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Original Article

Prevalence of non-thyroidal illness syndrome and 2-year survival in elderly male inpatients

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Abstract: This study aimed to investigate the relationship between FT_3, TT_3 and nutritional status, liver and kidney function, chronic diseases and the effects of FT_3 and TT_3 on mortality. Using a cross-sectional study design, a survey was carried out among 931 male subjects aged 60 or over who were hospitalized between January 2012 and December 2013. All patients were divided into nonthyroidal illness syndrome (NTIS) and control group according to whether the patient was complicated by NTIS. Indicators surveyed included thyroid hormone levels, liver and kidney function, chronic diseases which might affect survival. The correlations between T_3 and these indicators and the value of NTIS in predicting 2-year mortality were also analyzed. Respiratory and cardiovascular diseases are the most common reasons of NTIS. TP, Alb, PA, Hb, BMI, UA, ALT and AST levels of NTIS group were lower compared to non-NTIS group, with UN and Cr levels higher compared to non-NTIS group. TT_3 levels had positive correlations with TP, Alb, PA, Hb, BMI, UA and ALT. TT_3 levels correlated negatively with AST, UN and Cr. FT_3 levels had positive correlations with TP, Alb, PA, Hb, BMI and UA. They had negative correlations with ALT, AST, UN and Cr. The probability of lower levels of FT_3 and TT_3 always coexisted with chronic kidney disease (CKD). The mortality of the NTIS group was higher than that of the control group. As the decline of thyroxine TP, Alb, PA, Hb and BMI or increase of UN and Cr or presence of respiratory diseases, CKD or tumors, the mortality of patients increased. After correction of other factors, as the decline of TT_3, FT_4, Alb, PA and BMI or increase of UN or presence of CKD or tumors, the mortality of patients increased. Even a greater proportion of elderly male inpatients were combined with NTIS of higher severity and lower two-year survival.

Keywords: Elderly male, NTIS, mortality

Introduction

Thyroid gland is the largest endocrine gland in human, and secretes thyroid hormones, which play pivotal roles in growth, substance and energy metabolism. Aging, chronic disease [1, 2], tumors [3] and severe diseases [4] can all alter thyroid function. Typically, the level of thyroid stimulating hormone remains normal or at a normal low level, while the serum level of T_3 decreases, that of rT_3 increases and that of T_4 is normal. This condition combined with an absence of hypothyroidism is known as nonthyroidal illness syndrome (NTIS) [5]. NTIS is common clinically. Simons RJ et al. [6] reported that 65% of the inpatients aged 60 and above were combined with NITS. It is generally believed that NTIS is a self-protective mechanism in response to reduced energy metabolism. NTIS may be favorable for the recovery of diseases and many researchers consider it as a prognostic marker.

With the prolongation of life expectancy, China has entered the elderly society. With the combination of a variety of chronic diseases, it is difficult to judge the prognosis of the disease. Elderly male patients account for a greater proportion at our department, and many of them are combined with several chronic diseases. A multiplicity of prognostic factors may be involved in it. We have also noticed that many inpatients are combined with NTIS, which is associated with more severe condition and worse prognosis. In order to determine the prognostic value of NTIS in elderly male

Table 1. Underlying diseases and constituent ratios in NTIS group

Underlying diseases	Cases	Constituent ratios (%)
Respiratory diseases	80	41.45
Cardiovascular diseases	30	15.54
Nervous system diseases	21	10.88
Digestive disorders	18	9.33
CKD	13	6.74
Surgical diseases	12	6.22
Tumor	12	6.22
Other	7	3.63
Total	193	100

patients, we designed and carried out the present study. This study focused on the elderly male inpatients, who were tested for thyroid hormone levels. The correlations between TT_3 and FT_3 and TP, Alb, PA, Ur, Cr, UA, ALT, AST and Hb, as well as the chronic diseases that might affect life were analyzed. The effect of NTIS on 2-year survival was evaluated.

