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Thyroxine changes in COVID-19 pandemic: A systematic review and meta-analysis

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Objective: COVID-19 infection may affect thyroid function. However, changes in thyroid function in COVID-19 patients have not been well described. This systematic review and meta-analysis assess thyroxine levels in COVID-19 patients, compared with non-COVID-19 pneumonia and healthy cohorts during the COVID-19 epidemic.

Methods: A search was performed in English and Chinese databases from inception to August 1, 2022. The primary analysis assessed thyroid function in COVID-19 patients, comparing non-COVID-19 pneumonia and healthy cohorts. Secondary outcomes included different severity and prognoses of COVID-19 patients.

Results: A total of 5873 patients were enrolled in the study. The pooled estimates of TSH and FT3 were significantly lower in patients with COVID-19 and non-COVID-19 pneumonia than in the healthy cohort ($P < 0.001$), whereas FT4 were significantly higher ($P < 0.001$). Patients with the non-severe COVID-19 showed significant higher in TSH levels than the severe ($I^2 = 89.9\%$, $P = 0.002$) and FT3 ($I^2 = 91.9\%$, $P < 0.001$). Standard mean differences (SMD) of TSH, FT3, and FT4 levels of survivors and non-survivors were 0.29 ($P = 0.006$), 1.11 ($P < 0.001$), and 0.22 ($P < 0.001$). For ICU patients, the survivors had significantly higher FT4 (SMD=0.47, $P = 0.003$) and FT3 (SMD=0.51, $P = 0.001$) than non-survivors.

Conclusions: Compared with the healthy cohort, COVID-19 patients showed decreased TSH and FT3 and increased FT4, similar to non-COVID-19 pneumonia. Thyroid function changes were related to the severity of COVID-19. Thyroxine levels have clinical significance for prognosis evaluation, especially FT3.

KEYWORDS

free triiodothyronine (FT3), free thyroxine (FT4), thyroid stimulating hormone (TSH), COVID-19, severity (S)

Introduction

COVID-19 pneumonia is caused by SARS-CoV-2 and broke out in 2019, causing unprecedented issues worldwide. SARS-CoV-2 infection can trigger systemic inflammatory symptoms involving systemic multi-organ multisystem dysfunction (1, 2). Since the pandemic outbreak, several studies have demonstrated varying degrees of impaired thyroid function in patients with COVID-19 (3, 4). Viral infections may affect thyroid function through hormones and immunoregulatory signaling molecules. However, changes in thyroid function in patients with COVID-19 have not been well described, and the particular mechanism is still controversial. Some mechanisms proposed are the virus's direct or indirect invasion of the thyroid gland, effects of systemic inflammatory immune responses, and nonspecific adaptive mechanisms (5, 6). Previous studies have examined whether thyroid diseases increase the risk of adverse outcomes in patients with COVID-19. Some studies concluded that thyroid diseases do not affect the progression of COVID-19, whereas some reported poor outcomes in patients with COVID-19 and thyroid diseases (7, 8). Several narrative and systematic reviews have revealed conflicting results about the relationship between thyroid and COVID-19, arguing that thyroid diseases are unrelated to SARS-CoV-2 infection and deterioration (9–11). Conclusions may be controversial due to the lack of large-scale clinical studies. This study aims to evaluate available evidences systematically, assess the level of thyroid function in patients with COVID-19 through meta-analysis, and analytically compare differences in thyroid function among different populations during the epidemic. Non-COVID-19 pneumonia patients and healthy people during the epidemic were included in the study as controls.

Methods

Protocols and registration

Our methods were based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (MOOSE) guidelines (eMethods 1 in the Supplement) and were registered in the International Prospective Register of Systematic Reviews (PROSPERO) database. The protocol number is CRD42022346568.

Search strategy

We systematically searched PubMed/MEDLINE, Cochrane Reviews, Cochrane Central Register of Controlled Trials (Central), Web of Science and Embase databases in August 2022 without language restrictions. All published articles related to thyroid-related hormones and COVID-19 were searched. The literature search strategy was based on the following keywords: ([T3 OR FT3 OR triiodothyronine] or [T4 OR FT4 OR thyroxine] or [TSH or thyrotropin]) and (COVID-19 OR SARS-CoV-2 OR 2019 novel coronavirus). We then performed a manual search of studies meeting our inclusion criteria to identify articles apart from those found in the electronic databases. Two independent reviewers (ZL

and PH) performed the first step of title/abstract screening and the second step of full-text assessment in the search process, and any disagreement that arose during this process was discussed until an agreement was reached.

