Journal of Endocrinological Investigation (2021) 44:1031–1040
https://doi.org/10.1007/s40618-020-01460-w

ORIGINAL ARTICLE

Thyroid hormone concentrations in severely or critically ill patients with COVID-19

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Received: 12 September 2020 / Accepted: 22 October 2020 / Published online: 2 November 2020

Abstract

Objective COVID-19 is a new coronavirus infectious disease. We aimed to study the characteristics of thyroid hormone levels in patients with COVID-19 and to explore whether thyroid hormone predicts all-cause mortality of severely or critically ill patients.

Methods The clinical data of 100 patients with COVID-19, who were admitted to Wuhan Tongji Hospital from February 8 to March 8, 2020, were analyzed in this retrospective study. The patients were followed up for 6–41 days. Patients were grouped into non-severe illness and severe or critical illness, which included survivors and non-survivors. Multivariate Cox proportional hazards analysis was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality in association with continuous and the lower two quartiles of thyroid hormone concentrations in severely or critically ill patients.

Results The means of free T3 (FT3) were 4.40, 3.73 and 2.76 pmol/L in non-severely ill patients, survivors and non-survivors, respectively. The lower (versus upper) two quartiles of FT3 was associated with all-cause mortality HR (95% CI) of 9.23 (2.01, 42.28). The HR (95% CI) for all-cause mortality in association with continuous FT3 concentration was 0.41 (0.21, 0.81). In the multivariate-adjusted models, free T4 (FT4), TSH and FT3/FT4 were not significantly related to all-cause mortality. Patients with FT3 less than 3.10 pmol/L had increased all-cause mortality.

Conclusion FT3 concentration was significantly lower in patients with severe COVID-19 than in non-severely ill patients. Reduced FT3 independently predicted all-cause mortality of patients with severe COVID-19.

Keywords Thyroid hormone · Nonthyroidal illness · COVID-19 · Mortality

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Introduction

Coronavirus disease 2019 (COVID-19) is an acute respiratory tract infection of unknown origin, which broke out in Wuhan, China in January 2020 and spread rapidly across the country and the world afterward. According to a previous report from the Chinese Center for Disease Control and Prevention, 14% of cases in mainland China were severe and 5% were critical. The mortality rate of COVID-19 was 2.3% [1]. Stratifying patients with COVID-19 according to their clinical severity may help improve their prognosis [2].

Decreased serum triiodothyronine (T3) concentration in euthyroid patients, which is termed nonthyroidal illness (NTIS) or euthyroid sick syndrome, is frequently present in critically ill patients. Reduced T3 concentration has been related to mortality in patients with chronic renal failure (CRF) [3], acute myocardial infarction [4], and surgical sepsis [5]. Other studies showed that decreased TSH

concentration was an independent predictor of mortality in patients with acute-on-chronic liver failure [6] or elderly people in community [7]. Little is known about the thyroid function characteristics and the utility of thyroid hormone for predicting clinical outcomes in patients with severe COVID-19.

In this retrospective study, we aimed to explore the characteristics of thyroid function and its role in predicting the risk of all-cause mortality in severely or critically ill patients with COVID-19. We hypothesized that thyroid hormone levels can predict the death of patients with severe COVID-19. This study used clinical data of COVID-19 patients admitted to two wards of Wuhan Tongji Hospital managed by reinforcement medical teams dispatched by Peking University Medical Center.

Materials and methods

Study population

After the outbreak of COVID-19 in Wuhan, China, Peking University Medical Center sent medical teams to Wuhan to manage three wards of Tongji Hospital. From February 8 to March 8 in 2020, 115 patients with COVID-19 pneumonia were admitted to two of the wards where thyroid hormone concentrations were routinely measured. After 14 patients were excluded due to missing data on thyroid hormones and one patient was excluded due to known hypothyroidism, 100 patients (aged 24–88 years) were included in the current study. The patients were followed up for 6 to 41 days, with median (25th, 75th percentile) follow-up of 22.0 days (14.0, 28.8) days. During the study period, 22 patients died during hospitalization, 66 patients recovered and were discharged, and 12 patients were still hospitalized. In total, among the 100 patients, there were 66 patients including severely ill people and critically ill people. Survival analysis was performed only in the severely or critically ill patients.

Data collection

We recorded patient demographic information, medical history, and medication history on the day of hospitalization. Body temperature, respiratory rate, blood pressure and blood oxygen saturation were measured. In the early morning of the day after admission, the patient's fasting venous blood was collected for complete blood count, biochemical tests, thyroid hormone, pro-inflammatory cytokines including interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α), high sensitive C-reactive protein (hs-CRP), N-terminal pro-brain natriuretic peptide (NT-proBNP), and D-dimer.

Laboratory test

A Roche Cobas 8000 automatic biochemical analyzer (Roche, Switzerland) was used for the determination of serum alanine aminotransferase, aspartate aminotransferase, total bilirubin, direct bilirubin, albumin, creatinine and hs-CRP. A Roche Cobas e602 electrochemical luminescence analyzer (Roche, Germany) was used for the determination of free T3 (FT3), free T4 (FT4), TSH, IL-6, TNF-α and NT-proBNP. The ratio of FT3 and FT4 (FT3/FT4) was calculated. D-dimer was determined using STAGO STA-R automatic blood coagulation analyzer (STAGO, France).

