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ORIGINAL ARTICLE

Spectrum of Thyroid Illness in COVID-19

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ABSTRACT

Background: De novo thyroid dysfunction can occur as a result of COVID-1. Patients have diverse manifestations of thyroid illness, ranging from asymptomatic hyperthyroidism to secondary hyperthyroidism.
Aim: To evaluate various thyroid diseases and compare them to mortality and clinicopathological features.
Methods: After approval from the institutional ethical review board, this observational cross sectional study was carried out at a private sector hospital in Karachi. Patients diagnosed with COVID-19 admitted between December 2020 to May 2021 were recruited using consecutive sampling. Patients who did not give informed consent and had known thyroid disorders or history of thyroidectomy were excluded. To analyse the relationship between thyroid laboratory reports, and clinicopathological features, the Chi-square test and "Fischer's exact test" were utilised. SPSS version 21 was used for statistical analysis. A statistically significant P value of 0.05 was used.
Results: Majority of the patients 105(72.9%) had higher FT3 levels and none of them reported with the decreased levels. 88(61.1%) came up with the higher FT4 levels while 9(6.3%) reported with decreased FT4. 9(6.3%) and 6(4.2%) were positive for the anti-thyroperoxidase and anti-thyroglobulin antibodies. The results showed statistical significance for free FT4 (p value 0.018), anti-TG (p-value 0.001) and anti-TP antibodies (p value 0.005).
Conclusion: COVID-19 patients had a high frequency of thyroid abnormalities. Thyroid dysfunction appears to fluctuate over time and to recover slowly and naturally.
Key words: TSH, Thyroid, COVID-19, Anti-thyroglobulin, Anti-Thyroperoxidase, FT4, FT3

INTRODUCTION

Coronavirus-2 illness started in November 2019 in Wuhan, China with new suspicious lung pathology. With the initiation of illness, it was an aggressive and contagious disease, spreads to various parts of the world and declared as a pandemic illness by WHO on March 11, 2020[1]. Since then, it has involved 114,428,211 cases, with more than 2,543,755 deaths all over the world[2]. The commonest system involved in COVID-19 is lung, and anticipating aetiology is thrombosis leading to pulmonary infarction[3]. It has been categorized into asymptomatic carrier, mild, moderate, severe and critical illness according to involvement of lung[4]. Asymptomatic carriers are those who have positive PCR but not having any symptoms. Mild cases are those who have constitutional symptoms along with few lung infiltrates in the bases with maintenance of 02 saturation >94%. Moderate cases are those with involvement of both the lung field as reticulonodular shadows but involvement should be less than 50%. These patients though drop the saturation below 94% with requirement of high flow O_2 via nasal cannula. Severity increases when the involvement of lung progressed to >50%. Critical patients are labelled with the circulatory collapse, ARDS, sepsis and cytokine storm syndrome[5,6]. Along with lung involvement during the past year it has seen that it also involved other organs of the body including kidneys, heart, brain and thyroid gland[7].

However, such broad guideline leaves out information about COVID-19 hazards in people who already have thyroid disorders. We also don't know if COVID-19 patients, symptomatic or not, are at risk[8]. After infection, one may develop de novo thyroid dysfunction[9]. It has been observed that patients develops various manifestation of thyroid disease with subclinical hyperthyroid to secondary hyperthyroid. Although past history of thyroid illness was also seen in these patients but increased mortality is not seen among them[10]. The mortality has been much higher in patients with other co-morbidities like Diabetes mellitus, Heart diseases, and hypertension or kidney diseases[11].

This study was done to assess various abnormalities of thyroid illness and analyse it in relation to mortality.

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METHODS

This observational cross sectional study was conducted at Private sector Hospital, Karachi after taking the approval from the institutional ethical review board (Ref# HCM&D/889/2021). All patients admitted to ICU, ward, HDU from December 2020 to May 2021, diagnosed with COVID-19 were recruited with consecutive sampling technique irrespective of age and gender. Patients with known thyroid diseases or having history of thyroidectomy and who did not give informed consent were excluded.

