European Geriatric Medicine (2023) 14:363–371
https://doi.org/10.1007/s41999-023-00761-6

RESEARCH PAPER

Analysis of clinical features and 7-year all-cause mortality in older male patients with non-thyroidal illness syndrome on general wards

Xinyu Miao[1] · Xiaomin Fu[1] · Hongzhou Liu[1] · Zhaoyan Gu[1] · Chunlin Li[1] · Kun Wang[2] · Xuefeng Chen[3] · Zhaohui Lyu[3] · Shuangtong Yan[1]

Received: 31 October 2022 / Accepted: 22 February 2023 / Published online: 22 March 2023

Key summary points

Aim The aim of the study was to investigate the association of non-thyroidal illness syndrome and all-cause mortality in older inpatients on general wards.

Findings Patients in the non-thyroidal illness syndrome group had a lower survival rate over 7 years follow-up. A lower free T_3 level was associated with higher risk of all-cause mortality. A higher free T_4 level in the normal range was associated with all-cause mortality risk even after adjusting for confounding factors.

Message The survival rate was lower in the non-thyroidal illness syndrome group. A reduced free T_3 level with low albumin and haemoglobin levels was associated with all-cause mortality; moreover, a higher free T_4 in the normal range may be a strong predictor for long-term mortality risk in hospitalised older male patients.

Abstract

Purpose Older patients with non-thyroidal illness syndrome (NTIS) have a poor prognosis. However, there are few studies on the association of NTIS and mortality among older inpatients on general wards. In a 7-year retrospective observational study, we aimed to investigate the clinical features of NTIS and the association of NTIS and all-cause mortality in older inpatients.

Methods A total of 959 older male inpatients whose average age was 86.3 ± 8.1 years were enrolled and divided into the NTIS group and non-NTIS group. Cox models were performed to explore the association of thyroid hormone level and mortality.

Results Patients had more respiratory disease and chronic kidney disease in the NTIS than in the non-NTIS group, especially in primary nursing care, respiratory failure and haemodialysis patients; serum total protein, albumin, prealbumin, haemoglobin, uric acid and high-density lipoprotein cholesterol levels were lower, and urea nitrogen and fasting blood glucose levels were higher, in the NTIS than in the non-NTIS group. Patients in the NTIS group had a lower survival rate over 7 years follow-up ($P < 0.01$). A lower free T_3 level was associated with all-cause mortality with a HR of 1.50 (1.36, 1.66). Lower free T_4 level was associated with reduced all-cause mortality with a HR of 0.91 (0.88, 0.94) even after adjusting for confounding factors ($P < 0.01$).

Conclusions Among older male inpatients, the survival rate was lower in the NTIS group. A reduced free T_3 level with low albumin and Hb levels was associated with all-cause mortality; moreover, a higher free T_4 in the normal range may be a strong predictor for long-term mortality risk in hospitalised older male patients.

Keywords NTIS · Mortality · Old age · Inpatients · General wards

Xinyu Miao and Xiaomin Fu contributed equally to this work.

✉ Zhaohui Lyu
metabolism301@126.com

✉ Shuangtong Yan
yanshuangtong@301hospital.com.cn

[1] Department of Endocrinology, The Second Medical Center & National Clinical Research Center for Geriatric Diseases, Chinese PLA General Hospital, No. 28 Fuxing Road, Haidian District, Beijing 100853, China

[2] Department of Neurology, The 3rd Hospital of Shijiazhuang, Shijiazhuang 050011, Hebei Province, China

[3] Department of Endocrinology, The First Medical Center, Chinese PLA General Hospital, No. 28 Fuxing Road, Haidian District, Beijing 100853, China

Introduction

Many changes in thyroid hormones occur as a result of illness or nutritional deprivation. These changes consist of decreased levels of serum triiodothyronine (T_3) and/or thyroxine (T_4), without an increase in the thyroid-stimulating hormone (TSH) level [1, 2]. The combination of these findings is termed non-thyroidal illness syndrome (NTIS), euthyroid sick syndrome, or low T_3 syndrome, indicating a systemic disease outside the thyroid that causes abnormal levels of thyroid hormones and is often considered a compensatory mechanism for the body. NTIS has been reported in patients with acute and chronic illnesses, including infectious diseases, cardiovascular and gastrointestinal diseases, cancer, and trauma [3, 4], which are quite common in patients in intensive care units (ICUs) [5, 6].

Older patients often have multiple chronic diseases and a poor nutritional status; thus, NTIS is quite common in these patients. Tognini [7] reported that among older patients (≥ 65 years of age) hospitalised for acute illness, the prevalence of NTIS was 31.9% and significantly associated with acute renal failure, New York Heart Association classification IV heart failure, and metastatic cancer. In previous studies, NTIS showed a high sensitivity and specificity for predicting patient mortality in ICU patients [8]. Serum T_3 levels further decrease as the severity of disease progresses. However, among hospitalised older patients on general wards, data on the association of NTIS and mortality are lacking.

In this study, we analyse clinical data from inpatients in advanced age with or without NTIS, and their long-term outcomes for 7 years, to investigate the association of NTIS and mortality.