Diagnostic criteria for COVID-19

The diagnosis of COVID-19 was based on symptoms such as fever, coughing, and dyspnea. The diagnostic imaging findings of COVID-19 infection were confirmed by a radiologist. The confirmation of COVID-19 was based on the detection of nucleic acid by polymerase chain reaction in the respiratory tract.

Diagnostic criteria for comorbidity

Severe illness was defined as patients with COVID-19 with blood oxygen saturation $\leq 93\%$ or respiratory rate ≥ 30 per min [1] on admission. When patients with COVID-19 were complicated by ARDS, sepsis shock, and/or organ failure including acute heart failure and acute kidney injury (AKI) or ongoing hemodialysis from the day of admission to one week after admission, they were defined as having critical illness [1]. Patients with COVID-19 who had only pneumonia without the above conditions were classified as non-severe illness.

The diagnosis of ARDS was in accordance with the Berlin definition [8], where the patient had impaired oxygenation and met all of the following criteria: the respiratory symptoms worsen within 1 week, bilateral lung infiltrating lesions had no other explanation, cardiogenic pulmonary edema was excluded, and the severity of oxygenation impairment was mild if the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) greater than 200 mmHg but less than or equal to 300 mmHg, oxygenation impairment was moderate if PaO_2/FiO_2 greater than 100 mmHg but less than or equal to 200 mmHg, and if PaO_2/FiO_2 was less than or equal to 100 mmHg, oxygenation impairment was severe. Septic shock was defined as the patient with hypotension requiring continuous administration of vasopressors to maintain a mean arterial pressure above 65 mmHg, and a serum lactate concentration greater than 2 mmol/L [9]. Organ failure includes acute heart failure, acute kidney injury or ongoing hemodialysis treatment. The diagnosis

of acute heart failure was based on the patient's medical history, assessment of the symptoms and signs of congestion and/or hypoperfusion, electrocardiograms, chest radiographs, and measurement of specific biomarkers according to the 2016 European Society of Cardiology guidelines [10]. According to Kidney Disease Improving Global Guidelines (KDIGO), the diagnosis of AKI was based on one of the following criteria: the increase in serum creatinine within 48 h was greater than or equal to 26.5 μmol/L, or it was known or speculated that the increase in serum creatinine was greater than or equal to 1.5 times the baseline within the previous 7 days, or urine volume was less than or equal to 0.5 ml/kg/h for 6 h [11].

Statistical analysis

Statistical analyses were performed using SPSS (version 22, SPSS, Inc., Chicago, IL). Continuous variables with normal distribution are presented as means ± SD and were compared using *t* tests. Variables with skewed distribution are presented as median (25th, 75th percentile) and were compared using Mann–Whitney *U* tests. Categorical data are presented as number and percentage and were compared using Chi-squared tests. Correlations between thyroid hormone and hs-CRP, IL-6 or TNF-α were determined by calculating the Pearson correlation coefficient after log-transformation of the skewed data. All-cause mortality rates per 100 person-days were calculated for severely or critically ill patients. Cox proportional hazards models were used to estimate covariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality in association with 50th percentiles and continuous FT3 concentration.

Results

Characteristics of patients

Severely or critically ill patients were more severe hypoxia had higher concentrations of NT-proBNP, D-dimers, hs-CRP, interleukin-6 and TNF-α than non-severely ill patients. Severely or critically ill patients had lower concentrations of serum albumin, FT3, TSH and FT3/FT4 than non-severely ill patients (Table 1). All the non-severely ill patients survived. A total of 22 all-cause deaths, including 21 deaths from COVID-19 and one death from acute cardiac infarction, occurred among 66 severely or critically ill patients during a median follow-up of 21.5 days. Patients who died were more hypoxic, had higher concentrations of NT-proBNP, D-dimers, hs-CRP, IL-6 and TNF-α, and lower concentrations of serum albumin, FT3, TSH and FT3/FT4 than survivors (Table 1).

In non-severely ill patients, survivors and non-survivors, the means (95% CI) of FT3 were 4.40 (4.09, 4.71), 3.73 (3.46, 4.00) and 2.76 (2.54, 2.98) pmol/L, respectively. The means (95% CI) of FT4 were 18.97 (17.93, 20.00), 18.97 (17.85, 20.09) and 17.46 (15.65, 19.27) pmol/L, respectively. The medians of TSH were 2.03, 1.34, 0.75 μIU/mL, respectively (Table 1, Fig. 1). No patients had FT3 concentrations above the normal upper limit of 6.80 pmol/L. There were 5.9, 18.2 and 81.8% patients who had FT3 concentrations below the normal lower limit of 3.10 pmol/L in non-severely ill patients, survivors and non-survivors, respectively (Table 1). A total of 17 patients had FT4 concentrations above the normal upper limit of 22 pmol/L, and two of them had FT3 below the normal lower limit of 3.1 pmol/L. Among the 17 patients with high FT4 concentrations, 13 patients (76.5%) were severely or critically ill and 12 patients (70.6%) were survivors (Table 1). After 3–8 days, eight patients were reexamined for thyroid hormone, three non-severely ill patients and three survivors returned to normal FT4 concentration (one patient's FT3 concentration decreased upon admission also returned to normal), and two survivors still had increased FT4. There were eight patients whose TSH concentration was higher than the upper limit of the normal value of 4.2 μIU/mL (Table 1). Among them, one patient also had an increase in FT4 and one had a decrease in FT3. Among all patients, only three patients (3%) had FT4 concentrations below the normal lower limit of 12 pmol/L, and seven patients (7%) had TSH concentrations below normal lower limit of 0.27 μIU/mL (Table 1).

