	0.070
DBP (mmHg)	77.16 ± 11.37	71.62 ± 11.34	−2.898[*]	0.004
Smoking, *n* (%)	36/84 (42.9)	32/60 (53.3)	1.541[†]	0.210
Drinking, *n* (%)	29/84 (34.5)	29/60 (48.3)	2.775[†]	0.100
Comorbidities and risk factors				
Hypertension, *n* (%)	24 (28.2)	23 (37.7)	1.459[†]	0.230
Diabetes, *n* (%)	15 (17.6)	7 (11.5)	1.057[†]	0.300
CAD, *n* (%)	11 (12.9)	6 (9.8)	0.333[†]	0.560
MI, *n* (%)	1 (1.2)	0	0.723[†]	0.400
Stroke, *n* (%)	5 (5.9)	2 (3.3)	0.527[†]	0.470
CKD, *n* (%)	2 (2.4)	1 (1.6)	0.090[†]	0.760
Hyperthyroidism, *n* (%)	2 (2.4)	5 (8.2)	2.657[†]	0.100
Dyslipidemia, *n* (%)	28 (32.9)	12 (19.7)	3.144[†]	0.080
Echocardiography				
LAD (mm)	47.28 ± 7.28	48.06 ± 8.93	0.553[*]	0.580
LVDd (mm)	71.07 ± 10.37	72.06 ± 9.15	0.566[*]	0.570
LVDs (mm)	58.01 ± 11.04	59.64 ± 10.00	0.864[*]	0.390
LVEF	0.35 ± 0.09	0.34 ± 0.08	−1.150[*]	0.250

All data are displayed as *n* (%) or mean ± standard deviation. [*]*t* value. [†]χ^2 value. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; CAD: Coronary artery disease; MI: Myocardial infarction; CKD: Chronic kidney diseases; LAD: Left anterior descending; LVDd: Left ventricular diastolic dimension; LVDs: Left ventricular systolic dimension; LVPW: Left ventricular posterior wall; IVS: Inter-ventricular septal; LVEF: Left ventricular ejection fraction.

Table 2: Laboratory parameters, medications and devices using data in survival and non-survival patients with dilated cardiomyopathy.

Items	Survival ($n = 85$)	Non-survival ($n = 61$)	Statistics	*P* values
Laboratory parameters				
RBC ($\times 10^9$/L)	4.57 ± 0.54	4.30 ± 0.76	−2.515[*]	0.010
HGB (g/L)	139.38 ± 17.19	133.25 ± 16.66	−2.141[*]	0.030
HDL-C (μmol/L)	1.01 ± 0.27	0.89 ± 0.32	−2.506[*]	0.010
LDL-C (μmol/L)	2.48 ± 0.70	2.44 ± 0.86	−0.296[*]	0.770
BUN (mmol/L)	7.31 ± 2.71	9.30 ± 4.55	3.286[*]	0.001
Cr (μmol/L)	87.18 ± 25.79	104.45 ± 34.57	3.419[*]	0.001
FT3 (pmol/L)	4.36 ± 1.91	3.65 ± 0.83	−3.062[*]	0.003
FT4 (pmol/L)	20.05 ± 8.56	19.59 ± 9.09	−0.313[*]	0.760
TSH (mIU/L)	3.37 ± 2.36	4.92 ± 5.60	2.019[*]	0.050
Medications, *n/N* (%)				
ACEI	53/70 (62.4)	33/44 (54.1)	0.007[†]	0.930
β blocker	64/69 (75.3)	42/45 (68.9)	0.014[†]	0.910
Antisterone	58/69 (75.3)	40/45 (65.6)	0.527[†]	0.470
Digoxin	19/69 (22.4)	20/45 (32.8)	3.460[†]	0.060
Diuretic	57/70 (67.1)	41/45 (67.2)	2.039[†]	0.150
Devices, *n/N* (%)				
ICD	10/85 (11.8)	3/58 (4.9)	1.813[†]	0.180
CRT	11/84 (12.9)	10/58 (16.4)	0.468[†]	0.490
CRTD	10/84 (11.8)	12/58 (19.7)	2.022[†]	0.160