Patients and methods

Study design

This study collected data from patients admitted to the First Medical Center and the Second Medical Center, Chinese PLA General Hospital retrospectively, and recorded their outcome in 7 years follow-up. The patients in our hospital with long term follow-up were military veterans, therefore, there were few female patients, the study only included male patients to reduce bias. The inclusion criteria for the study were as follows: (1) aged 60 years or above, (2) hospitalised between January 2011 and December 2012, because the electronic medical record in our hospital can be obtained from 2011, (3) admitted on general internal medicine wards and (4) complete data on thyroid function obtained within 1 day of admission. The exclusion criteria were as follows: (1) diagnosed with thyroid disease such as hyperthyroidism, hypothyroidism, subclinical hyperthyroidism, subclinical hypothyroidism, or Hashimoto's thyroiditis, (2) history of thyroid surgery, (3) taking amiodarone, levothyroxine, glucocorticoid, dopamine, or interferon. A total of 8552 patients were admitted to the hospital from January 2011 to December 2012, and 959 of whom were enrolled in the present study and followed up for 7 years, until December 2019 (see Fig. 1). A total of 35 patients (3.7%) were lost to follow up including 8 patients in the NTIS group, and 27 patients in the non-NTIS group for migration or the change of medical designated hospitals.

Venous blood samples were collected early in the morning after an overnight fast on the second day after admission, including thyroid hormone (total T_4, triiodothyronine, free T_3, free T_4, TSH), biochemical indicators (total protein (TP), albumin, prealbumin (PA), urea nitrogen (UN), fasting blood glucose (FBG), blood lipid, creatinine (Cr), uric acid (UA), alanine transaminase (ALT), aspartate transaminase (AST), and haemoglobin (Hb)). Radioimmunoassay was used to measure the serum levels of triiodothyronine, free T_3, total T_4, free T_4, and TSH. The Sysmex Xt-1800 Automated Hematology Analyzer (SYSMEX Corporation, Japan) was used for routine blood tests. Biochemistry measurements were performed using i-CHROMA Reader (Boditech Med Inc. Korea). Primary nursing care is for (1) critically or severely ill patients with unstable vital signs; (2) patients at high risk of cardiovascular events or other life-threatening events; (3) patients cannot take care of themselves. Secondary/tertiary nursing care are for patients with stable vital signs and can partially or completely take care of themselves. The time and cause of death were reported for all deceased patients by doctors.

The study was conducted in accordance with the ethical rules of the Helsinki Declaration. The study protocol was approved by the Ethics Committee of Chinese PLA General Hospital.

Indicators and outcomes

The subjects were divided based on the presence of NTIS into the NTIS group and normal thyroid function (non-NTIS) group. Decreased serum triiodothyronine and/or free T_3, normal or mildly reduced total T_4 or free T_4, and normal TSH levels were the diagnostic criteria for NTIS [9]. Normal thyroid hormone levels are as follows: total T_4 (55.34–160.88 nmol/L), triiodothyronine (1.01–2.95 nmol/L), free T_3 (2.76–6.30 pmol/L), free T_4 (10.42–24.32 pmol/L), and TSH (0.35–5.50 uIU/mL).

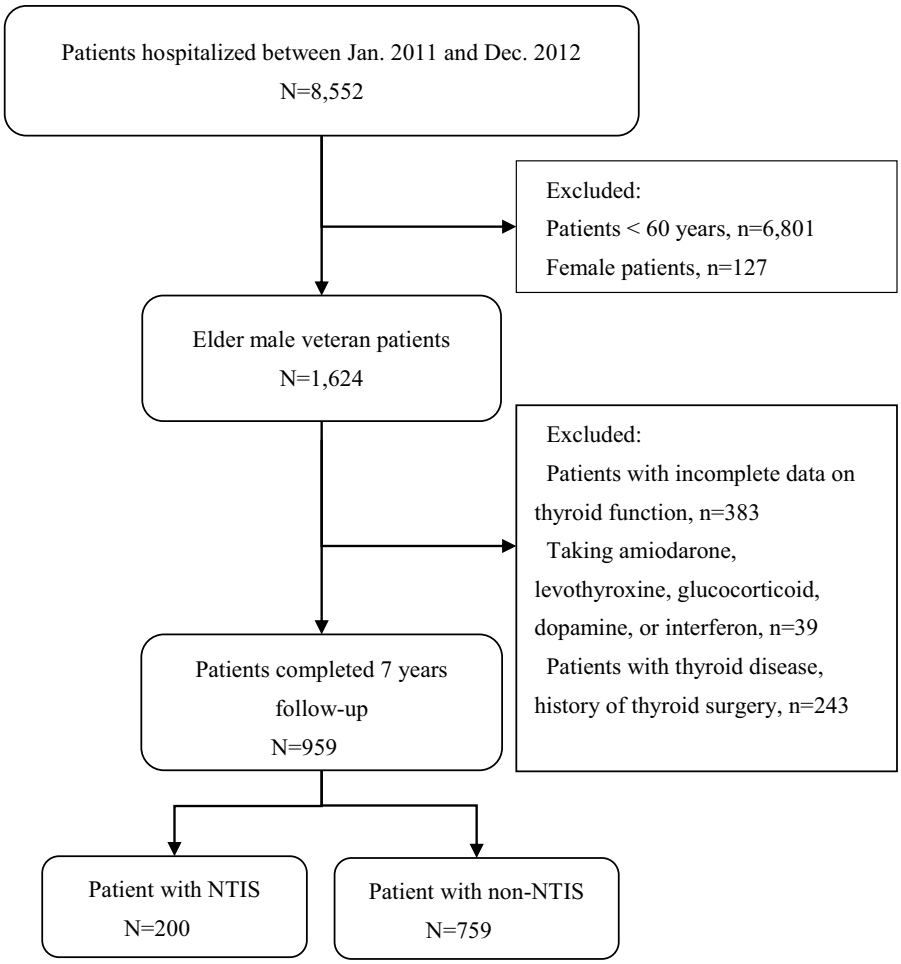

Fig. 1 Flowchart illustrating the inclusion/exclusion of individuals in this study

Intra-batch and batch-to-batch variations were < 3.35% and < 5.04%, respectively. The outcome was defined as all-cause mortality during the 7 years follow-up.