Material and methods

Subjects

Inclusion criteria: (1) male; (2) age greater than or equal to 60 years old; (3) hospitalized in our hospital from January 2012 to December 2013; (4) thyroid function during hospitalization. Those with the following conditions were excluded: (1) confirmed as hyperthyroidism; (2) thyroid diseases such as hypothyroidism, subclinical hyperthyroidism, subclinical hypothyroidism or Hashimoto's thyroiditis; (3) currently on amiodarone and Euthyrox; (4) history of thyroid surgery. A total of 931 patients were enrolled in the study. They were divided into NTIS group and non-NTIS group, with 193 subjects in the NTIS group and 738 subjects in the non-NTIS group; the prevalence of NTIS was 20.73%. They were included upon the first testing of thyroid functions, and 2-year survival was observed. The study was approved by the ethics committee of General Hospital of PLA.

Methods

The clinical data of the cases were reviewed, including the reasons for visit, history of cardiovascular diseases (coronary heart disease, hypertension, arrhythmia, and heart failure), respiratory diseases (pulmonary infection, chronic obstructive pulmonary disease, and chronic bronchitis), nervous system diseases (cerebral infarction, and cerebral hemorrhage), diabetes, cancer, and chronic kidney disease (CKD). The medical history was recorded.

The subjects were fasted on the night before, and venous blood samples were collected 8-10 h later in the morning. The levels of TT_4, TT_3, FT_3, FT_4, TSH, TP, Alb, PA, Ur, Cr, UA, ALT, AST and Hb were detected. Radioimmunoassay (RIA) was used to detect the serum levels of TT_3, FT_3, TT_4, FT_4 and TSH. Sysmex Xt-1800 Automated Hematology Analyzer (SYSMEX) was used for routine blood test. Biochemistry measurement was performed with i-CHROMA Reader (Boditech Med Lnc). The normal ranges of thyroid hormone levels were as follows: TT_4 55.34-160.88 nmol/L, TT_3 1.01-2.95 nmol/L, FT_3 2.76-6.3 pmol/L, FT_4 10.42-24.32 pmol/L, TSH 0.35-5.5 uIU/mL. Intrabatch CV<3.35%, and interbatch CV<5.04%.

Diagnostic criteria for NTIS

NTIS was diagnosed when the serum level of TT_3 and (or) FT_3 was decreased, and the TT_4 or FT_4 level was normal or mildly decreased, with normal TSH [7].

Statistical analysis

SPSS 20.0 software was used for statistical analyses. Measurements obeying normal distribution were expressed as mean ± standard deviation ($\bar{x}$ ± s). t-test or *t'*-test was used for intergroup comparisons, and one-way ANOVA was employed to the means among multiple groups. Counts were analyzed by χ^2 test or Fisher's test. Coexistence of lower T_3 levels with concurrent chronic diseases was analyzed using correspondence analysis model. Multiple correspondence analysis is a dimension reduction technique which plays a large role in the analysis of tables with categorical nominal variables. The two variables were correlated with each other, and the two were located in the same quadrant and close to each other. All tests were two-sided. Kaplan-Meier analysis was used to generate survival-time data, and difference in the survival between the two groups was analyzed using Log-rank test.

Table 2. Comparison of thyroid function between NTIS group and non-NTIS group ($\bar{x} \pm s$)

	Total (n=931)	NTIS group (n=193)	Non-NTIS group (n=738)	*t*	*P*
Age (year)	86.2±8.1	87.9±6.0	85.7±8.6	4.120	<0.001
TT_4 (nmol/L)	86.9±17.1	75.2±16.4	90.0±15.9	-11.473	<0.001
TT_3 (nmol/L)	1.3±0.3	0.9±0.2	1.4±0.3	-33.684	<0.001
FT_3 (pmol/L)	3.7±0.9	2.6±0.5	4.0±0.7	-28.606	<0.001
FT_4 (pmol/L)	16.0±2.7	15.6±2.9	16.1±2.6	-2.155	0.031
TSH (uIU/mL)	2.1±1.1	2.0±1.2	2.2±1.1	-2.008	0.046