All data are displayed as *n* (%) or mean ± standard deviation. [*]*t* value. [†]χ^2 value. RBC: Red blood cell; HGB: Hemoglobin; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; BUN: Blood urea nitrogen; Cr: Creatinine; FT3: Free triiodothyronine; FT4: Free thyroxin; TSH: Thyroid-stimulating hormone; ACEI: Angiotensin converting enzyme inhibitor; ICD: Implantable cardiac defibrillator; CRT: Cardiac resynchronization therapy; CRTD: Cardiac resynchronization therapy defibrillator.
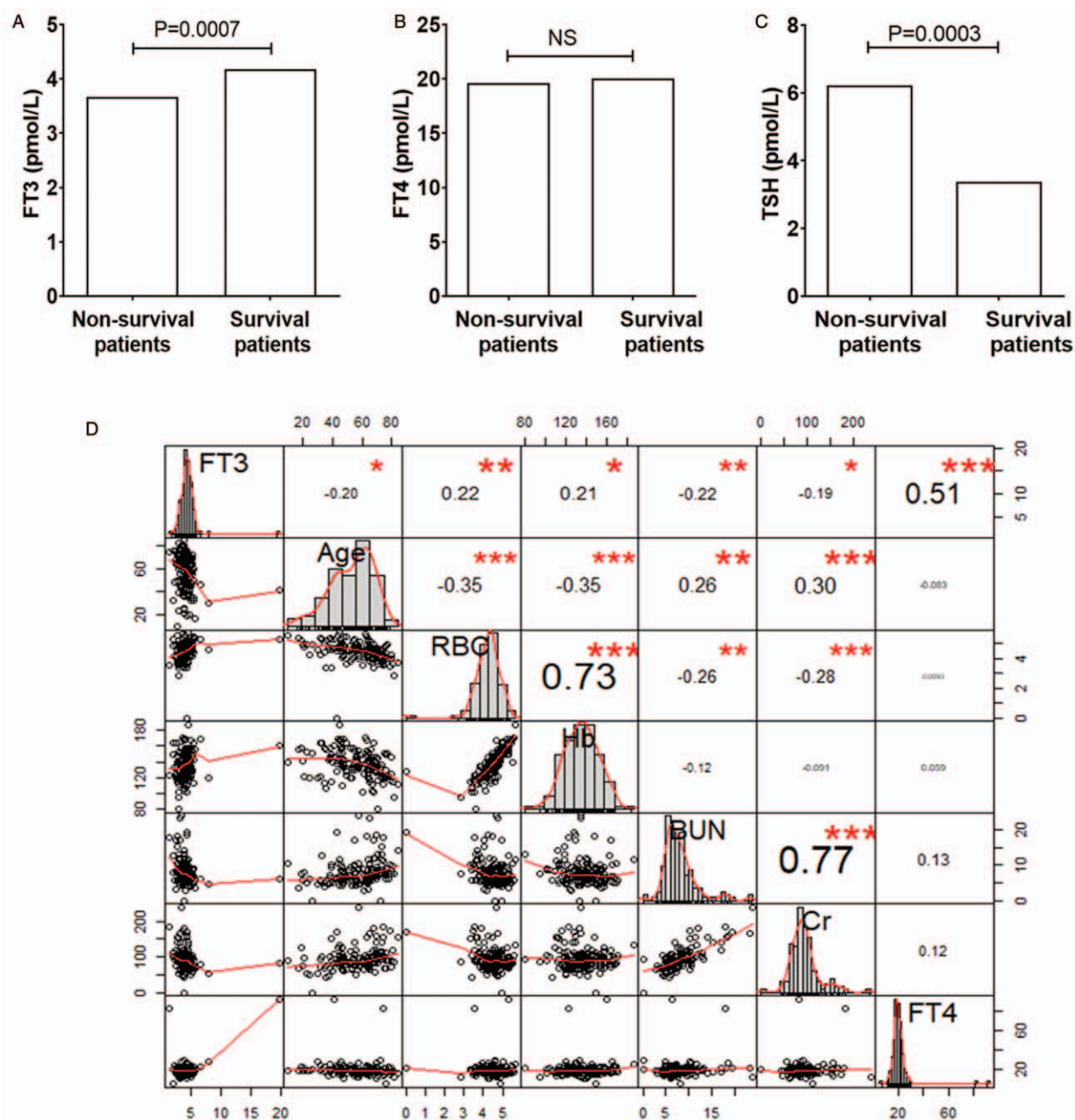
Figure 1: Plasma levels of (A) FT3, (B) FT4, and (C) TSH according to survival state. (D) Correlation of variables in DCM. The diagonals show the distribution; the lower left part shows a two-variable scatter diagram with fitting lines; the upper right shows the correlation coefficient and significance level, and the numbers represent the correlation coefficient. *P < 0.05; **P < 0.01; ***P < 0.001. FT3: Free triiodothyronine; FT4: Free thyroxin; TSH: Thyroid-stimulating hormone; DCM: Dilated cardiomyopathy.