Statistical analysis

Normally distributed data are expressed as means ± standard deviation, non-normally distributed data as medians and quartiles, and category data are express as frequency and percentage. Normally distributed data were compared between the two groups using *t* test or *t*' test. The rank sum test was used to compare the data distribution between the two groups. Chi square test was used to compare the difference of category data. Overall survival at 7-year was estimated using the Kaplan–Meier method, and log-rank test was used to test the difference of mortality between two groups. To further evaluate the associations of thyroid hormone levels with all-cause mortality, bivariate and multivariate Cox proportional hazards models were used. Hazard ratio (HR) and 95% confident interval (95% CI) of each model was reported.

SPSS 24.0 and R was used for the statistical analysis. All data were evaluated using two-sided tests. Statistical significance was set at $P < 0.05$.

Results

Comparison of baseline data between the NTIS and non-NTIS groups

Most patients in both groups were in advanced age, and patients in the NTIS group were older (87.9 ± 6.0 vs. 85.8 ± 8.5, $P < 0.01$). Compared to the non-NTIS group, triiodothyronine, free T_3, total T_4, free T_4 and TSH levels were lower, moreover, respiratory disease was the more common cause of hospitalization and the length of hospitalization was longer in the NTIS group. The percentage of patients accompanied by respiratory disease and chronic kidney disease

Table 1 Comparison of baseline characteristics between the NTIS and non-NTIS groups

	Total ($n=959$)	NTIS group ($n=200$)	Non-NTIS group ($n=759$)	$t/Z/\chi^2$	*P value*
Age (years)	86.3 ± 8.1	87.9 ± 6.0	85.8 ± 8.5	3.92	< 0.01
BMI (kg/m^2)	24.0 ± 3.2	23.8 ± 3.8	24.1 ± 3.1	− 0.85	0.40
Triiodothyronine (nmol/L)	1.29 ± 0.32	0.90 ± 0.16	1.39 ± 0.27	− 24.85	< 0.01
Free T_3 (pmol/L)	3.68 ± 0.86	2.65 ± 0.56	3.95 ± 0.70	− 24.56	< 0.01
Total T_4 (nmol/L)	86.7 ± 16.5	75.3 ± 16.2	89.7 ± 15.2	− 11.81	< 0.01
Free T_4 (pmol/L) 10.42–24.32	15.99 ± 2.72	15.61 ± 2.98	16.09 ± 2.64	− 2.24	0.03
TSH (uIU/mL)	1.94 (1.36, 2.93)	1.68 (1.06, 2.81)	2.08 (1.48, 2.95)	3.75	< 0.01
Causes of hospitalization					
RD	246 (25.7%)	82 (41.0%)	164 (21.6%)	31.21	< 0.01
NSD	147 (15.3%)	22 (11.0%)	125 (16.5%)	3.65	0.06
CVD	224 (23.4%)	34 (17.0%)	190 (25.0%)	5.71	0.02
KD	71 (7.4%)	16 (8.0%)	55 (7.2%)	0.13	0.76
DD	99 (10.3%)	19 (9.5%)	80 (10.5%)	0.19	0.70
Tumor	106 (11.1%)	14 (7.0%)	92 (12.1%)	4.07	0.06
Others	66 (6.9%)	13 (6.5%)	53 (7.0%)	0.06	0.88
Length of hospitalization (d)	15.0 (11.0, 22.0)	21.0 (17.0, 30.0)	15.0 (10.0,19.0)	− 10.66	< 0.01
Comorbidities					
RD	309 (32.2%)	113 (56.5%)	196 (25.8%)	68.21	< 0.01
NSD	179 (17.6%)	43 (21.5%)	136 (17.9%)	1.34	0.25
CVD	847 (88.3%)	182 (91.0%)	665 (87.6%)	1.76	0.19
CKD	126 (13.10%)	48 (24.00%)	78 (10.3%)	26.12	< 0.01
Tumor	206 (21.5%)	30 (15.0%)	176 (23.2%)	6.29	0.01
Diabetes	298 (31.1%)	63 (31.5%)	235 (31.0%)	0.02	0.88
Biochemical indicators					
TP (g/L)	66.5 ± 6.1	64.7 ± 6.9	66.9 ± 5.8	− 4.59	< 0.01
Albumin (g/L)	38.3 ± 4.5	35.0 ± 4.4	39.2 ± 4.1	− 12.64	< 0.01
PA (mg/dL)	22.9 ± 7.0	21.5 ± 8.4	23.3 ± 6.5	− 3.26	< 0.01
Hb (g/L)	119.1 ± 18.4	112.1 ± 18.2	121.0 ± 18.0	− 6.18	< 0.01
UA (μmol/L)	336.5 ± 100.2	322.2 ± 122.3	340.3 ± 93.2	− 2.28	0.02
FBG (mmol/L)	5.89 ± 1.87	6.70 ± 2.31	5.68 ± 1.68	7.05	< 0.01
TC (mmol/L)	3.94 ± 0.87	4.04 ± 1.03	3.92 ± 0.82	1.72	0.09
TG (mmol/L)	1.23 (0.90, 1.65)	1.18 (0.82, 1.61)	1.27 (0.91, 1.67)	1.42	0.16
HDL-C (mmol/L)	1.16 ± 0.35	1.11 ± 0.39	1.17 ± 0.34	− 2.28	0.02
LDL-C (mmol/L)	2.29 ± 0.74	2.35 ± 0.90	2.27 ± 0.69	1.31	0.19
ALT (U/L)	14.0 (10.0, 20.0)	13.0 (9.3, 22.0)	14.0 (10.0, 19.0)	0.74	0.46
AST (U/L)	18.0 (15.0, 22.00)	19.00 (14.0, 26.1)	18.0 (15.0, 22.0)	− 0.80	0.42
UN (mmol/L)	6.40 (5.10, 8.80)	7.75 (5.90, 11.30)	6.20 (4.90, 8.20)	− 6.58	< 0.01
Cr (μmol/L)	81.0 (69.0, 98.0)	82.0 (65.3, 121.8)	81.0 (70.0, 95.0)	− 1.28	0.20