Study selection

We included observational studies in China and English language, to evaluate the correlation between COVID-19 disease and thyroxine levels. The complete list of articles obtained through the systematic search was screened to remove duplicates and exclude ineligible articles, including reviews, case reports, and studies with less than 20 patients. According to the inclusion or exclusion criteria, the full texts of all potentially qualified studies were independently reviewed by two reviewers (ZL) and (PH). Disagreements were addressed through discussion. A third reviewer (SM) resolved disagreements when a consensus could not be reached.

Main outcomes and measures

The primary analysis assessed thyroid function in COVID-19 patients, comparing non-COVID-19 pneumonia and healthy cohorts. Secondary outcomes included different severity and prognoses of COVID-19 patients. Thyroxine levels of follow-up were also included.

Data extraction

Basic Information, including author, country, type of study, sample size, mean or median age, sex ratio, and primary outcomes, such as death, severity, and survival, was extracted from the selected studies. The levels of thyroid hormones (FT3, FT4, and TSH) were extracted from patients in acute admission, survivors during follow-up, and deceased patients, in addition to those of healthy people and non-COVID-19 pneumonia patients during the pandemic. All extracted data were tabulated, and indexes measured by each research center were converted and unified.

We extracted data using standardized data abstraction forms. In case of missing data needed to conduct our meta-analyses, we contacted the authors, with a reminder 2 weeks later. Non-published data obtained from authors by communication are mentioned in the results section below, as applicable, with permission, and authors who responded are listed in Acknowledgments section.

Quality assessment

Two reviewers independently assessed the risk of biases, including selection, performance, detection, attrition, and reporting biases, rated as low, high, or unclear risk. The quality of the included studies was evaluated using the Newcastle–Ottawa scale (eTables 1, 2 in the Supplement). The scale has a score of nine, and a seven or

higher indicates high quality. Two reviewers performed data extraction and quality assessment independently, and a third reviewer checked the results. Disagreements were resolved by discussion.

Statistical analysis

Continuous data (thyroxine levels: TSH, FT3, and FT4) were synthesized using mean difference (MD) with standard deviation from each study for the calculation of the average MD with a 95% confidence interval (CI). We applied Wan's formula to estimate the relative means and standard deviations when continuous data were presented as medians and ranges (12). Adjusted SMD based on corrected data and other potential confounders were also presented. Meta-analyses were performed using the inverse variance method with the random-effects model when heterogeneity was statistically significant. The DerSimonian-Laird method with the fixed-effect model was used when heterogeneity was not statistically significant. Heterogeneity was assessed using Cochrane Q-test and I^2 statistic, and a p -value of <0.05 indicated statistically significant heterogeneity. According to the Cochrane Handbook for Systematic Reviews of Interventions, the ranges of interpretation for I^2 are as follows: 0%–40%, unimportant; 30%–60%, moderate heterogeneity; 50%–90%, substantial heterogeneity; and 75%–100%, considerable heterogeneity. All analyses were conducted using RevMan (version 5.4.1).

Results

The search time was up to August 2022, 635 relevant articles were screened, and 523 articles were excluded according to the titles and

abstracts (Figure 1). The full texts of 112 articles were reviewed. Finally, 41 articles from 38 studies were included in the final analysis, totaling 5873 COVID-19 patients (13–38) (Figure 2). The control group included 269 patients with non-COVID-19 pneumonia and 1052 healthy people during the epidemic. The Characteristics of the included studies are presented in Table 1.