Table 3. Comparison of baseline data between the two groups

	Total	NTIS group	Non-NTIS group	*t*	*P*
TP (g/L)	66.1±7.9	64.1±8.2	66.6±7.8	-3.959	<0.001
ALb (g/L)	38.3±4.8	34.6±5.1	39.3±4.2	-12.984	<0.001
PA (mg/dl)	21.5±8.4	18.4±10.9	22.9±6.7	-5.381	<0.001
Hb (g/L)	119.0±20.9	109.1±24.0	121.9±18.9	-7.659	<0.001
BMI (kg/m^2)	21.5±7.9	12.9±12.2	24.1±3.0	-12.609	<0.001
UA (umol/L)	337±99.7	317.6±122.2	342.8±92.2	-2.674	0.008
ALT (U/L)	20.0±29.9	19.2±18.8	20.2±32.3	-0.449	0.653
AST (U/L)	23.0±24.8	22.9±14.9	23.0±26.8	-0.105	0.939
UN (mmol/L)	7.8±4.9	10.3±8.3	7.1±3.2	5.237	<0.001
Cr (umol/L)	94.7±63.5	119.7±121.4	88.1±31.9	3.578	<0.001

Results

TT_4, FT_4, TT_3, FT_3 and TSH levels in non-NTIS group were higher than that in NTIS group

In order to investigate whether the incidence of NTIS was correlated with underlying diseases, chronic diseases were concerned. Of 193 NTIS patients, respiratory diseases and cardiovascular diseases were the most common reasons of NTIS (**Table 1**).

There were 193 cases in the NTIS group, and 739 cases in the non-NTIS group, the control group. The age of cases in the non-NTIS group was significantly smaller than that in the NTIS group (P<0.001). TT_4, TT_3 and FT_3 levels were higher in the non-NTIS group than those in the NTIS group (P<0.001). FT_4 (*P*=0.031) and TSH (*P*=0.046) were higher in the non-NTIS group than those in the NTIS group (**Table 2**).

Comparison of baseline data between the two groups

Levels of TP, Alb, PA, Hb and BMI were significantly lower in the NTIS group than in the non-NTIS group (P<0.001). UA, ALT and AST levels of the NTIS group were respectively lower than those of the non-NTIS group (P=0.008; P=0.653; P=0.939). UN and Cr levels of the NTIS group (P<0.001 and P<0.001) were higher compared with the non-NTIS group (**Table 3**).

Correlations between T_3 levels and other tested indicators

TT_3 levels had positive correlations with TP (*r*=0.137, *P*<0.001), Alb (*r*=0.410, *P*<0.001), PA (*r*=0.244, *P*<0.001), Hb (*r*=0.386, *P*<0.001), BMI (*r*=0.443, P<0.001), UA (*r*=0.100, *P*=0.008) and ALT (*r*=-0.051, *P*=0.121). TT_3 levels correlated negatively with AST (*r*=-0.111, *P*=0.001), UN (*r*=-0.310, *P*<0.001) and Cr (*r*=-0.193, *P*<0.001).

FT_3 levels had positive correlations with TP (*r*=0.125, *P*<0.001), Alb (*r*=0.470, *P*<0.001), PA (*r*=0.285, *P*<0.001), Hb (*r*=0.384, *P*<0.001), BMI (*r*=0.456, *P*<0.001) and UA (*r*=0.137, *P*<0.001). They had negative correlations with ALT (*r*=-0.818, *P*=0.059), AST (*r*=0.-808, *P*=0.072), UN (*r*=-0.241, *P*<0.001) and Cr (*r*=-0.173, *P*<0.001) (**Table 4**).