RD respiratory disease, *NSD* nervous system disease, *CVD* cardiovascular disease, *CKD* chronic kidney disease, *KD* kidney disease, *DD* digestive diseases, T_3 triiodothyronine, T_4 thyroxine, *TSH* thyroid-stimulating hormone. *TP* total protein, *PA* prealbumin, *Hb* haemoglobin, *UA* uric acid, *FBG* fasting blood glucose, *TC* total cholesterol, *TG* triglyceride, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *ALT* alanine transaminase, *AST* aspartate transaminase, *UN* urea nitrogen, *Cr* creatinine

Normally distributed data are expressed as means ± standard deviation, non-normally distributed data as medians and quartiles, and category data are express as frequency and percentage

were more in the NTIS group than in the non-NTIS group ($P<0.01$). TP, albumin, PA, Hb, UA and high-density lipoprotein cholesterol (HDL-C) levels were significantly lower ($P<0.05$), while FBG and UN levels were higher, in the NTIS group than in the non-NTIS group ($P<0.01$), see Table 1.

Comparison of respiratory, cardiovascular, kidney and tumor disease severity between the NTIS and non-NTIS groups

The percentage of patients in primary nursing care was more in the NTIS group than in the non-NTIS group ($P<0.01$). Furthermore, compared with the non-NTIS group, there were more patients accompanied by respiratory failure and renal dysfunction on haemodialysis in the NTIS group ($P<0.01$), but no significant differences were observed in patients with heart failure or metastatic cancer (Table 2).

Comparison of 1-year, 3-year and 7-year mortality between the NTIS and non-NTIS groups

During the 1-year follow-up period, 131 patients died: 55 (27.5%) in the NTIS group and 76 (10.0%) in the non-NTIS group ($P<0.01$). At 3-years, the mortality was 46.0% in the NTIS group and 21.3% in the non-NTIS group ($P<0.01$). A total of 622 patients died during the 7-year follow-up period, with 152 in the NTIS group and 470 in the non-NTIS group ($P<0.01$, Fig. 2a). At 7-years, the survival rate was 24.0% in the NTIS group and 38.1% in the non-NTIS group (Fig. 2b). Furthermore, Kaplan–Meier survival analysis according to tertiles, showed that 7-year survival rate in the NTIS group obviously reduced with the decrease of free T_3 ($P<0.01$, Fig. 3a), and 7-year survival rate reduced with the increase of free T_4 ($P<0.01$, Fig. 3b).

Associations of thyroid hormone levels with all-cause mortality according to Cox proportional hazards models

Cox proportional hazards models showed that the reduced triiodothyronine and free T_3 levels were significantly associated with higher mortality ($P<0.01$). However, after adjustment for albumin and Hb, triiodothyronine and free T_3 levels were not associated with all-cause mortality. Furthermore, lower free T_4 level was shown to be associated with reduced all-cause mortality with a HR (95% CI) of 0.91 (0.88, 0.94), even after adjusting for all other confounding factors ($P<0.01$; Table 3).

Discussion

In the older population, thyroid hormone levels can help monitor health status, predict short-term and long-term clinical prognoses, predict disease severity, and assess quality of life and survival status. In previous studies, the frequency of thyroid dysfunction increased with advancing age in the hospitalised older patients. The prevalence of NTIS in hospitalised severely or debilitated older patients can be as high as 32–62% [8, 10, 11]. In the present study, we investigated 959 male patients in advanced age hospitalised for various reasons with a long follow-up for 7 years. We found that there were 200 patients with NTIS (20.9%) whose albumin levels were lower, and the 7-year survival rate was significantly lower in the NTIS group than in the non-NTIS group;