Association between all-cause mortality risk and thyroid hormone

In the Cox proportional hazards models, survived/non-survived was used as the dependent variable, and the independent variables included FT3, FT4, TSH and FT3/FT4, which were separately fitted into the models. Other independent variables were confounding factors including age, gender, duration of COVID-19, blood oxygen saturation reflecting the severity of COVID-19 and hs-CRP, a commonly used indicator reflecting the degree of inflammation. The all-cause mortality risk decreased with increased FT3 concentration, the HR (95% CI) was 0.37 (0.20, 0.69) after adjusting for age [HR (95%CI) 1.02 (0.98, 1.06)], sex [men versus women 0.95 (0.40, 2.28)], duration of COVID-19 [0.91 (0.82, 1.02)] and blood oxygen saturation [0.98 (0.94, 1.02)]. The HR (95% CI) was 0.41 (0.21, 0.81) after further adjusting for hs-CRP [1.003 (0.997, 1.009)] (Table 2). In the multivariate-adjusted models, FT4, TSH and FT3/FT4 were not significantly related to all-cause mortality (Table 2). To exclude the effect of glucocorticoid on thyroid function, sensitivity analyses were performed after excluding 11 patients

Table 1 Baseline characteristics of 100 patients with COVID-19 by severity and survival status

	Non-severely ill Patients	Severely or critically ill patients	*P* value*	All-cause mortality in severely or critically ill patients		
				Survivors	Non-survivors	*P* value**
N	34	66		44	22	
Age (years)	61.4 ± 15.2	63.2 ± 13.4	0.535	61.8 ± 13.3	66.0 ± 13.5	0.232
Men *n* (%)	16 (47.1)	36 (54.5)	0.478	23 (52.3)	13 (59.1)	0.600
Duration (days)	14 ± 6	13 ± 6	0.488	14 ± 5	11 ± 5	0.068
Blood oxygen saturation (%)	96 ± 1	87 ± 9	< 0.001	89 ± 8	83 ± 8	0.005
Temperature (℃)	38.3 ± 0.9	38.5 ± 0.9	0.455	38.4 ± 1.0	38.7 ± 0.9	0.182
Respiratory rate (times/min)	21 ± 3	29 ± 5	< 0.001	28 ± 4	32 ± 5	< 0.001
Systolic blood pressure (mmHg)	135 ± 17	132 ± 27	0.525	133 ± 24	128 ± 33	0.489
Diastolic blood pressure (mmHg)	80 ± 13	78 ± 17	0.648	79 ± 14	78 ± 21	0.957
White blood cells ($\times 10^9$/L)	5.48 ± 2.14	7.78 ± 4.59	0.001	6.20 ± 3.13	10.93 ± 5.44	0.001
Neutrophil count ($\times 10^9$/L)	3.53 ± 1.93	6.43 ± 4.56	< 0.001	4.72 ± 2.85	9.84 ± 5.43	< 0.001
Lymphocyte count ($\times 10^9$/L)	1.40 ± 0.53	0.81 ± 0.42	< 0.001	0.95 ± 0.43	0.55 ± 0.25	< 0.001
Alanine aminotransferase (U/L)	19 (12, 30)	29 (15, 43)	0.059	28 (13, 42)	29 (17, 56)	0.406
Aspartate aminotransferase (U/L)	23 (17, 28)	35 (20, 47)	0.002	30 (19, 45)	41 (23, 62)	0.129
Total bilirubin (pmol/L)	9.5 (6.7, 13.0)	10.1 (7.0, 15.7)	0.321	8.8 (6.8, 14.2)	13.9 (10.2, 24.9)	0.008
Direct bilirubin (pmol/L)	4.1 (2.5, 5.3)	4.6 (3.0, 8.2)	0.064	3.7 (3.0, 6.8)	7.6 (4.4, 15.5)	0.004
Serum albumin (g/L)	36.1 ± 4.4	31.6 ± 4.6	< 0.001	32.9 ± 4.2	28.9 ± 4.1	< 0.001
NT-proBNP (pg/mL)	76 (38, 201)	360 (169, 2503)	< 0.001	242 (114, 595)	1535 (377, 11,246)	0.001
Serum creatinine (μmol/L)	75 (58, 90)	78 (64, 112)	0.196	72 (63, 99)	92 (62, 154)	0.399
FT3 (pmol/L)	4.40 ± 0.88	3.41 ± 0.90	< 0.001	3.73 ± 0.88	2.76 ± 0.49	< 0.001
FT3 by reference range (pmol/L)						
< 3.10	2 (5.9)	26 (39.4)	< 0.001	8 (18.2)	18 (81.8)	< 0.001
3.10–6.80	32 (94.1)	40 (60.6)		36 (81.8)	4 (18.2)	
> 6.8	–	–		–	–	
FT4 (pmol/L)	18.97 ± 2.97	18.47 ± 3.86	0.514	18.97 ± 3.69	17.46 ± 4.08	0.135
FT4 by reference range (pmol/L)†						
< 12	1 (2.9)	2 (3.0)	–	2 (4.5)	0 (0)	–
12–22	29 (85.3)	51 (77.3)		30 (68.2)	21 (95.5)	
> 22	4 (11.8)	13 (19.7)		12 (27.3)	1 (4.5)	
TSH (μIU/mL)	2.03 (1.24, 3.31)	1.20 (0.45, 2.05)	0.002	1.34 (0.83, 2.19)	0.75 (0.29, 1.78)	0.029
TSH by reference range (μIU/mL)††						
< 0.27	0 (0)	7 (10.6)	–	2 (4.5)	5 (22.7)	–
0.27–4.2	32 (94.1)	53 (80.3)		38 (86.4)	15 (68.2)	
> 4.2	2 (5.9)	6 (9.1)		4 (9.1)	2 (9.1)	
FT3/FT4	0.24 ± 0.06	0.19 ± 0.05	< 0.001	0.20 ± 0.06	0.16 ± 0.04	0.001
Fasting plasma glucose (mmol/L)	6.30 ± 2.63	8.22 ± 4.73	0.010	7.41 ± 4.42	9.85 ± 5.02	0.047
D-dimers (μg/mL)	0.58 (0.38, 1.46)	2.10 (1.19, 6.62)	< 0.001	1.66 (1.07, 2.78)	11.30 (2.20, 21.00)	< 0.001
hs-CRP (mg/L)	6.1 (2.0, 36.4)	71.2 (25.2, 180.7)	< 0.001	42.6 (23.0, 134.0)	178.2 (46.9, 261.9)	0.002
IL-6 (pg/mL)	4.86 (1.99, 18.15)	40.52 (14.89, 67.78)	< 0.001	38.11 (11.23, 53.62)	54.10 (34.29, 152.90)	0.014