Lower T_3 levels was associated with concurrent CKD

The role of chronic diseases that might affect the prognosis was analyzed, according to the WHO's list of the 10 leading causes of death. The chronic diseases considered were cardiovascular diseases (coronary heart disease, hypertension, arrhythmia, and heart failure), respiratory diseases (pulmonary infection, chronic obstructive pulmonary disease, and chronic bronchitis), nervous system diseases (cerebral infarction, and cerebral hemorrhage), diabetes, cancer, and CKD. Correspondence analysis models were constructed for TT_3 and FT_3 related to the 6 categories of chronic diseases, respectively. There was coexistence of

Table 4. Correlations between T_3 levels and other tested indicators

	TT_3		FT_3	
	r	*P*	*r*	*P*
TP	0.137	<0.001	0.125	<0.001
ALb	0.410	<0.001	0.470	<0.001
PA	0.244	<0.001	0.285	<0.001
Hb	0.386	<0.001	0.384	<0.001
BMI	0.443	0.003	0.456	<0.001
UN	-0.310	<0.001	-0.241	<0.001
Cr	-0.193	<0.001	-0.173	<0.001
UA	0.100	0.003	0.137	<0.001
ALT	-0.051	0.114	-0.818	0.059
AST	-0.111	0.001	-0.808	0.072

lower levels of TT_3 and FT_3 with different chronic diseases (**Figures 1**, **2**).

Among 931 cases, TT_3 levels decreased in 157 cases, accounting for 16.9%. It can be seen from the correspondence analysis model that lower TT_3 levels and concurrent CKD were located in the right lower quadrant, indicating the high probability of the coexistence of the two conditions (**Figure 1**).

Among 931 cases, TT_3 levels decreased in 127 cases, accounting for 13.6%. It can be seen from the correspondence analysis model that lower FT_3 levels and concurrent CKD were located in the right upper quadrant, indicating the high probability of the coexistence of the two conditions (**Figure 2**).

Comparison of mortality between the NTIS group and the non-NTIS group

At the end of 2-year follow-up, 169 cases died, including 69 deaths in the NTIS group (35.7%) and 100 deaths in the non-NTIS group (13.5%); the overall mortality was 18.15%, and the overall survival rate was 79.27%. The medical records of the death cases were reviewed, and the reasons and time of deaths were recorded. The survival rates of the two groups decreased over time, and the cumulative survival rate of the NTIS group was significantly lower than that of the non-NTIS group (*log-rank* χ^2=60.332, *P*<0.001) (**Figure 3**).

The deregulated T_3 levels correlated with the mortality of patients

Among the 931 cases, TT_3 levels decreased in 157 cases and FT_3 levels decreased in 127 cases; 91 cases had a decrease in both TT_3 and FT_3 levels. According to the univariate Cox regression model, as the decline of thyroxine, TP, Alb, PA, Hb and BMI or increase of UN and Cr or presence of respiratory diseases, CKD or tumor, the mortality of patients increased. After correction of other factors, as the decline of TT_3, FT_4, Alb, PA and BMI or increase of UN or presence of CKD or tumor, the mortality of patients increased (P<0.001) (**Table 5**).

Discussion

Many elderly inpatients are combined with several chronic diseases. Though there is usually an absence of clinical manifestations of thyroid disease, thyroid function testing usually reveals abnormally high thyroid hormone levels. Typically, T_3 levels decrease or both T_3 and T_4 levels decrease, without an apparent increase of rT_3 levels. While the thyroid hormone levels decrease, pituitary TSH levels are usually normal or decreased instead. This condition is known as NTIS, which is closely associated with the nutritional status, kidney function and prognosis of patients. This study shows that in the elderly male population, the nutritional status and kidney function in the NTIS group were lower. And, the probability of lower levels of FT_3 and TT_3 always coexisted with chronic kidney disease (CKD). The mortality of the NTIS group was higher than that of the control group. NTIS patients were in a poor general condition and the 2-year survival rate was lower. NTIS is an independent risk factor for the prognosis of patients.