Table 2 Comparison of disease severity between the NTIS and non-NTIS groups

	Total ($n=959$)	NTIS group ($n=200$)	Non-NTIS group ($n=759$)	$\chi 2$	*P value*
Nursing degree					
Primary	261 (27.2%)	77 (38.5%)	184 (24.2%)	16.24	<0.01
Secondary or tertiary	698 (72.8%)	123 (61.5%)	575 (75.8%)		
RD					
RF	45 (4.7%)	30 (15.0%)	15 (2.0%)	60.04	<0.01
Non-RF	264 (27.5%)	83 (41.5%)	181 (23.8%)		
CVD					
HF	42 (4.4%)	11 (5.5%)	31 (4.1%)	0.76	0.44
Non-HF	805 (83.9%)	171 (85.5%)	634 (83.5%)		
CKD					
Haemodialysis	20 (2.1%)	15 (7.5%)	5 (0.7%)	36.28	<0.01
Non-haemodialysis	106 (11.1%)	33 (16.5%)	73 (9.6%)		
Tumor					
Metastasis	22 (2.3%)	6 (3.0%)	16 (2.1%)	0.56	0.43
Non-metastasis	184 (19.2%)	24 (12.0%)	160 (21.1%)		

RF respiratory failure, *HF* heart failure

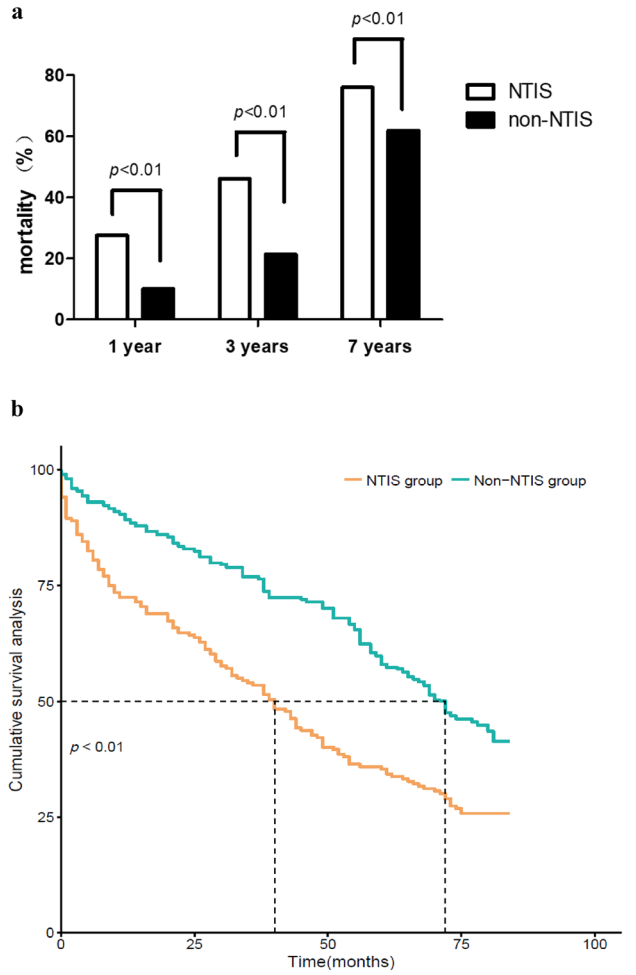

Fig. 2 Comparison of all-cause mortality and 7-year Kaplan–Meier survival curve of the NTIS and non-NTIS groups. **a** Comparison of mortality at 1 year, 3 years and 7 years in the NTIS and non-NTIS groups. **b** Seven-year Kaplan–Meier survival curve of the NTIS and non-NTIS groups

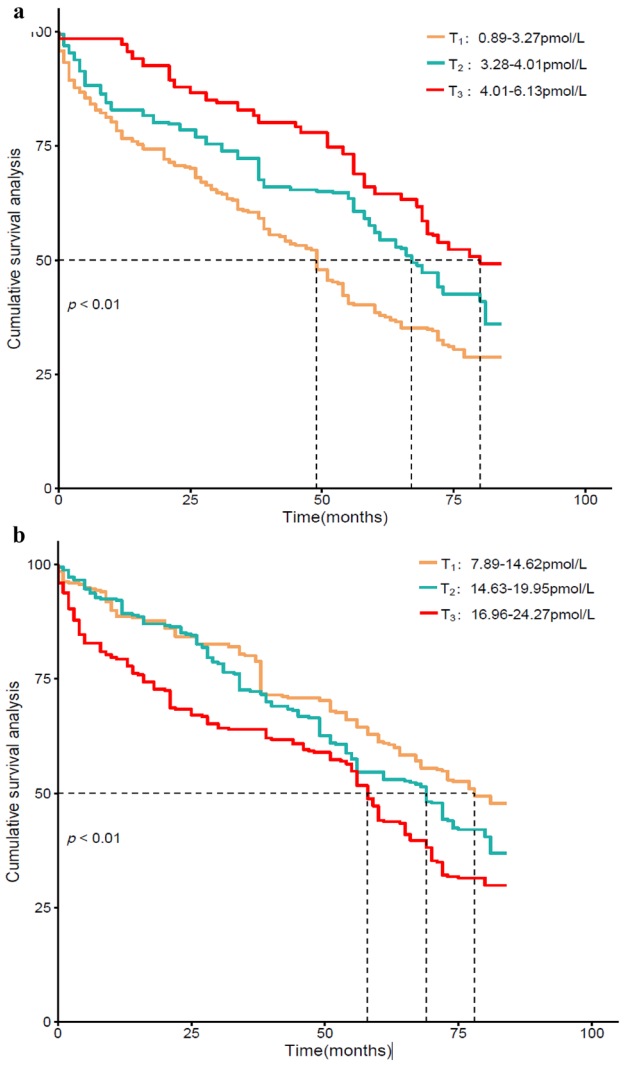

Fig. 3 Seven-year Kaplan Meier survival curves according to tertiles of free T_3 (**a**) and free T_4 (**b**) in the NTIS group

in addition, a reduced free T_3 level with low albumin and Hb levels was associated with all-cause mortality, and a higher free T_4 in the normal range was also a strong predictor for long-term mortality risk in hospitalised older patients.