P < 0.05). And in contrast, FT3 showed negatively correlation with age (r = −0.20, P < 0.05), BUN (r = −0.22, P < 0.01) and Cr (r = −0.19, P < 0.05) [Figure 1D].

According to the quartile method of FT3 level, 146 patients were divided into four groups: Q1 group FT3 ≤ 3.49 pmol/L (n = 37), Q2 group FT3 from 3.50 to 3.99 pmol/L (n = 36), Q3 group FT3 4.00 to 4.54 pmol/L (n = 37), Q4 group FT3 > 4.54 pmol/L (n = 36). Patients in the Q1 group suffered from the highest risk for all-cause mortality (P for log-rank = 0.001) [Figure 2]. The univariate analysis for all-cause mortality showed that the concentration

of FT3 was an independent predictor of all-cause mortality in DCM patients (hazard ratio 0.43, 95% CI 0.27–0.67, P < 0.001). Other variables such as age, HDL-C (P = 0.02), BUN (P = 0.01), Cr (P = 0.003), and DBP (P = 0.004) were also found to be associated with the endpoint, respectively (P all < 0.05) [Table 3]. Finally, a multivariate model was constructed based on inclusion of quartiles of FT3 as a continuous variable. In this multivariate Cox regression analysis, FT3 level was significantly associated with all-cause mortality (hazard ratio: 0.70, 95% CI 0.52–0.95, P for trend = 0.021) [Table 4].
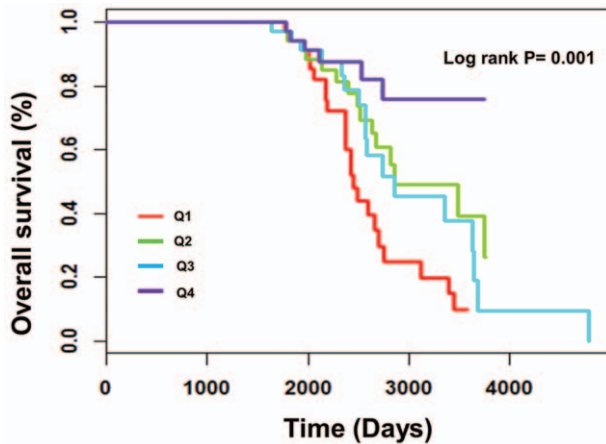
Figure 2: Kaplan-Meier survival curves comparing the probability of outcomes for all-cause mortality. The survival curves show significant difference in FT3 quartile 1 to 4 groups (P = 0.001, log-rank test). FT3: Free triiodothyronine.

Table 3: Univariate Cox analysis for all-cause mortality in patients with dilated cardiomyopathy.

Items	HR	95% CI	P values
FT3 (pmol/L) (per 1 SD)	0.43	0.27–0.67	<0.001
Age (years)	1.04	1.02–1.07	0.001
Male, n (%)	0.86	0.38–1.94	0.710
HGB (g/L)	0.98	0.96–1.00	0.060
HDL-C (μmol/L)	0.25	0.08–0.82	0.020
BUN (mmol/L)	1.15	1.04–1.27	0.010
Cr (μmol/L)	1.02	1.01–1.03	0.003
DBP (mmHg)	0.96	0.93–0.99	0.004

HR: Hazard ratio; CI: Confidence interval; FT3: Free triiodothyronine; HGB: Hemoglobin; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; BUN: Blood urea nitrogen; Cr: Creatinine; DBP: Diastolic blood pressure.

Table 4: Multivariate Cox analysis for all-cause mortality in patients with dilated cardiomyopathy.

Items	HR	95% CI	P values
Age (years)	1.01	0.99–1.03	0.357
Male, n (%)	0.70	0.33–1.50	0.363
HGB (g/L)	1.00	0.98–1.02	0.875
HDL-C (μmol/L)	0.46	0.18–1.15	0.097
BUN (mmol/L)	0.99	0.88–1.10	0.821
Cr (μmol/L)	1.00	0.99–1.01	0.614
DBP (mmHg)	1.00	0.97–1.02	0.677
FT3 (pmol/L)	0.70	0.52–0.95	0.021

This model was constructed based on inclusion of quartiles of FT3 as a continuous variable. HR: Hazard ratio; CI: Confidence interval; HGB: Hemoglobin; HDL-C: High-density lipoprotein cholesterol; BUN: Blood urea nitrogen; Cr: Creatinine; DBP: Diastolic blood pressure; FT3: Free triiodothyronine.