Table 1 (continued)

	Non-severely ill Patients	Severely or critically ill patients	*P* value*	All-cause mortality in severely or critically ill patients		
				Survivors	Non-survivors	*P* value**
TNF-α (pg/mL)	6.0 (4.3, 8.9)	11.4 (7.6, 14.8)	< 0.001	11.4 (6.5, 13.9)	11.7 (7.8, 15.3)	0.563
Glucocorticoid using	4 (11.8)	11 (16.7)	0.515	5 (11.4)	6 (27.3)	0.199

Data were expressed as means ± SD for continuous data with normal distribution, median (25th, 75th percentile) for continuous data with skewed distribution, and *n* (%) for categorical data. *P* value was for the difference between groups using *t* test for normal distributed data, Mann–Whitney *U* test for skewed distributed data, and Chi-squared test for categorical data

NT-proBNP N-terminal pro-brain natriuretic peptide, *FT3* free T3, *FT4* free T4, *hs-CRP* high-sensitivity C-reactive protein, *IL-6* interleukin-6, *TNF-α* tumor necrosis factor α

*Compared between non-severely ill patients and severely or critically ill patients

**Compared between the survivors and non-survivors in severely or critically ill patients

†Comparing between categories was not performed because more than 20% of the cells have expected count less than 5

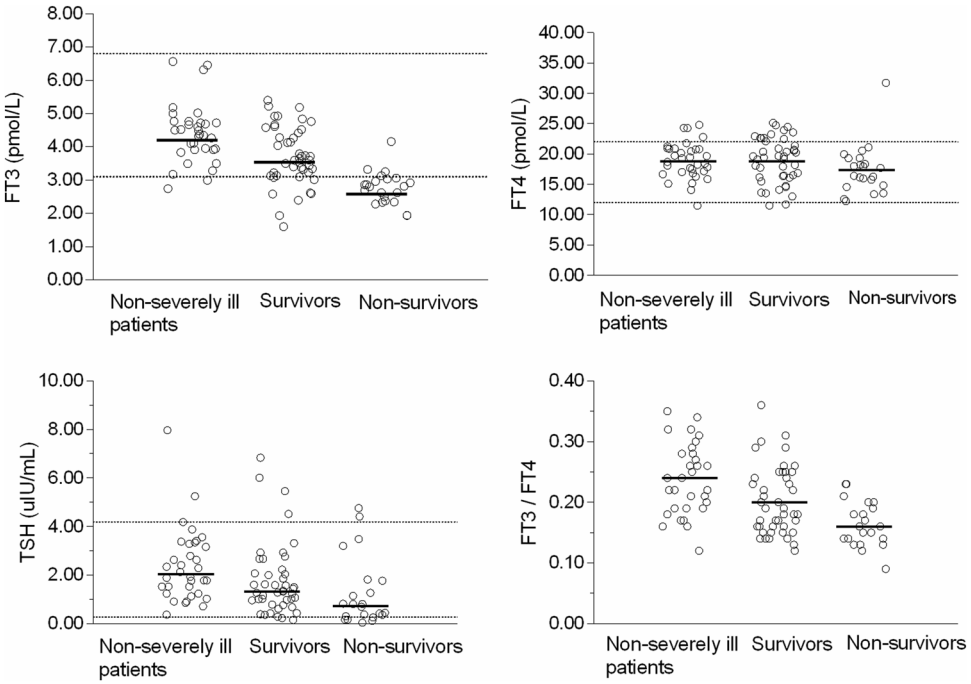

Fig. 1 Distribution of thyroid hormone according to severity and outcome of patients. The solid line indicates the mean of FT3, FT4 or median of TSH, and the dashed line indicates the upper and lower limits of the reference range. *FT3* free T3, *FT4* free T4

who had used glucocorticoid before thyroid function examination. The results did not change substantially. The HR (95% CI) for mortality of FT3 was 0.39 (0.20, 0.79) in the Cox proportional risk model adjusted for age, sex, duration of COVID-19 and blood oxygen saturation and the HR (95% CI) was 0.42 (0.20, 0.87) after further adjusting for hs-CRP.

Severely or critically ill patients were classified according to median of FT3 (3.29 pmol/L), FT4 (18.24 pmol/L), TSH (1.20 μIU/mL) and FT3/FT4 (0.18). All-cause mortality rates (95% CI) were 3.10 (1.90, 4.74) and 0.26 (0.03, 0.92) per 100 person-day in patients with FT3 < 3.29 pmol/L and in those with FT3 ≥ 3.29 pmol/L, respectively. The mortality rates were 1.96 (1.07, 3.26) and 1.13 (0.49, 2.21) per 100 person-day in patients with FT4 < 18.24 pmol/L and FT4 ≥ 18.24 pmol/L, respectively. In patients with TSH < 1.20 μIU/mL and TSH ≥ 1.20 μIU/mL, the mortality rates were 2.14 (1.20, 3.50) and 0.97 (0.39, 1.98), respectively (Table 2). Compared with FT3 ≥ 3.29 pmol/L, the HR (95% CI) was 10.75 (2.43, 47.57) after adjusting for age, sex, duration of COVID-19 and blood oxygen saturation and the HR (95%CI) was 9.23 (2.01, 42.28) after further adjusting for hs-CRP (Table 2). Compared with patients in the upper two quantiles of FT4, TSH and FT3/FT4, the mortality risk of patients in the lower two quantiles did not differ significantly (Table 2).

The all-cause mortality rate by 0.5 pmol/L intervals of FT3 in all patients in this study is shown in Fig. 2 The mortality rate was low at high levels of FT3 and began to increase from the FT3 range of 3.10–3.59 pmol/L.

Table 2 All-cause mortality (per 100 person-day) and multivariable-adjusted HR in relation to thyroid hormone in 66 severely or critically ill patients with COVID-19

	FT3 (pmol/L)	Median of FT3 (pmol/L)	
		≥ 3.29	< 3.29
No. of death	22	2	20
Mortality	1.54	0.26	3.10
HR (95% CI)*	0.37 (0.20, 0.69)	1.00	10.75 (2.43, 47.57)
HR (95% CI)**	0.41 (0.21, 0.81)	1.00	9.23 (2.01, 42.28)
	FT4 (pmol/L)	Median of FT4 (pmol/L)	
		≥ 18.24	< 18.24
No. of death	22	8	14
Mortality	1.54	1.13	1.96
HR (95% CI)*	0.93 (0.82, 1.05)	1.00	1.69 (0.70, 4.09)
HR (95% CI)**	0.95 (0.84, 1.08)	1.00	1.30 (0.52, 3.28)
	TSH (μIU/mL)	Median of TSH	
		≥ 1.20 (μIU/mL)	< 1.20
No. of death	22	7	15
Mortality	1.54	0.97	2.14
HR (95% CI)*	1.01 (0.67, 1.51)	1.00	1.54 (0.57, 4.16)
HR (95% CI)**	1.16 (0.76, 1.77)	1.00	1.13 (0.41, 3.14)
	FT3/FT4	Median of FT3/FT4	
		≥ 0.18	< 0.18
No. of death	22	8	14
Mortality	1.54	1.17	1.89
HR (95% CI)*†	0.50 (0.25, 1.01)	1.00	1.40 (0.57, 3.47)
HR (95% CI)**†	0.60 (0.29, 1.22)	1.00	1.00 (0.38, 2.62)

FT3 free T3, *FT4* free T4

*Adjusted for age, sex, duration of COVID-19, blood oxygen saturation

**Adjusted for age, sex, duration of COVID-19, blood oxygen saturation and high-sensitivity C-reactive protein (hs-CRP)

†Corresponding to a one standard deviation increase in FT3/FT4

Correlation between FT3, FT4, TSH and inflammatory factors

Due to the skewed distribution, TSH, hs-CRP, IL-6 and TNF-α were transformed logarithmically. In all patients, FT3 was negatively correlated with hs-CRP, IL-6 and TNF-α (all $P < 0.001$). TSH was negatively correlated with hs-CRP and IL-6 (both $P < 0.001$). FT4 was not correlated with hs-CRP, IL-6 and TNF-α (Table 3).