Proteins are indicators of nutritional status and play an important role in the synthesis and transport of thyroid hormones. Albumin, prealbumin, total protein BMI and uric acid are important indicators of nutritional status. Our results indicated that these indicators were lower in the NTIS group as compared with the non-NTIS group. Correlation analysis also demonstrated that these indicators decreased along with lower TT_3 and FT_3 levels, which meant worse nutritional status in the NTIS group. Kaptein, E. M. et al. [8] found that negative nitrogen balance occurred in response to hunger, which might lead to NTIS. This is consistent with our findings. Under low energy intake, albumin reduction will lead to decreased conversion from T_4 to T_3 and a decrease in the T_3 level [9]. Thyroid hormones cannot be trans-

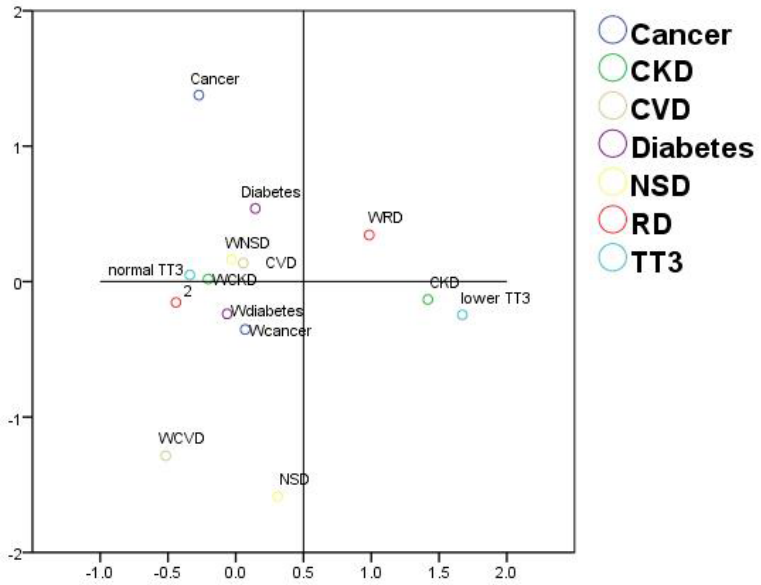

Figure 1. Lower TT_3 levels and concurrent CKD were located in the right lower quadrant. RD, Respiratory diseases; WRD, Without respiratory diseases; NSD, Nervous system diseases; WNSD, Without nervous system diseases; Wdiabetes, Without diabetes; CVD, Cardiovascular diseases; WCVD, Without cardiovascular diseases; Wcancer, Without cancer; WCKD, Without CKD.

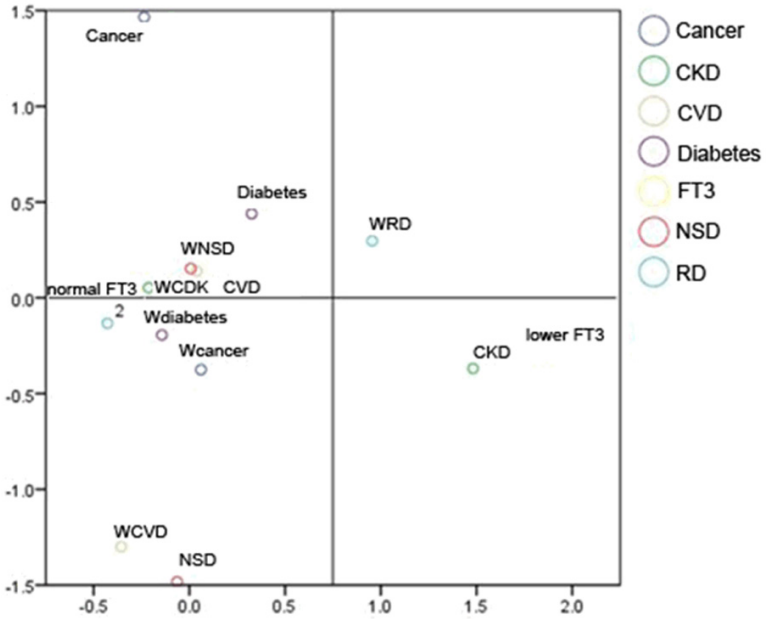

Figure 2. Lower FT_3 level and concurrent CKD were located in the right upper quadrant. RD, Respiratory diseases; WRD, Without respiratory diseases; NSD, Nervous system diseases; WNSD, Without nervous system diseases; Wdiabetes, Without diabetes; CVD, Cardiovascular diseases; WCVD, Without cardiovascular diseases; Wcancer, Without cancer; WCKD, Without CKD.