Thyroxine levels at admission

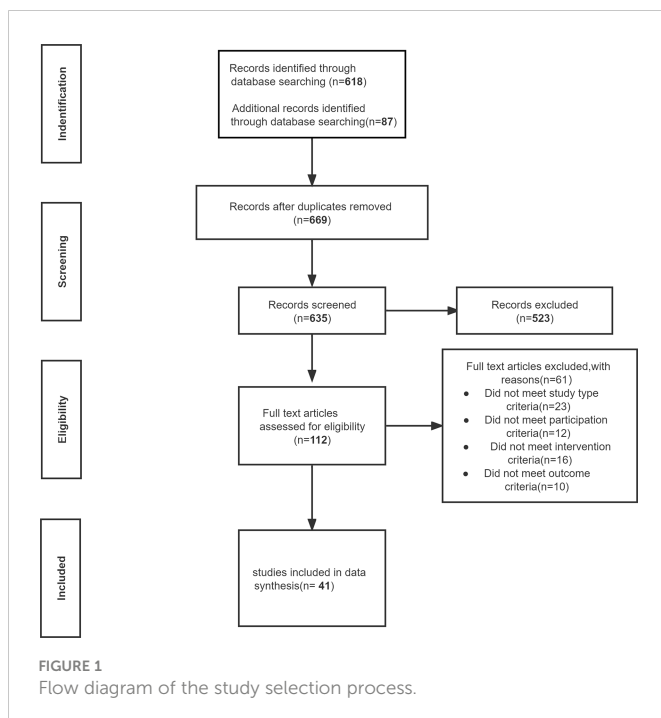
A total of 36 studies recorded thyroxine levels at admission, including 5752 cases (13–24, 26, 38, 39). eFigure 1 in the Supplement depicts the pooled estimates of TSH (SMD = 1.46, 95% CI, [1.29, 1.62]), FT3 (SMD = 3.86, 95% CI, [3.59, 4.13]), and FT4 levels (SMD = 15.97, 95% CI, [15.24, 16.70]) by a mixed-effected model, including thirteen East Asian studies, six South Asian studies, three Asian studies, twelve European studies, one American study, and one African study. Subgroup analyses of Asian and European studies were performed (eFigure 2 in the Supplement). The pooled results suggested that high heterogeneity in TSH level ($I^2 = 92.9\%$, $p < 0.001$) and FT3 level ($I^2 = 80.3\%$, $p = 0.02$) but not in FT4 levels ($I^2 = 0.0\%$, $p = 0.81$).

Thyroxine levels in non-COVID-19 pneumonia and healthy cohort in the COVID-19 pandemic

Six studies recorded the thyroxine levels of healthy cohorts as control groups ($n = 1052$). The pooled estimates of TSH, FT3, and FT4 levels were 1.78 (95% CI, [1.56, 2.01]), 4.76 (95% CI, [4.44, 5.08]), and 14.03 (95% CI, [12.93, 15.13]), respectively (eFigure 3 in the Supplement) (14, 18, 36, 40–42). Five studies included the thyroxine levels of non-COVID-19 pneumonia patients ($n = 269$) (14, 18, 42–44). The pooled estimates of TSH, FT3, and FT4 levels were 1.22 (95% CI, [1.05, 1.40]), 3.66 (95% CI, [3.48, 3.83]), and 18.19 (95% CI, [15.61, 20.78]), respectively. TSH and FT3 levels were significantly lower in patients with COVID-19 and non-COVID-19 pneumonia than in the healthy cohort ($p < 0.001$), whereas FT4 levels were significantly higher than in the healthy cohort ($p < 0.001$).

Thyroxine levels in patients with different levels of COVID-19 severity

According to the results of single-arm meta-analysis (eFigure 4 in the Supplement), patients with non-severe COVID-19 ($n = 1697$) and severe COVID-19 ($n = 1022$) showed significant heterogeneity in TSH level ($I^2 = 89.9\%$, $P = 0.002$) and FT3 level ($I^2 = 91.9\%$, $P < 0.001$). Patients with non-severe COVID-19 had higher TSH and FT3 levels, and no heterogeneity in FT4 levels was found between the groups ($I^2 = 0.0\%$, $P = 0.72$). Ten articles compared patients with severe and non-severe COVID-19 in terms of thyroid function. Differences in the three indicators were statistically significant, and the pooled estimates of TSH, FT3, and FT4 levels were 0.40 ($P = 0.010$), 0.79 ($P < 0.001$), and -0.18 ($P = 0.03$), respectively. Three studies of the WHO classified COVID-19 severity compared patients with non-severe and severe COVID-19 (7, 28, 45). The results