The patients were divided into non-severely ill patients, survivors, and non-survivors according to the severity and clinical outcome. In non-severely ill patients, FT3 was negatively correlated with hs-CRP ($r = -0.50$, $P = 0.003$) and IL-6 ($r = -0.39$, $P = 0.023$). In survivors, FT3 was negatively correlated with hs-CRP ($r = -0.57$, $P < 0.001$), IL-6 (r = − 0.59, $P < 0.001$) and TNF-α ($r = -0.48$, $P = 0.001$) (Table 3, Fig. 3). In non-survivors, however, FT3 was not correlated with hs-CRP, IL-6 or TNF-α. TSH was only negatively correlated with hs-CRP in survivors ($r = -0.45$, $P = 0.002$) (Table 3, Fig. 3).

Discussion

The results of this study show that among patients with COVID-19, FT3, TSH and FT3/FT4 decreased with clinical deterioration of COVID-19 and were lowest in patients who died. In severely or critically ill patients, the reduction in FT3 was independently associated with all-cause mortality. Patients with FT3 less than 3.10 pmol/L had increased all-cause mortality, suggesting that intensive treatment measures should be taken to reduce the risk of death for the patients with lower FT3 concentrations.

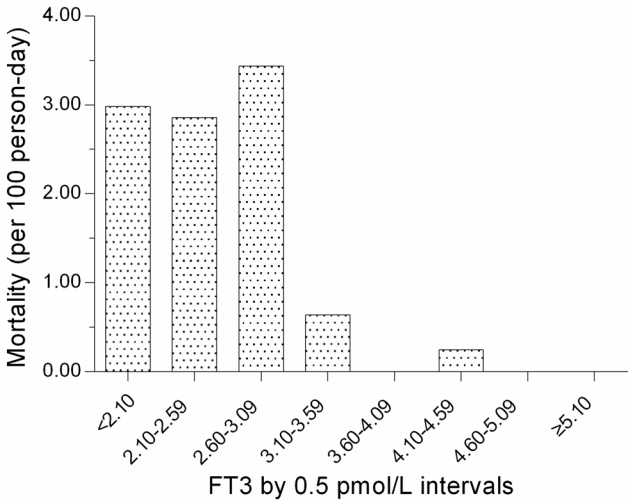

Fig. 2 All-cause mortality within each interval by 0.5 pmol/L intervals for FT3 in all patients. *FT3* free T3

NTIS or euthyroid sick syndrome is characterized by a decrease in T3 concentration in people with normal thyroid function, which is common in critically ill patients or people with severe nutritional deficiencies. Although the clinical significance of NTIS is unclear, the use of thyroxine for patients with NTIS did not produce additional benefits [12], suggesting that NTIS may be a self-protection mechanism of the body. On the other hand, many studies have shown that NTIS was a risk factor of poor prognosis in critically ill patients. In previous reports, T3, T4 and TSH had different predictive effects on prognosis. The results of two studies conducted in intensive care unit (ICU) mechanically ventilated patients were similar to ours. That was, the reduction of FT3, whether FT4 and TSH were normal or reduced, can predict the adverse outcomes of these critical patients, including death [13] and prolonged mechanical ventilation time [13, 13]. Another observation in ICU patients showed that decreases in both FT3 and FT4, rather than FT3 declined alone, was an independent risk factor for death [15]. The difference in the predictive effect of FT3 and FT4 on adverse outcomes in various studies may be related to the difference in the etiological diagnosis and development period of the severely ill patients in ICU. With the spread of COVID-19 worldwide, accumulated evidences showed that the clinical manifestations of thyroid involvement in patients with COVID-19 were not consistent. Several Italian studies reported subacute thyroiditis or painless thyroiditis in patients with COVID-19 [16, 16]. Thyroid function of patients with COVID-19 can be manifested as thyrotoxicosis or hypothyroidism. The mortality rate of patients with normal TSH was lower than that of patients with abnormal TSH [18]. The results of another Chinese study showed that TT3 and TSH levels decreased with the severity of COVID-19 [19]. These evidences reflected that the effects of SARS-CoV-2 on the thyroid were different.