Patient characterization and data collection: Data will be collected after informed consent of the patient. All patients subjected to have COVID-PCR, TSH, FT3 and FFT4. Thyroid antibodies were done in patients with deranged TSH or low normal TSH level after approval from attendants. For statistical analysis, laboratory values were divided into groups as shown in table: 1

Table 1: Cut off for Lab reports

Test	Values		
	Below normal	Normal range	Increased levels
Thyroid stimulating hormone (TSH)	< 0.4 mIU/L	0.4-4.0mIU/L	> 4mIU/L
Free T_3 (FT3)	< 2.1 pg/ml	2.1-4.4 mg/ml	> 4.4 pg/ml
Free FT4 (FFT4)	< 0.89 ng/dl	0.89-1.76 ng/dl	> 1.76 ng/dl
Anti-Thyroglobulin (Anti-TG)	-	< 40 IU/ml	> 40 IU/ml
Anti-Thyropeoxidase (Anti-TP)	-	< 35 IU/ml	> 35 IU/ml

Data analysis: Statistical values will be taken as mean ± SD for continuous variables and % for categorical variables. In order to examine the normality of data "Shapiro-Wilk test" was applied. "The Chi-square ($\chi 2$) test" and "Fischer's exact test" were used to assess the association between outcome, thyroid laboratory reports and clinicopathological characteristics. For statistical analysis, SPSS version 20 was used. P value of <0.05 was considered as statistically significant.

Potential benefit to the community: This study might help in treatment of COVID patients with thyroid illness and may decrease mortality among them if it is directly related to thyroid abnormalities.

RESULTS

We evaluated results for a total of 144 cases. Gender, age, outcome, TSH, T3, FT4 levels, anti-thyroglobulin and anti-thyroid peroxidase antibodies were recorded. Patients were divided into two age group <=40 years and >40 years for statistical analysis. Out of 144 cases most of the participants were above 40 years of age 124(86.1%). Majority of them were males 54(51.4%) having the mean TSH levels 0f 3.39±11.0, mean FT3 levels 1.7±0.69 and mean FFT4 3.93±3.32.

Association between outcome with clinicopathological characteristic and thyroid levels of cases: On categorical ground we analysed outcome correlation with clinicopathological features and thyroid levels of cases. The results showed statistical significance for free FT4 (p value 0.018), anti-TG (p-value 0.001) and anti-TP antibodies (p value 0.005). Among them 70(48.6%) had decreased TSH levels and 17(11.8%) had higher TSH levels. Majority of the patients 105(72.9%) had higher FT3 levels and none of them reported with the decreased levels. 61.1% (n= 88) came up with the higher FT4 levels while 9(6.3%) reported with decreased FT4. 9(6.3%) and (4.2%) were positive for the anti-thyroperoxidase and anti-thyroglobulin antibodies. 2 out of 9 patients were expired who had positive anti-thyroperoxidase antibodies as compare to 3 out of 6 deaths from anti-thyroglobuline positive patients (Table 2).

Association between age with clinicopathological characteristic and thyroid levels of cases: We also tried to find the association of age with the different clinicopathological characteristics and thyroid levels. Though anti thyroglobuline and anti thyroperoxidase levels were found to be high or very high in age group of more than 40 years but we did not find any significant statistical association among these variables (Table 3).

Association between gender with clinicopathological characteristic and thyroid levels of cases: We further sought to evaluate the statistical association of gender of the patients with the clinicopathological characteristics and thyroid levels of the cases. Though the males are more affected with the thyroid diseases in current study, we did not find any statistical link (Table 4).

Table 2: Association of outcome of cases with Clinicopathological characteristics and Thyroid levels

Characteristic	n=144	Outcome		P value
		Discharge	Discharge	
Outcome				
Discharged	20	17	3	0.717[b]
Expired	124	109	15	
GENDER				
Male	74	62	12	0.210[b]
Female	70	64	6	
TSH Levels				
Blow Normal (< 0.4 mIU/L)	70	58	12	
Normal (0.4-4.0 mIU/L)	57	54	3	0.104[a]
Increased (> 4 mIU/L)	17	14	3	
FT3 Levels				
Blow Normal (< 2.1 pg/ml)	105	92	13	
Normal (2.1-4.4 pg/ml)	39	34	5	1.00[b]
Increased (> 4.4 pg/ml)	0	0	0	
FFT4				
Blow Normal (< 0.89 ng/dl)	9	6	3	
Normal (0.89-1.76 ng/dl)	47	38	9	0.018[a]
Increased (> 1.76 ng/dl)	88	82	6	
Anti-Thyroglobulin (AntiTG)				
Normal (< 40 IU/ml)	138	15	123	0.001[a]
Raised (> 40 IU/ml)	6	3	3	
Anti-Thyroperoxidase (AntiTP)				
Normal (< 35 IU/ml)	135	119	16	0.005[a]
Raised (> 35 IU/ml)	9	7	2	