NTIS is often associated with nutritional deficiencies or acute and chronic diseases. Protein and UA levels are indicators of nutritional status. Proteins also play an important role in the synthesis and transport of thyroid hormones. Previous studies showed that in patients with NITS, the serum albumin level was reduced, and the free T_3 level was positively correlated with the albumin level [12, 13]. In this study, the albumin level was also significantly reduced in the NTIS group compared with the non-NTIS group. It is supposed that decreased albumin level leads to a decrease in the conversion of T_4 to T_3, resulting in a decrease in T_3 levels or a decrease in T_4 binding to the protein, which accelerates the removal of thyroid hormones [14]. In the present study, a reduced free T_3 level with low albumin and Hb levels was associated with all-cause mortality which further confirming that malnutrition is closely related with NTIS.

NTIS is a common thyroid dysfunction in CKD patients [12, 15], and its mechanism is associated with the kidney's involvement in the synthesis, secretion, and metabolism of thyroid hormones. In kidney disease, chronic metabolic acidosis and inflammatory factors lead to the inhibition of deiodinase activity, and the conversion of T_4 to T_3 in kidney tissue and other tissue types is reduced [16]. Hypothalamic-pituitary-thyroid axis dysfunction combined with loss of T_4 in the urine causes triiodothyronine and total T_4 levels decreased [17]. A decrease in the glomerular filtration rate (GFR) reduces iodine excretion, resulting in an

Table 3 Cox proportional hazards models of the associations of thyroid hormone levels with all-cause mortality

	Crude model			Model 2			Model 3			Model 4		
	β	HR (95% CI)	*P value*	β	HR (95% CI)	*P value*	β	HR (95% CI)	*P value*	β	HR (95% CI)	*P value*
Triiodothyronine, nmol/L	0.870	2.39 (1.80, 3.16)	< 0.01	0.646	1.91 (1.42, 2.56)	< 0.01	0.240	1.27 (0.94, 1.72)	0.12	− 0.07	0.93 (0.69, 1.27)	0.66
Free T_3, pmol/L	0.410	1.50 (1.36, 1.66)	< 0.01	0.301	1.35 (1.22, 1.50)	< 0.01	0.098	1.10 (0.98, 1.24)	0.10	0.024	1.02 (0.90, 1.16)	0.71
Total T_4, nmol/L	− 0.002	0.998 (0.990, 1.010)	0.35	− 0.005	0.995 (0.990, 1.000)	0.07	− 0.006	0.994 (0.989, 1.000)	0.03	− 0.010	0.991 (0.986, 0.997)	< 0.01
Free T_4, pmol/L	− 0.100	0.91 (0.88, 0.93)	< 0.01	− 0.119	0.89 (0.86, 0.92)	< 0.01	− 0.080	0.92 (0.90, 0.95)	< 0.01	− 0.092	0.91 (0.88, 0.94)	< 0.01
TSH, uIU/mL	0.090	1.10 (1.02, 1.18)	0.02	0.134	1.14 (1.06, 1.23)	< 0.01	0.090	1.09 (1.01, 1.18)	0.02	0.040	1.04 (0.97, 1.13)	0.30

T_3 triiodothyronine, *T_4* thyroxine, *TSH* thyroid-stimulating hormone

Model 2, adjustment for age and BMI. Model 3, adjustment for age, BMI, albumin and Hb. Model 4, adjustment for age, BMI, albumin, Hb, UA, FBG, TC, ALT, length of hospitalization, RD, NSD, CVD, CKD and tumor

iodine-blocking effect (Wolff-Chaikoff effect) [17]. Song et al. [18] retrospectively analysed 2,284 subjects with normal TSH levels and found that as the estimated GFR (eGFR) decreased in CKD patients, the prevalence of low T_3 syndrome gradually increased; the eGFR was positively correlated with the serum T_3 level independent of age and serum protein levels. In patients with chronic haemodialysis, reduced free T_3 levels were a strong predictor of all-cause mortality [19]. Similar with previous studies, we found that among hospitalised older patients, the UN level in the NTIS group were higher, and there were more patients accompanied by chronic kidney disease, especially renal dysfunction on haemodialysis in the NTIS group than in the non-NTIS group.

NTIS also has been reported in patients with chronic obstructive pulmonary disease (COPD) accompanied by severe hypoxemia, and patients with obstructive sleep apnea accompanied by severe nocturnal hypoxemia [20, 21]. Moreover, recent research found that NTIS was common in mild-to-moderate COVID-19 patients and could predict clinical deterioration independent of SARS-CoV-2 viral load, age, inflammatory indicators and tissue injury [22]. Hypoxemia causes hypothalamic-pituitary-thyroid axis impairment and hypercapnia disrupts free T_3 and free T_4 production, which may be the main mechanism in NTIS development [20]. Our data demonstrated that more hospitalised older patients suffered from respiratory disease and even respiratory failure in the NTIS group than in the non-NTIS group.