Table 3 Correlation between thyroid hormone and hs-CRP, TNF-α or IL-6

	FT3		FT4		log-transformed TSH	
	Pearson correlation coefficient	*P* value	Pearson correlation coefficient	*P* value	Pearson correlation coefficient	*P* value
Total (*N* = 100)						
log-transformed hs-CRP	− 0.66	< 0.001	− 0.06	0.546	− 0.47	< 0.001
log-transformed IL-6	− 0.60	< 0.001	− 0.11	0.258	− 0.44	< 0.001
log-transformed TNF-α	− 0.44	< 0.001	− 0.12	0.223	− 0.18	0.070
Non-severely ill patients (*N* = 34)						
log-transformed hs-CRP	− 0.50	0.003	− 0.08	0.657	− 0.23	0.198
log-transformed IL-6	− 0.39	0.023	− 0.20	0.259	− 0.14	0.416
log-transformed TNF-α	− 0.22	0.206	0.003	0.985	0.001	0.995
Survivors (*N* = 44)						
log-transformed hs-CRP	− 0.57	< 0.001	0.13	0.395	− 0.45	0.002
log-transformed IL-6	− 0.59	< 0.001	0.04	0.793	− 0.27	0.082
log-transformed TNF-α	− 0.48	0.001	− 0.16	0.286	− 0.05	0.752
Non-survivors (*N* = 22)						
log-transformed hs-CRP	− 0.35	0.109	− 0.12	0.595	− 0.30	0.174
log-transformed IL-6	− 0.04	0.864	− 0.07	0.771	− 0.40	0.063
log-transformed TNF-α	0.10	0.672	− 0.06	0.785	− 0.03	0.879

FT3 free T3, *FT4* free T4, *hs-CRP* high-sensitivity C-reactive protein, *IL-6* interleukin-6, *TNF-α* tumor necrosis factor α