ported unless being bound to plasma albumin. However, thyroid hormones bound to the carrier proteins are not easily cleared by the kidney. As less albumin is synthesized, there will be a reduction in the protein-bound thyroid hormones, and the thyroid hormones will be cleared at an accelerating rate. Since a larger proportion of T_3 binds to albumin compared to T_4, there will be a greater reduction in the T_3 level compared to the T_4 level. Moreover, hunger also inhibits TRH expression, thus reducing the synthesis of thyroid hormones [10]. Han G et al. [11] reveal that because thyroid hormones are involved in energy metabolism, low thyroxine may lead to malnutrition. Hypoproteinemia and elderly age are also the risk factors of NTIS. In other words, NTIS and malnutrition have simultaneously causal effects upon each other.

In the human body, two thirds of the uric acid is excreted through the kidney. When glomerular filtration rate (GRF) decreases as a result of abnormal renal function, the uric acid level will increase. In malnutrition, albumin and prealbumin levels decrease, leading to a reduction in uric acid. Therefore, for CKD combined with malnutrition, the uric acid level will increase or decrease. In the NTIS group, the uric acid level was lower than that of the non-NTIS group, indicating that the degree of reduction of uric acid levels caused by malnutrition exceeded the degree of increase of uric acid levels caused by CKD.

In addition, the hemoglobin level of the NTIS group was lower than that of the non-NTIS group. Correlation analysis indicated that T_3 levels correlated negatively with hemoglobin levels. Hence the T_3 level was related to hemoglobin metabolism. Thyroid hormone deficiency

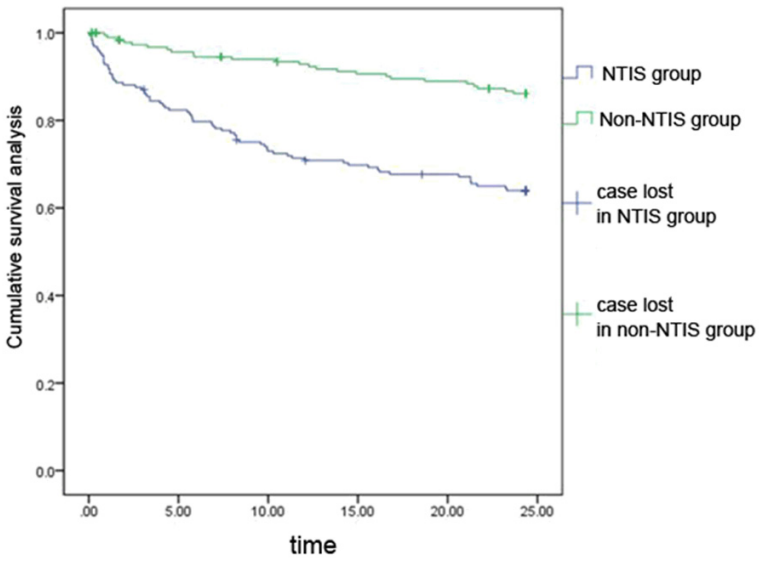

Figure 3. Survival curves of the two groups. The survival rates of the two groups decreased over time, and the cumulative survival rate of the NTIS group was significantly lower than that of the non-NTIS group (P<0.001). NTIS, Nonthyroidal illness syndrome; Non-NTIS.

and anemia have mutual influence upon each other [12]. Bremner AP et al. [13] surveyed 1179 subjects with normal thyroid function or mild thyroid dysfunction. They found that FT_4 and FT_3 levels had positive correlation with the hemoglobin level and that TSH also correlated negatively with the hemoglobin level. Any mild changes of thyroid hormones will cause the changes of hemoglobin levels. Anemia can also lead to the reduction in thyroid hormones. This is probably because anemia can lead to hypoxia and alter the regulatory effect by the central nervous system to the thyroid hormone metabolism [14]. Hess SY et al. [14] showed that iron deficiency anemia caused a reduction in thyroid hormone levels by reducing the activity of thyroid peroxidase. This condition can be corrected by taking iron supplement.