In this study, Kaplan–Meier survival analyses showed that the survival rate was significantly lower in the NTIS group than in the non-NTIS group. Cox proportional hazards models showed that the reduced free T_3 level increased all-cause mortality, however, after adjustment for albumin and Hb, free T_3 levels did not predict mortality which indicated that patients with nutritional deficiencies presenting with lower free T_3 level had poor prognosis. Unexpectedly, lower free T_4 level was shown to be associated with reduced all-cause mortality even after the adjustment for all other confounding factors which suggested that a higher free T_4 in the normal range might be a predictor for mortality risk in hospitalised older patients. At present, the association between thyroid hormone levels and mortality in older people are inconsistent. Some studies demonstrated that low free T_3 levels were associated with all-cause mortality in patients with acute heart failure or admitted to ICUs [23, 24]. However, some other studies found that free T_3 levels were non-specifically related with mortality after adjustment for potential confounders [25], whereas free T_4 positively associated with death in advanced age [26]. Rozing et al. found that offspring of nonagenarian siblings had lower serum free T_4 levels compared with their partners and reduced free T_4 levels are associated with familial longevity [27]. In a study of 3885 community-dwelling men aged 70–89 years

with a follow-up of 6.4 ± 1.5 years, Yeap et al. reported that higher free T_4 levels are associated with increased all-cause mortality in euthyroid older men, after accounting for age, smoking, physical factors, and medical comorbidities [28]. Another retrospective cohort analysis with a mean follow-up of 3 years also showed that free T_4 level is an independent predictor for mortality risk in hospitalized NTIS patients with chronic diseases [29]. Similar with above studies, a higher free T_4 level in the normal range was associated with a worse prognosis among hospitalised older patients with long-term follow-up in the present study. Moreover, Kaplan–Meier survival analysis according to tertiles showed that survival rate at 7-year reduced with the increase of free T_4. However, the underlying mechanism is unclear, which may be the consequence of low activity of deiodinase that converts T_4 into the biologically active T_3, and the details need to be further investigated.

The present study had several limitations including failure to evaluate many factors such as functional, nutritional, cognitive, frailty information that affect the patient prognosis. In this retrospective cohort study, the treatment protocols and response to the treatment may also have affected the patients' outcomes. Due to the small sample size, many influencing factors were difficult to quantify, and the patients were not stratified according to the above-mentioned factors. In addition, only older male inpatients were analysed. Whether the study results can be generalised to the general population need to be further investigated.

In conclusion, the 7-year survival rate was lower in the NTIS group than non-NTIS group among older male patients on general wards. Patients with nutritional deficiencies presenting with free T_3 level had poor prognosis, and a higher free T_4 in the normal range was also a strong predictor for long-term mortality risk in hospitalised older male patients.

Acknowledgements We acknowledge all patients involved in this study.

Author contributions Conceptualization: SY and ZL; Data collection: XM, XF and HL; Methodology: HL; Formal analysis and investigation: ZG, KW and XC; Writing—original draft preparation: XM and XF; Writing—review and editing: CL and SY; Supervision: SY and ZL. All authors read and approved the final manuscript.

Funding The authors did not receive support from any organization for the submitted work.

Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose. A pre-print of early findings similar with the present study can be accessed at https://www.researchsquare.com/article/rs-29177/v2, and there was no discussion or comment in the server.

Ethical approval This research study was conducted retrospectively from data obtained for clinical purposes. Approval was granted by the Ethics Committee of Chinese PLA General Hospital (No. S2022-015-01).

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. de Vries EM, Fliers E, Boelen A (2015) The molecular basis of the non-thyroidal illness syndrome. J Endocrinol 225(3):R67-81
2. Fliers E, Boelen A (2021) An update on non-thyroidal illness syndrome. J Endocrinol Invest 44(8):1597–1607
3. Wang B, Liu S, Li L, Yao Q, Song R, Shao X et al (2017) Non-thyroidal illness syndrome in patients with cardiovascular diseases: A systematic review and meta-analysis. Int J Cardiol 226:1–10
4. Nakamura S, Kido N, Watanabe M, Ohmachi Y, Inayama Y, Kashitani Y et al (2022) Analysis of thyroid function in Japanese patients with coronavirus disease 2019. Endocr J 69(6):643–648
5. Fliers E, Bianco AC, Langouche L, Boelen A (2015) Thyroid function in critically ill patients. Lancet Diabetes Endocrinol 3(10):816–825
6. Rothberger GD, Valestra PK, Knight K, Desai AK, Calixte R, Shapiro LE (2021) Low free T(3) is associated with worse outcomes in patients in the ICU requiring invasive mechanical ventilation. J Intensive Care Med 36(3):313–318
7. Tognini S, Marchini F, Dardano A, Polini A, Ferdeghini M, Castiglioni M et al (2010) Non-thyroidal illness syndrome and short-term survival in a hospitalised older population. Age Ageing 39(1):46–50
8. Wang YF, Heng JF, Yan J, Dong L (2018) Relationship between disease severity and thyroid function in Chinese patients with euthyroid sick syndrome. Medicine (Baltimore) 97(31):e11756
9. Melmed S, Polonsky KS, Larsen PR, Kronenberg HM (2008) Williams textbook of endocrinolgy, 13th edn. Saunders Elsevier, Canada
10. Iglesias P, Muñoz A, Prado F, Guerrero MT, Macías MC, Ridruejo E et al (2009) Alterations in thyroid function tests in aged hospitalized patients: prevalence, aetiology and clinical outcome. Clin Endocrinol (Oxf) 70(6):961–967
11. Iglesias P, Ridruejo E, Muñoz A, Prado F, Macías MC, Guerrero MT et al (2013) Thyroid function tests and mortality in aged hospitalized patients: a 7-year prospective observational study. J Clin Endocrinol Metab 98(12):4683–4690
12. Pan B, Du X, Zhang H, Hua X, Wan X, Cao C (2019) Relationships of chronic kidney disease and thyroid dysfunction in non-dialysis patients: a pilot study. Kidney Blood Press Res 44(2):170–178
13. Chávez Valencia V, Mejía Rodríguez O, Viveros Sandoval ME, Abraham Bermúdez J, Gutiérrez Castellanos S, Orizaga de la Cruz C et al (2018) Prevalence of malnutrition-inflammation complex syndrome and its correlation with thyroid hormones in chronic haemodialysis patients. Nefrologia (Engl Ed) 38(1):57–63