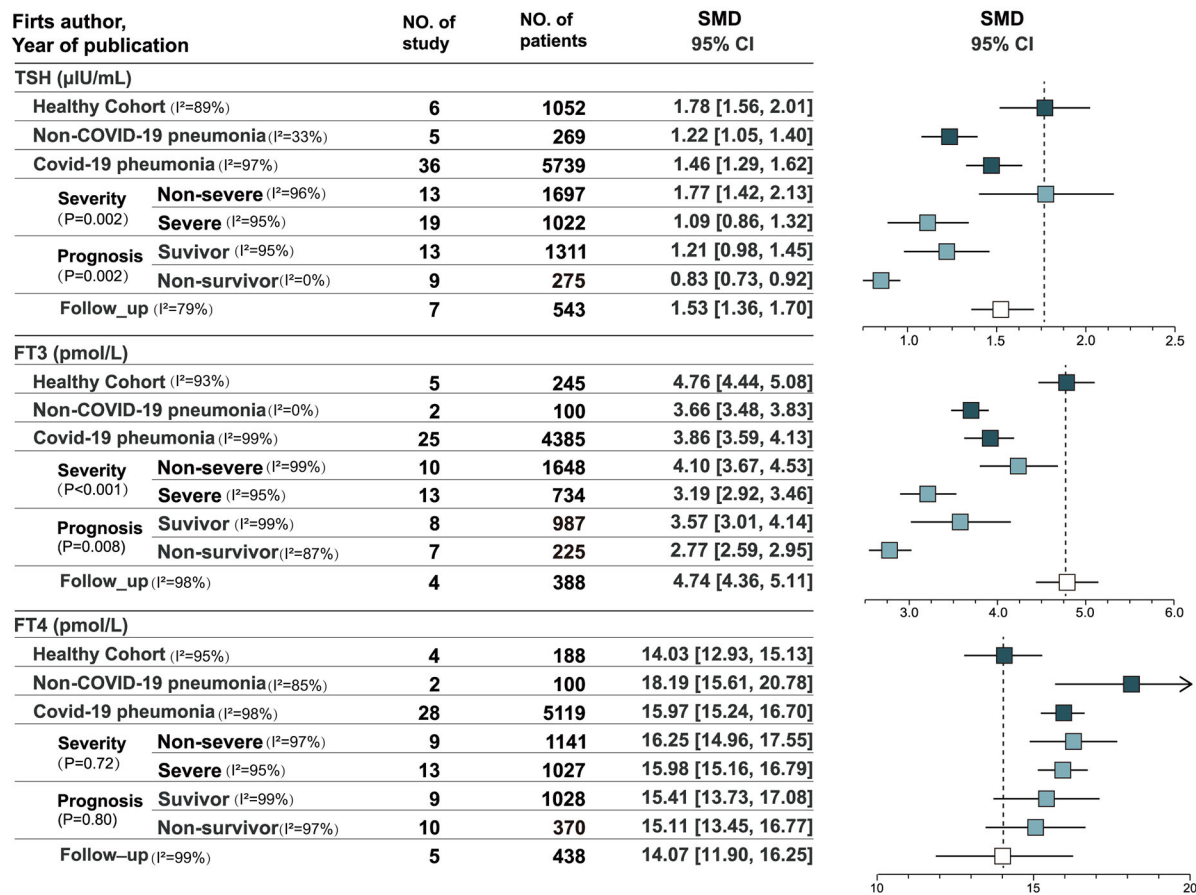


FIGURE 2
Forest plot for all studies.

suggested no significant differences in TSH level ($P = 0.54$) and FT3 level ($P = 0.06$) between non-severe and severe patients, and only FT4 levels ($P = 0.006$) were significantly different (eFigure 5 in the Supplement), which were higher in patients with severe COVID-19. Significant heterogeneity in differences in TSH level ($I^2 = 91.0\%$, $P < 0.001$) and FT3 level ($I^2 = 91.0\%$, $P < 0.001$) was found in studies that used the WHO's classification, whereas no significant heterogeneity was found in difference in FT4 levels ($I^2 = 0.0\%$, $P = 0.39$). Non-WHO analysis used an SpO₂ of 93% or 94% as the cutoff between severe and non-severe COVID-19. Seven studies that used non-WHO criteria compared the thyroid functions of patients with severe and non-severe COVID-19 (13, 14, 18, 29, 43, 46, 47). The pooled estimates suggested that TSH levels were significantly lower in patients with severe COVID-19 ($P < 0.001$), and moderate heterogeneity in differences in TSH levels was found ($I^2 = 52.0\%$, $P = 0.05$). FT3 levels were lower in patients with severe COVID-19 ($P < 0.001$), and no significant heterogeneity in differences in FT3 levels was found ($I^2 = 0.0\%$, $P = 0.47$). However, no difference in FT4 level was observed ($P = 0.61$). Only differences in FT4 levels were heterogeneous in the subgroup heterogeneity analysis ($I^2 = 64.9$, 6%, $P = 0.09$). No significant differences in TSH level ($I^2 = 0.0\%$, $P = 0.61$) and FT3 level ($I^2 = 0.0\%$, $P = 0.92$) were found between the WHO and non-WHO clinical classifications.