In the present study, levels of urea and creatinine were higher in the NTIS group compared with the non-NTIS group. Correlation analysis indicated negative correlations between FT_3 and TT_3 levels and levels of urea and creatinine. Correspondence analysis showed that there was a higher probability of coexistence between lower levels of FT_3 and TT_3 and CKD. These results indicated that the kidney was closely related to synthesis secretion and metabolism of thyroid hormones, and CKD can lead to abnormal thyroid hormone levels through several pathways: (1) Disorder of thyroid hormone synthesis [15]. Iodides are cleared in the kidney through glomerular filtration. The reduction in GFR caused by kidney diseases will reduce the excretion of iodides. As the level of iodides increases in the blood circulation, the iodine uptake of the thyroid gland increases; (2) Reduced conversion from T_4 to T_3 [16]. Activity of deiodinase decreases in CKD patients due to impairment of kidney function, which results in a reduction of T_3 levels; (3) Changes in the level of thyroid hormone-related proteins. Over 99% of T_3 and T_4 in the blood bind to carrier proteins, and only less than 1% are transported freely. The two states are mutually convertible. Free T_3 and T_4 are the active forms, which performs psychological function in the target cells. Thyroid hormones in a bound state serve as the reservation and are not filtered through the glomeruli. However, for CKD patients, thyroid hormones in bound state will be also secreted through urine, leading to a reduction in TT_3 and TT_4 levels. This can be corrected by heavy proteinuria and a large dose of glucocorticoids which inhibit protein synthesis; (4) End-stage renal disease (ERSR) can cause a reduction in the tubular reabsorption rate, an increase of glomerular permeability and glomerulotubular imbalance. As T_3 and T_4 in a bound state are secreted through the urine, the thyroid hormone levels decline dramatically. Moreover, ESRD patients maintain negative nitrogen balance by reducing catabolism, which further causes a reduction in the T_3 and T_4 levels; (5) Endotoxins, such as BUN and PTH, accumulate in ESRD patients, which further affects the conversion from T_4 to T_3. Besides, toxins can inhibit the binding of T_4 to the carrier proteins, affecting the transport of T_4 and reducing the T_4 level. Some CKD patients are treated with heparin anticoagulation, which also interferes the binding of T_4 to thyroglobulin; (6) CKD has an impact on HPT axis