Discussion

The main findings in this study were that thyroid dysfunction showed to be of predictive value for poor prognosis for DCM. The result strongly suggests that patients with low levels of FT3 have increased mortality in long-term prognosis compared to those with normal levels of FT3. After adjusting for conventional risk factors, low FT3 levels were still independently associated with poor long-term outcomes. In other words, low thyroid function may contribute to poor long-term prognosis in DCM.

Previous studies have shown that down-regulation of thyroid function frequently occurs in cardiac diseases, which can be explained by an adaptive response to lower metabolic consumption. Other animal experiments and clinical studies have shown that there are important changes in cardiac structure and function with subclinical hypothyroidism.[21,22] Hypothyroid status was a strong predictor of poor prognosis in DCM patients,[23] which might be associated with worse systolic and diastolic function, larger heart chambers, and lower flow velocities in the left atrial appendage.[24] Hypothyroidism causes a hypodynamic circulation, characterized by decreased cardiac contractility, decreased preload, and increased systemic vascular resistance, which causes significant elevations in DBP. Dysregulation of the renin-angiotensin-aldosterone system in hypothyroidism may contribute to these states.[25] Our study found that the non-survival group shows a lower DBP trend which can be explained by the decompensation of the renin-angiotensin-aldosterone system. The results in this study have been mirror in similar researches.

The down-regulation of FT3 levels was thought to be adaptive mechanisms to diseases by reducing catabolism and conserving energy expenditure.[26] Although low FT3 status is thought to have a beneficial effect on the activation of adaptive mechanisms under stress for long periods of time, some studies have shown that low FT3 levels may have adverse prognostic effects in various acute and chronic heart diseases. The relationship between HF and TH changes resembles a vicious circle where impairment in heart function leads to lower T3 levels which in turn further decrease contractility and diastolic dysfunction. Theoretically, early detection and intervention are very important. In clinical work, HF treatment is mostly treated with levothyroxine sodium on the basis of conventional treatment, and it is a low-dose treatment. In this way, TH level in HF patients can be improved, especially FT3 level. Abnormal expression of inflammatory cytokines can be significantly observed through neuroendocrine and other reactions of the body, so as to reduce its damage to myocardial cells and improve cardiac function. However, the effect of T3 supplementation in patients with DCM remains to be further investigated. Stimulation of the TH axis by continuous infusion of the hypothalamic releasing factor seems to have clinical benefits. Thyroid hormone receptor-specific agonists may also be used to selectively treat these patients. DCM is a serious threat to human health myocardial diseases. More research is still needed on the etiology, pathogenesis and treatment of the disease. We expect that large randomized clinical trials will confirm the efficacy of low FT3 levels in the treatment of specific diseases.

There are also some interesting findings in our baseline data. In this study, age is associated with all-cause mortality in DCM patients. We found that older age indicates poor long-term prognosis ($P < 0.001$) [Table 1]. Anemia and renal dysfunction were much more prevalent in the non-survival groups with lower levels of HGB and RBC, but higher levels of BUN and Cr. Maybe it can be explained by that renal dysfunction was an independent predictor of increased risk of anemia in HF, so it can be easily understood the simultaneous high prevalence of these two diseases.[27] Lower levels of HDL-C are found in the non-survival group, previous studies had confirmed that high HDL-C levels are associated with better outcome in patients with CAD with HF.[28] and we think it is also the same in DCM. However, the relationship between DCM and HDL-C levels is unclear. Hypertension ($P = 0.23$), diabetes ($P = 0.30$), chronic kidney diseases ($P = 0.76$), and many risk factors are prognosis for poor long-term death in patients with cardiac diseases. However, in this study, these factors failed to reach statistical significance ($P > 0.05$) [Table 2].

Limitation

There are some limitations in this study: (1) all patients were from a single center, and therefore the results may not be generalizable to other clinical settings. (2) Thyroid hormone measurements were performed only at admission for DCM. Whether FT3 would change after discharge is unknown. (3) The role of FT3 levels in DCM needs to be further evaluated in a large population.

In conclusion, in DCM patients, FT3 levels have a gradual and independent relationship with the occurrence of all-cause mortality and it will provide physicians with more comprehensive information with implications for TH therapeutic efficiency in DCM.

Funding

Conflicts of interest

None.

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