14. Flier JS, Harris M, Hollenberg AN (2000) Leptin, nutrition, and the thyroid: the why, the wherefore, and the wiring. J Clin Invest 105(7):859–861
15. Iglesias P, Bajo MA, Selgas R, Díez JJ (2017) Thyroid dysfunction and kidney disease: an update. Rev Endocr Metab Disord 18(1):131–144
16. Zoccali C, Tripepi G, Cutrupi S, Pizzini P, Mallamaci F (2005) Low triiodothyronine: a new facet of inflammation in end-stage renal disease. J Am Soc Nephrol 16(9):2789–2795
17. Basu G, Mohapatra A (2012) Interactions between thyroid disorders and kidney disease. Indian J Endocrinol Metab 16(2):204–213
18. Song SH, Kwak IS, Lee DW, Kang YH, Seong EY, Park JS (2009) The prevalence of low triiodothyronine according to the stage of chronic kidney disease in subjects with a normal thyroid-stimulating hormone. Nephrol Dial Transplant 24(5):1534–1538
19. Fragidis S, Sombolos K, Thodis E, Panagoutsos S, Mourvati E, Pikilidou M et al (2015) Low T3 syndrome and long-term mortality in chronic hemodialysis patients. World J Nephrol 4(3):415–422
20. Gumus A, Ozyurt S, Ozcelik N, Kara BY (2020) Prevalence of non-thyroidal illness syndrome in COPD exacerbation and effect of hypoxaemia and hypercapnia on thyroid functions. Clin Respir J 14(9):806–812
21. Petrone A, Mormile F, Bruni G, Quartieri M, Bonsignore MR, Marrone O (2016) Abnormal thyroid hormones and non-thyroidal illness syndrome in obstructive sleep apnea, and effects of CPAP treatment. Sleep Med 23:21–25
22. Lui DTW, Lee CH, Chow WS, Lee ACH, Tam AR, Fong CHY et al (2021) Role of non-thyroidal illness syndrome in predicting adverse outcomes in COVID-19 patients predominantly of mild-to-moderate severity. Clin Endocrinol (Oxf) 95(3):469–477
23. Asai K, Shirakabe A, Kiuchi K, Kobayashi N, Okazaki H, Matsushita M et al (2020) Relation of low triiodothyronine syndrome associated with aging and malnutrition to adverse outcome in patients with acute heart failure. Am J Cardiol 125(3):427–435
24. Shigihara S, Shirakabe A, Kobayashi N, Okazaki H, Matsushita M, Shibata Y et al (2021) 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. Circ Rep 3(10):578–588
25. Pearce SH, Razvi S, Yadegarfar ME, Martin-Ruiz C, Kingston A, Collerton J et al (2016) Serum thyroid function, mortality and disability in advanced old age: the Newcastle 85+ Study. J Clin Endocrinol Metab 101(11):4385–4394
26. Waring AC, Arnold AM, Newman AB, Bùzková P, Hirsch C, Cappola AR (2012) Longitudinal changes in thyroid function in the oldest old and survival: the cardiovascular health study all-stars study. J Clin Endocrinol Metab 97(11):3944–3950
27. Ozing MP, Westendorp RG, de Craen AJ, Frölich M, Heijmans BT, Beekman M et al (2010) Low serum free triiodothyronine levels mark familial longevity: the Leiden Longevity Study. J Gerontol A Biol Sci Med Sci 65(4):365–8
28. Yeap BB, Alfonso H, Hankey GJ, Flicker L, Golledge J, Norman PE et al (2013) Higher free thyroxine levels are associated with all-cause mortality in euthyroid older men: the health in men study. Eur J Endocrinol 169(4):401–408
29. Ataoğlu HE, Ahbab S, Serez MK, Yamak M, Kayaş D, Canbaz ET et al (2018) Prognostic significance of high free T4 and low free T3 levels in non-thyroidal illness syndrome. Eur J Intern Med 57:91–95