Table 5. The correlation between thyroid function and the death risk

	β	Univariate *HR*	95% *CI*	*P*	*β*	Multi-variate *HR*	95% *CI*	*P*
Age (1)	*1.815*	*6.134*	*1.508-25.000*	*0.011*	*0.745*	*2.106*	*0.419-10.594*	*0.366*
Age (2)	*0.839*	*2.315*	*1.1161-4.7847*	*0.024*	*0.781*	*2.184*	*0.503-9.487*	*0.297*
Age (3)	*0.185*	*1.2034*	*0.8811-1.6420*	*0.245*	*0.535*	*1.707*	*0.383-7.609*	*0.483*
TT_4 (umol/L)	*1.020*	*2.773*	*1.417-5.427*	*0.003*	*0.040*	*1.041*	*0.461-2.347*	*0.923*
TT_3 (umol/L)	*1.102*	*3.009*	*2.187-4.140*	*<0.001*	*0.627*	*1.873*	0.405-0.705	<0.001
FT_3 (pmol/L)	*1.111*	*3.038*	*2.174-4.245*	*<0.001*	*0.411*	1.508	0.693-3.289	0.300
FT_4 (pmol/L)	*1.510*	*4.529*	*1.445-14.196*	*0.010*	*1.343*	*3.831*	*0.925-15.869*	*0.064*
TP (g/L)	*1.586*	*4.882*	*2.713-8.785*	*<0.001*	*0.790*	*2.202*	*1.149-4.222*	*0.017*
Alb (g/L)	*1.496*	*4.462*	*3.298-6.037*	*<0.001*	*0.581*	*1.787*	*1.213-2.634*	*0.003*
PA (mg/dl)	*1.368*	*3.929*	*2.899-5.324*	*<0.001*	*0.694*	*2.001*	*1.334-3.000*	*0.001*
Hb (g/L)	*1.569*	*4.800*	*2.252-10.231*	*<0.001*	*0.487*	*1.627*	*0.727-3.644*	*0.237*
BMI (kg/m^2)	*-0.099*	*0.906*	*0.853-0.963*	*0.001*	*0.178*	*1.195*	*1.106-1.290*	*<0.001*
UN (mmol/L)	*1.264*	*3.541*	*2.580-4.860*	*<0.001*	*0.950*	*2.585*	*1.758-3.800*	*<0.001*
Cr (umol/L)	*0.730*	*2.075*	*1.494-2.883*	*<0.001*	*0.153*	*1.166*	*0.737-1.842*	*0.512*
UA (umol/L)	*0.143*	*1.153*	*0.737-1.806*	*0.532*	*0.048*	*1.049*	*0.633-1.740*	*0.852*
RD	*1.271*	*3.566*	*2.628-4.839*	*<0.001*	*0.331*	*1.393*	*0.960-2.020*	*0.081*
NSD	*0.063*	*1.065*	*0.645-1.759*	*0.805*	*0.019*	*1.019*	*0.578-1.795*	*0.948*
CVD	*0.522*	*1.685*	*0.937-3.031*	*0.081*	*0.026*	*1.026*	*0.552-1.908*	*0.953*
CKD	*1.027*	*2.793*	*1.969-3.961*	*<0.001*	*0.790*	*2.204*	*1.376-3.528*	*0.001*
Tumor	*1.136*	*3.115*	*2.293-4.232*	*<0.001*	*1.089*	*2.970*	*2.078-4.245*	*<0.001*
Diabetes	*0.138*	*1.148*	*0.833-1.582*	*0.398*	*0.037*	*1.038*	*0.737-1.462*	*0.832*

HR, hazard ratio; 95% *CI*, 95% confidence interval; RD, Respiratory diseases; NSD, Nervous system diseases; CVD, Cardiovascular diseases; CKD, chronic kidney diseases.

and metabolism of thyroid hormones [15]. Thyroid gland is usually enlarged in CKD patients, with normal or mildly lower levels of TT_4, FT_4, TT_3 and FT_3. For these patients, abnormal thyroid function is caused by heavy proteinuria due to dysfunction of thyroxine 5'-deiodinase, rather than by thyroid gland diseases.

At the end of the 2-year follow-up in this study, 169 cases died, accounting for 18.2%. As indicated by survival analysis, mortality of both groups increased over time. The mortality was 35.7% in the NTIS group and 13.5% in the non-NTIS group, with significant difference. Thus NTIS is an independent predictor of higher all-cause mortality within 2 years. Selcuk Yazıcı et al. [17] observed 274 patients with acute coronary syndrome and found that the 1-month and 1-year mortality of those combined with NTIS was higher than that without NTIS, respectively. This agrees with our study. It has been proved through animal experiments [18] that thyroid hormones can promote angiogenesis, which may be the reason of lower mortality in the non-NTIS group in our study. However, the lower T_3 level is only a predictor of higher mortality. The lower T_3 level indicates greater severity of the disease and lower resistance to diseases; it is not a direct cause of death or poor diagnosis. Therefore, the true causes of death after 2 years are not necessarily the same as the causes of NTIS.

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Disclosure of conflict of interest

None.

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