Thyroxine levels in different prognoses of patients with COVID-19

The single-arm meta-analysis (eFigure 6 in the supplement) showed no significant heterogeneity in FT4 levels ($I^2 = 0.0\%$, $P=0.80$) and significant heterogeneity in TSH level ($I^2 = 89.4\%$, $P=0.002$) and FT3 level ($I^2 = 85.8\%$, $P=0.008$) in survivors ($n = 1311$) and non-survivors ($n = 275$). Nine articles compared the thyroxine levels of survivors and non-survivors (eFigure 7 in the Supplement). Differences in TSH, FT3, and FT4 levels were statistically significant, with a SMD values of 0.29 ($P = 0.006$), 1.11 ($P < 0.001$), and 0.22 ($P < 0.001$), respectively. According to the reference ranges, differences in TSH and FT4 levels were small. In the analysis of ICU patients, three studies compared survivors and non-survivors (17, 24, 32). No significant difference in TSH ($P = 0.74$) levels was found among ICU patients, but significant difference in FT4 ($P = 0.003$) and FT3 ($P = 0.001$) levels were found. The survivors had significantly higher FT4 and FT3 levels than non-survivors. The pooled mean differences in FT3 and FT4 levels were 0.51 (95% CI, [0.21, 0.82]) and 0.47 (95% CI, [0.16, 0.77]). Six studies included COVID-19 patients in all wards (13, 19, 24, 29, 35, 48). Significant differences in TSH ($P < 0.001$), FT3 ($P < 0.001$) and FT4 ($P = 0.02$) levels were found, with mean differences of 0.46 (95% CI, [0.25, 0.67]),

TABLE 1 Description of eligible studies reporting the association between thyroid-related hormones and COVID-19.

Author	Country	No. patients	Sex	Average age	Severity	Outcome	Control group	Thyroxine
Ahn (2021)	Korea	119	Male: 62	64	Non-severe: 32	Survivor: 85		TSH FT4
			Female: 57		Severe: 87	Non-survivor: 34		FT4
Ardes (2021)	Italy	118	Male: 64	73	Non-severe: 75	Survivor: 92		TSH
			Female: 54		Severe: 43	Non-survivor: 26		
Assimakopouls (2021)	Greece	22	Male: 11	62	Non-severe: 13		Healthy cohort: 19	TSH
			Female: 11		Severe: 9		Non-COVID-19 pneumonia: 19	FT3
								FT4
Baldelli (2021)	Italy	46	Male: 32	60	Non-ICU: 23			TSH
			Female: 14		ICU: 23			FT3
Beltrao (2021)	Brazil	245	Male: 145		Non-critical: 181	Survivor: 204		TSH
			Female: 100		Critical: 64	Non-survivor: 41		FT3
								FT4
Campi (2021)	Italy	73			ICU: 73	Survivor(ICU): 57		TSH
					Non-survivor(ICU): 16			
Chen (2020)	China	274	Male: 171	59		Recover: 161		TSH
			Female: 103			Death: 113		FT3
Chen (2021)	China	50	Male: 33	48	Non-severe: 15	Survivor: 50	Healthy cohort: 54	TSH
			Female: 21		Severe: 35		Non-COVID-19 pneumonia: 50	
Clarke (2021)	UK	70	Male: 47	56	Non-severe: 42	Survivor: 70		TSH
			Female: 23		Severe: 28			FT3
								FT4
Clausen (2021)	Denmark	116	Male: 44	71		Survivor: 82		TSH
			Female: 72			Non-survivor: 34		FT4
Dabas (2021)	India	164	Male: 107	41	Non-severe: 100			TSH
			Female: 57		Severe: 64			FT3
								FT4
Das (2021)	India	84	Male: 42	41	Non-severe : 499			TSH

(Continued)