[a]Chi-square test for association of outcome of cases with clinicopathological variables
[b]Fischer's exact test for association of outcome of cases with clinicopathological variables

Table 3: Association of age of cases with Clinicopathological characteristics and Thyroid levels

Characteristic	n=144	Age		p value
		<= 40 years	> 40 Years	
Outcome				
Discharged	126	17	109	0.717[b]
Expired	18	3	15	
GENDER				
Male	74	10	64	1.00[b]
Female	70	10	60	
TSH Levels				
Blow Normal (< 0.4 mIU/L)	70	7	63	
Normal (0.4-4.0 mIU/L)	57	10	47	0.423[a]
Increased (> 4 mIU/L)	17	3	14	
FT3 Levels				
Blow Normal (< 2.1 pg/ml)	105	11	94	
Normal (2.1-4.4 pg/ml)	39	9	30	0.062[b]
Increased (> 4.4 pg/ml)	0	0	0	
FFT4				
Blow Normal (< 0.89 ng/dl)	9	3	6	
Normal (0.89-1.76 ng/dl)	47	6	41	0.219[a]
Increased (> 1.76 ng/dl)	88	11	77	
Anti-Thyroglobulin (AntiTG)				
Normal (< 40 IU/ml)	138	20	118	0.514[a]
Raised (> 40 IU/ml)	6	0	6	
Anti-Thyroperoxidase (AntiTP)				
Normal (< 35 IU/ml)	135	19	116	0.757[a]
Raised (> 35 IU/ml)	9	1	8	

[a]Chi-square test for association of outcome of cases with clinicopathological variables
[b]Fischer's exact test for association of outcome of cases with clinicopathological variable

Table 4: Association of gender of cases with Clinicopathological characteristics and Thyroid levels

Characteristic	n=144	Gender		p value
		Male	Female	
Age				
<= 40 years	20	10	10	1.00[b]
> 40 Years	124	64	60	
Outcome				
Discharged	126	62	64	1.00[b]
Expired	18	12	6	
TSH Levels				
Blow Normal (< 0.4 mIU/L)	70	42	28	
Normal (0.4-4.0 mIU/L)	57	27	30	0.057[a]
Increased (> 4 mIU/L)	17	5	12	
FT3 Levels				
Blow Normal (< 2.1 pg/ml)	105	54	51	
Normal (2.1-4.4 pg/ml)	39	20	19	1.00[b]
Increased (> 4.4 pg/ml)	0	0	0	
FFT4				
Blow Normal (< 0.89 ng/dl)	9	2	7	
Normal (0.89-1.76 ng/dl)	47	24	23	0.181[a]
Increased (> 1.76 ng/dl)	88	42	40	
Anti-Thyroglobulin (AntiTG)				
Normal (< 40 IU/ml)	138	73	65	0.168[a]
Raised (> 40 IU/ml)	6	1	5	
Anti-Thyroperoxidase (AntiTP)				
Normal (< 35 IU/ml)	135	71	64	0.372[a]
Raised (> 35 IU/ml)	9	3	6	

[a]Chi-square test for association of outcome of cases with clinicopathological variables
[b]Fischer's exact test for association of outcome of cases with clinicopathological variables