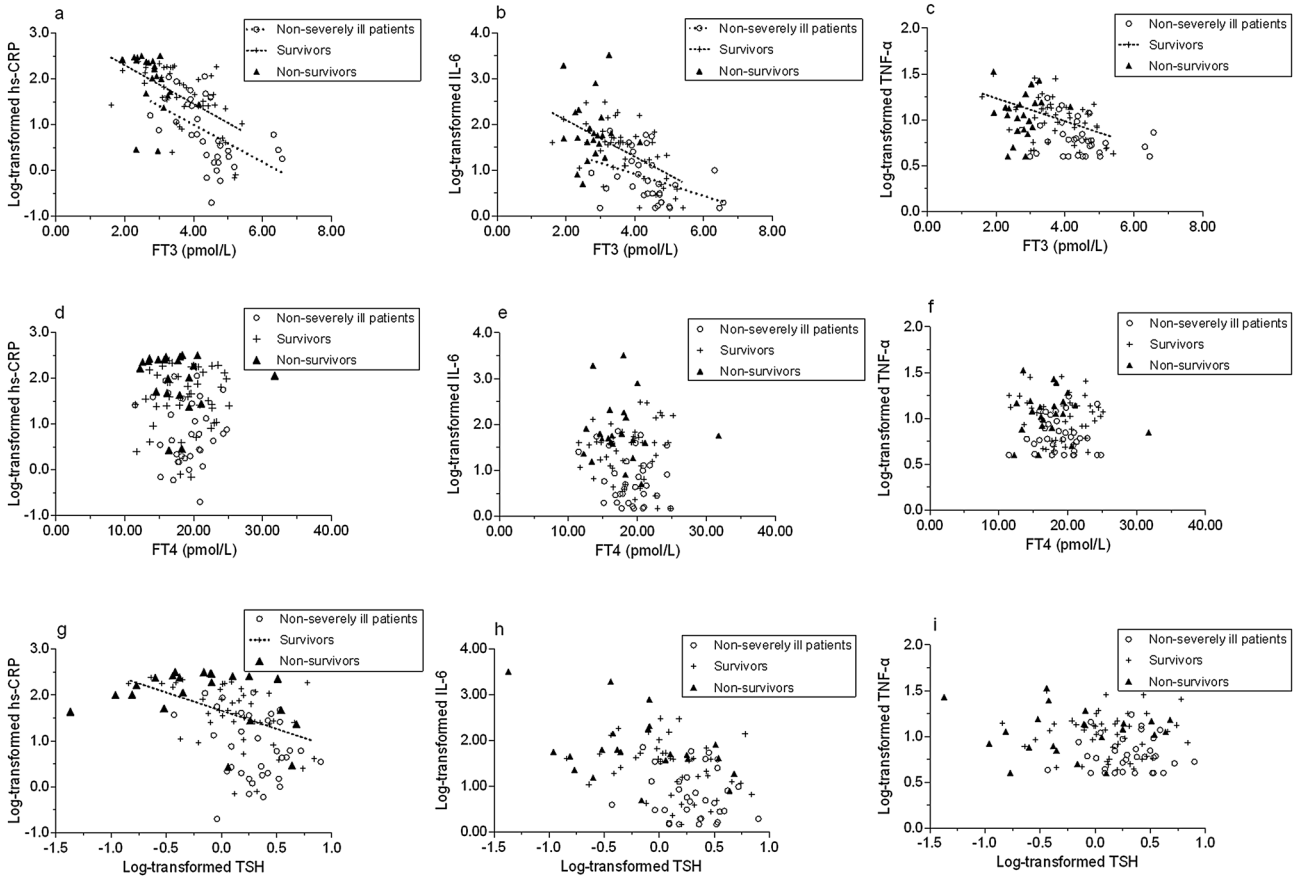

Fig. 3 Scatterplots of thyroid hormone and hs-CRP, IL-6 or TNF-α according to clinical severity and outcome of COVID-19. **a** log-transformed hs-CRP versus free T3. **b** log-transformed IL-6 versus free T3. **c** log-transformed TNF-α versus free T3. **d** log-transformed hs-CRP versus free T4. **e** log-transformed IL-6 versus free T4. **f** log-transformed TNF-α versus free T4. **g** log-transformed hs-CRP versus log-transformed TSH. **h** log-transformed IL-6 versus log-transformed TSH. **i** log-transformed TNF-α versus log-transformed TSH. *FT3* free T3, *FT4* free T4, *hs-CRP* high-sensitivity C-reactive protein, *IL-6* interleukin-6, *TNF-α* tumor necrosis factor α

Some studies focused on thyroid function in patients with specific causes of illness. In hospitalized patients with acute heart failure, low FT3 was associated with longer hospital stay and increased ICU admission rate. Low T3 was also a predictor of in-hospital cardiovascular death in patients with acute myocardial infarction [4] and all-cause mortality in patients with chronic renal failure [3]. In patients with acute-on-chronic liver failure, reduced TSH, rather than low T3 or low T4, was an independent predictor of death [6]. In a community of elderly people who were followed up over 9 years, lower TSH was found to be associated with an increased risk of death [7]. Studies have shown that in the acute phase of critically ill patients, the reduction of T4 to T3 in peripheral tissues was the main reason for the decrease in T3 concentration. In the acute phase, short-term increases in TSH and T4 were observed as well. During the prolonged period of critical illness, central suppression of the thyroid axis may play an important role, causing probably T3, T4, and TSH concentrations to be reduced [20]. In a previous report on COVID-19 critically ill patients admitted to the ICU, the median time from symptom onset to admission to the ICU was 9 days for survivors and 11 days for non-survivors [21]. In the current exploration, NTIS mainly manifested as a reduction of FT3 (28%), while only a low proportion of patients showed a reduction in FT4 (3%) and TSH (7%). These findings might reflect the characteristics of rapid progression in critically ill COVID-19 patients.

The cause of NITS remains unclear. Excessive inflammatory response triggered by SARS-CoV-2 infection is likely one of the reasons that COVID-19 patients develop critical illness or death [22]. The process by which the body overproduces cytokines and chemokines is called "cytokine storm", which is considered to be an important mechanism for the occurrence of ARDS [23]. Pro-inflammatory cytokines such as tumor necrosis factor [24] and IL-6 [25] were also speculated to be involved in the pathogenesis of NITS. But a study in patients undergoing abdominal surgery found that T3 had already decreased