Continued

Author	Country	No. patients	Sex	Average age	Severity	Outcome	Control group	Thyroxine
			Female: 42		Severe: 35			FT3
								FT4
Dutta (2021)	India	236	Male: 159	54	Non-severe: 200	Survivor: 225		TSH
			Female: 77		Severe: 36	Non-survivor: 11		FT3
								FT4
Gao (2021)	China	100	Male: 52	63	Non-sever: 34	Survivor: 44		TSH
			Female: 48		Severe: 66	Non-survivor: 22		FT3
								FT4
Gong (2021)	China	150	Male: 81	70	Non-sever: 25	Survivor: 118		TSH
			Female: 69		Severe: 125	Non-survivor: 42		FT3
								FT4
Grondman (2021)	Netherlands	161	Male: 56	65	Non-ICU: 120	Survivor: 141		TSH
			Female: 105		ICU: 41	Non-survivor: 20		FT4
Gliven (2021)	Turkey	250	Male: 157	67	Non-ICU: 125	Survivor(ICU): 88		TSH
			Female: 93		ICU: 125	Non-survivor(ICU): 37		FT3
								FT4
Khoo (2020)	UK	334	Male: 203	66		Survivor: 239		TSH
			Female: 131			Non-survivor: 95		FT4
Kumar (2021)	India	235	Male: 147	49	Non-severe: 202	Survivor: 222		TSH
			Female: 88		Severe: 33	Non-survivor: 13		FT3
								FT4
Lang (2021)	China	127	Male: 62	64	Non-severe: 56	Survivor: 116		TSH
			Female: 65		Severe: 71	Non-survivor: 11		FT3
								FT4
Li (2020)	China	40		44	Non-severe: 40		Healthy cohort: 57	TSH
								FT3
								FT4
Lui (2020-2021)	China	541	Male: 245	50	Non-severe: 499	Survivor: 283		TSH
			Female: 196		Severe: 42			FT3

(Continued)

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Author	Country	No. patients	Sex	Average age	Severity	Outcome	Control group	Thyroxine	
								FT4	
Malik (2021)	Pakistan	48	Male: 31	51	Non-severe: 22	Survivor: 48	Non-COVID-19 pneumonia: 28	TSH	
			Female: 17		Severe: 26				
Nakamura (2021)	Japan	147	Male: 95	70	Non-severe: 63			TSH	
			Female: 52		Severe: 84			FT3	
								FT4	
Okoye (2022)	Italy	95	Male: 50	82		Survivor: 70	Non-COVID-19 pneumonia: 81	TSH	
			Female: 45			Non-survivor: 25		FT3	
								FT4	
Okwor (2021)	Nigeria	45	Male: 95	35			Healthy cohort: 45	TSH	
			Female: 52						FT3
									FT4
Schwarz (2021)	Israel	54	Male: 37	59	Non-ICU: 37	Survivor: 44		TSH	
			Female: 17		ICU: 17	Non-survivor: 10		FT3	
								FT4	
Sciacchitano (2021)	Italy	62	Male: 29	67				TSH	
			Female: 33						FT3
									FT4
Sen (2021)	India	60			Non-severe: 42			TSH	
					Severe: 18				FT3
									FT4
Sparano (2022)	Italy	506	Male: 315	69	Non-severe: 506			TSH	
			Female: 191						FT4
Urhan(2022)	Turkey	64	Male: 32	39	Non-severe: 38	Survivor: 64	Healthy cohort: 70	FT3	
			Female: 32		Severe: 26				
Vassiliadi (2021)	Greece	102	Male: 76	55	Non-ICU: 61	Survivor: 88		TSH	
			Female: 26		ICU: 41	Non-survivor: 14		FT4	
Vizoso (2021)	Spain	78	Male: 55	62	ICU: 78	Survivor(ICU): 55		TSH	
			Female: 23			Non-survivor(ICU): 23		FT3	
									FT4

(Continued)

Continued

Author	Country	No. patients	Sex	Average age	Severity	Outcome	Control group	Thyroxine	
Wang (2021)	China	84	Male: 53	57	Non-severe: 21	Survivor: 84	Healthy cohort: 807	TSH	
			Female: 31		Severe: 63			Non-COVID-19 pneumonia: 91	
Yazan (2021)	Turkey	205	Male: 113	58	Non-ICU: 174	Survivor: 196		TSH	
			Female: 92		ICU: 31			Non-survivor: 95	FT3
									FT4
Zhao (2022)	China	384	Male: 197	64	Non-severe: 161	Survivor: 219		TSH	
			Female: 87		Severe: 212			Non-survivor: 16	FT3
									FT4
Zheng (2021)	China	235	Male: 112	60		Survivor: 219		TSH	
			Female: 123					Non-survivor: 16	FT3
									FT4
Zou (2020)	China	149	Male: 71	49	Non-severe: 123	Survivor: 146		TSH	
			Female: 78		Severe: 26			Non-survivor: 1	FT4

1.39 (95% CI,[0.86,1.92]), and 0.17 (95% (49) CI,[0.03,0.31]), respectively. All three indexes were higher in survivors.