DISCUSSION

Coronaviruses have been shown to have direct effects on the thyroid gland and other endocrine glands. Damage to the follicular and parafollicular cells of the thyroid was observed at post-mortem in patients infected with SARS-CoV, a coronavirus that is linked to SARS-CoV-2[12,13]. Coronaviruses have also been found in the pituitary gland after death, as well as diminished thyrotropin (TSH) staining in the anterior pituitary gland of SARS-CoV patients[14]. The angiotensin-converting enzyme 2(ACE2) receptor, which is extensively expressed in the thyroid gland, is also used by SARS-CoV-2 to enter cells[15]. Hyperthyroidism and subclinical hyperthyroidism affect 5.1 percent and 5.8 percent of Pakistan's population, respectively, whereas hypothyroidism affects 4.1%[16]. Despite the fact that hyperthyroidism is very uncommon in Pakistan. Our prevalence appears to be significantly higher than that of both disorders in Europe (0.7%) and the United States (0.5%), whereas subclinical and overt hyperthyroidism was found in 1.6% and 1.3%, respectively, in our closest neighbour, India, and hypothyroidism was found in 3.4%[17]. In contrast to other countries where COVID-19 has ravaged population bases, Pakistan appears to have escaped the epidemic relatively intact. However, given the thyroid abnormalities found in our study sample, it appears that the long-term effects of COVID-19, particularly in terms of follow-up of critically ill patients, may be overlooked, particularly in elderly patients, for whom the symptoms of excessive FT3 in circulation, body aches, confusion, and an increased heart rate might be dismissed as the result of a viral infection[18].

The acute effects of COVID-19 on thyroid function were studied in this observational study. The majority of COVID-19 patients were euthyroid at the time of admission. We did notice a slight decrease in TSH and FT4 in COVID-19 patients compared to non-COVID-19 instances. Our study, on the other hand, included complete sets of FT4 and TSH values, as well as thyroid function testing as part of a normal workup. Increases in proinflammatory cytokines like interleukin-6, which are adversely linked with TSH, are most likely to blame for TSH suppression. Cortisol, which has been shown to decrease TSH release even at healthy levels, could be another cause. A third possibility is that SARS-CoV-2 has a direct cytotoxic effect on thyrotrophs because the virion binding receptor, ACE2, is expressed in the pituitary[19,20].

Nonthyroidal illness syndrome (NTI) or euthyroid sick syndrome refers to a group of patients with serious diseases other than thyroid disorders who have abnormal thyroid hormone levels (21). However, during the course of their COVID-19 infection, 48.6% (70/144) of the patients in our study had lower-than-normal TSH levels, which may not be entirely explained by NTI. Same findings were observed in a study done by Min Chen in 2021 where he found low TSH levels in 34% of COVID-19 patients. According to a previous study, extensive injury to the follicular epithelial and parafollicular cells in the thyroid glands of SARS patients had a significant impact[9]. Another study found that during both the progression and recovery phases of SARS, patients' T3, T4, and TSH levels were significantly lower than those of controls[22,23].

There are various constraints that could lead to prejudice. The study is single-centred and has a small sample size, which could lead to bias. Secondly we only included T3, T4, and TSH values at the time of hospitalisation and did not follow up after that. Thyroid hormones were also measured while the majority of the patients were taking glucocorticoids. As a result, it was difficult to rule out the effect of hormonal alterations in the pituitary–endocrine axis feedback loops. In future investigations, more patients from several sites should be evaluated and complete records and dynamic changes in thyroid function should be considered and investigated prospectively.

CONCLUSION

In conclusion, the current study found that COVID-19 patients had a high proportion of thyroid function abnormalities. Thyroid dysfunction appears to vary dynamically over time and to recover gradually and spontaneously. While this could be explained in part by non-thyroidal sickness syndrome, the thyroid gland could also be a direct target of the SARS CoV-2 virus. As a result, patients with thyroid problems should be urged to take special precautions to avoid viral contact. Thyroid illness patients with probable COVID-19 should be closely monitored by doctors in order to detect indicators of disease progression early. Finally, the existence of thyroid disease will be taken into account in future COVID-19 risk classification models.

Conflict of interest: The authors declared no conflict of interest and all authors have studied and approved the final manuscript.

Ethical approval: IRB: Approved by Ethical Review Committee, Ziauddin Medical University, Ref# HCM&D/889/2021. Dated: November 28th, 2021

Author's declaration: RJ conceived the idea, designed the project, and did bench work. She also supervised the whole

project. SK wrote the manuscript done the statistics, MR and RK helped in sampling, reviewing and extraction of data.

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