when IL-6 had not yet increased [26]. Our data did not dynamically observe changes in FT3 and inflammatory factors; furthermore, we cannot speculate on the relationship between low FT3, hs-CRP and pro-inflammatory cytokines in patients with COVID-19. In our study, however, hs-CRP and IL-6 were negatively correlated with FT3 only in non-severely ill patients and survivors; TNF-α was negatively correlated with FT3 only in survivors; while in non-survivors, hs-CRP, IL-6 and TNF-α were not related to FT3. It is suggested that in different clinical stages of patients with COVID-19, the inflammatory response may play different roles in the pathogenesis of NITS.

After the outbreak of COVID-19, the centralized admission and quarantine of the patients and the dispatch of the medical support team of the Peking University Medical Center allowed us to treat and collect clinical data on a large number of COVID-19 patients in a short time to observe thyroid function characteristics and its predictive effect on clinical outcome. The limitations of our study include that this is a single-center study. The ward taken over by our medical team was assigned higher severity patients with COVID-19. Therefore, the results of this study are more representative of thyroid function characteristics of patients with severe COVID-19. The median time from the patient's presentation of COVID-19 infection symptoms to admission to the ward was about 2 weeks. Many patients only had a thyroid function measurement at the time of admission, so it was difficult to determine whether the change in thyroid function was related to progression of the disease. Moreover, 12 patients were not discharged at the end of follow-up. The patients we studied included a small number of people who had used glucocorticoids. However, the sensitivity analysis results after removing these patients were not different from the main research results, indicating that use of glucocorticoids in these patients did not substantially affect the results of this study.

In conclusion, the FT3 concentration was significantly lower in patients with severe COVID-19 than in non-severely ill patients. The reduced FT3 independently predicted all-cause mortality of patients with severe COVID-19. FT3 may become a simple tool for stratified management of patients with severe COVID-19.

Acknowledgements We sincerely thank the medical team members dispatched by Peking University Medical Center to Wuhan for assistance in the treatment of COVID-19 and for their contributions to the data collection.

We thank Jennifer Shine, Song Zhang and Leyi Cui for their help in revising the English language of this article.

Funding This work is supported by Grants 2016YFC1305600, 2016YFC1305603 from the Major Chronic Non-communicable Disease Prevention and Control Research, National Key R&D Program of China.

Compliance with ethical standards

Conflict of interest All authors have no conflict of interest to declare.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study, formal consent is not required.

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