Thyroxine levels during follow-up

Seven studies reassessed thyroid function after acute COVID-19 (eFigure 8 in the Supplement) (17, 18, 27, 34, 41, 43, 50). The pooled estimates of TSH, FT3, and FT4 levels were 1.53 (95% CI, [1.36, 1.70]), 4.74 (95% CI, [4.36, 5.11]), and 14.07 (95% CI, [11.90, 16.25]), respectively, without significant heterogeneity across studies. TSH, FT3, and FT4 levels were recovered during follow-up compared with the acute period. TSH and FT3 levels increased, whereas FT4 levels decreased compared with the acute phase.

Discussion

SARS-CoV-2 can damage multiple organs, including the lungs, liver, heart, brain, and kidneys, leading to systemic symptoms. The thyroid gland highly expresses the ACE2 receptor. Thus, the hypothalamic–pituitary–thyroid axis may be susceptible to the disturbance in patients with COVID-19 (22, 34, 41, 51, 52). SARS-CoV, a coronavirus related to SARS-CoV-2, injures thyroid parafollicular and follicular cells (53). Lui et al. found that high SARS-CoV-2 viral loads were associated with small thyroid volumes (37). This association suggested a direct viral effect on the thyroid gland. Lania et al. revealed that COVID-19 might be associated with the high risk of thyrotoxicosis (n = 31, 10.8%) in a

retrospective study that enrolled 287 patients (54). However, the autopsy results suggested the absence of the virus was in thyroid tissues (55–57). The number of reported thyrotoxicosis cases in literature did not exponentially increase, including critically ill patients (13, 15, 28, 32, 34). Thyrotoxicosis may be a rare complication of COVID-19 (51).

Many studies revealed that thyroid function significantly changes during COVID-19 infection. The trends of thyroxine level fluctuations in patients with COVID-19 and non-COVID-19 pneumonia were similar (decreased TSH and FT3 levels and increased FT4 levels). This similarity suggests that COVID-19 and non-COVID-19 pneumonia affect the thyroid gland through similar mechanisms. In addition, thyroxine levels during follow-up indicated progressive improvement and transient hormone changes (17, 34). Patients suffering from COVID-19 and thyroxine fluctuation potentially encountered non-thyroidal illness syndrome (NTIS) induced by systemic inflammation (58, 59). NTIS is an adaptive response to stress, critical illness, and malnutrition, manifested by a decrease in FT3 levels or decreases in TSH, FT3, and FT4 levels in severe disease (58, 60). Since systemic inflammation potentially impacts the de-iodinase activity, it inhibits T4–T3 conversion decreases FT3 levels and increases FT4 levels (17, 61, 62). Elevated FT4 level upon admission tends to be mistaken for thyrotoxicosis. Most studies have investigated thyroxine changes in COVID-19 at admission. NTIS in patients with long-term critical illness shows symptoms similar to hypothyroidism (59, 63, 64). Unlike thyrotoxicosis, treatment with thyroid hormone is not recommended without clinical signs of hypothyroidism. Even mild hypothyroidism can be considered a physiologically favorable

condition that can suppress energy expenditure and eventually restrict catabolism by decreasing thyroid hormone activity (63). Thyroid function can recover in patients without intervention (18, 58, 65, 66).

Immunoassays for thyroxine can be affected by alterations in serum binding protein that occurs in various physiological states (20). Decreased TSH and increased FT4 levels were reported in the healthy cohort during the COVID-19 outbreak (67). During the pandemic, relationships were found between thyroid diseases and psychiatric factors, such as anxiety and depression (68, 69). The pandemic socio-psychological sequelae can constitute stressors for the population, potentially affecting the thyroid gland. Collectively, patients with COVID-19 are at risk of thyroid diseases and require attention.

Thyroid function parameters have clinical significance in determining disease severity and prognosis of COVID-19. Whether the severity of COVID-19 is associated with thyroid function remains unclear. Some studies reported no significant relationship between COVID-19 severity and thyroid function, whereas other studies have suggested that only some statistically significant indicators compare disease severity (7, 13, 14, 28, 45, 47). It may be related to multiple factors, including different criteria adopted in different regions. The classifications of COVID-19 severity vary. The WHO uses SpO₂ of less than 90% as a cutoff between severe and non-severe COVID-19. By contrast, the United States, China, and Japan use 93% or 94% as a division basis in diagnosis and treatment guidelines (14, 19, 47, 70). In the present study, the single-arm meta-analysis results revealed that only TSH and FT3 levels were significantly different compared to patients with severe-critical and non-severe COVID-19. The case-control study showed that although the FT4 levels differed significantly, the difference was only 0.18, with minor practicality. In the acute phase, TSH and FT3 levels at admission in COVID-19 patients can be used in assessing patient severity.

Thyroid function is not a routine test indicator in patients infected with COVID-19. Some studies have suggested that thyroid function cannot be used in evaluating the prognosis of patients, or only some indicators can be used in the prognostic analysis (13, 32, 48, 71). In the present study, TSH, FT3, and FT4 levels presented significant differences between survivors and deceased patients at admission. The results of the single-arm meta-analysis suggested that only TSH and FT3 levels were heterogeneous between survivors and non-survivors. The controlled studies showed statistically significant differences in the three thyroid function parameters. However, we found that differences in TSH (SMD = 0.29) and FT4 (SMD = 0.22) levels were limited for assessing prognosis. Compared with TSH and FT4, FT3 levels may be more effective (SMD = 0.79). A low FT3 level is an outcome predictor, especially in severe patients (5). The excessive production of proinflammatory cytokines during SARS-CoV-2 infection aggravates ARDS and tissue damage resulting in multi-organ failure and death (72, 73). In patients with COVID-19, FT3 levels decrease with the increasing levels of inflammatory cytokines. Some studies have suggested that improving thyroid function can improve patient outcomes. However, a reduction in FT3 levels occurs before clinical symptoms worsen. This reduction can be used in assessing changes in patient condition and prognosis (74).

Survivor bias may have been present when prognostic thyroid function was being determined. Thyroid function is an

unconventional test indicator for patients with COVID-19. Medical centers tend to assess the thyroid function in patients with underlying thyroid diseases or other severe illnesses. Moreover, the pharmacological doses of steroids in severe COVID-19 can affect thyroid function. Therefore, comprehensive extensive clinical studies are needed to evaluate the significance of thyroid function assessment for patients with COVID-19.

Limitations

This study has several limitations. First, thyroid function is not a routine test indicator for COVID-19. Many studies have a selection bias for patients tested for thyroid function levels and have an incomplete recording of test results, especially TT3 and TT4 results. Second, heterogeneity was found among the included studies. Third, thyroid function often showed non-normal distribution. The median percentage transformation was used in the meta-analysis. Fourth, the cohort studies' sample size with a detailed thyroxine record was limited after reasonable sorting.

Conclusion

Thyroxine levels (TSH, FT3, and FT4) fluctuated in patients with COVID-19. Compared with the healthy cohort, patients with COVID-19 showed decreased TSH and FT3 levels and increased FT4 levels. There were differences in thyroxine levels between severe and non-severe patients. No significant difference in TSH levels between severe and non-severe patients according to the WHO classification criteria, whereas FT4 levels were not significantly different in the studies using non-WHO classification criteria. However, FT3 levels were significantly lower in severe patients than in non-severe patients in the included study. In addition, different thyroid function parameters were assessed differently with regard to patient outcomes. TSH and FT4 levels have limitations in the prognostic evaluation of ICU patients and are ineffective in assessing patient outcomes. In general wards, TSH and FT4 are still effective, but the clinical application value is limited due to slight differences. FT3 levels can be adapted as an outcome assessment indicator for patients in ICU or not, with a reliable scope of application. Following the resolution of COVID-19 pneumonia, thyroid function gradually recovers in survivors during follow-up.

Data availability statement

The original contributions presented in the study are included in the article/[Supplementary Material](#). Further inquiries can be directed to the corresponding authors.

Ethics statement

This is a meta-analysis based on observational studies. Informed consent from patients and ethical approval for this type of study are not required.

Author contributions

ZL and PH had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. ZL and PH contributed equally. Concept and design: ZL, PH, HM, SM, MF, SW, YF. Acquisition, analysis, or interpretation of data: ZL, PH, SM, MF, HW, WZ, YC, SW, YF. Drafting of the manuscript: ZL, PH, SW, YF. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: ZL, SW, YF. Administrative, technical, or material support: SM, MF, HW, WZ. Supervision: HM, SM, MF, HW, WZ, YC, PH, SW, YF. Other - protocol review: ZL. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer CL declared a shared affiliation with the authors PH and SM to the handling editor at the time of review.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fendo.2023.1089190/full#supplementary-material>

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