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THYROID ABNORMALITIES AMONG HOSPITALIZED PATIENTS WITH COVID-19: A RETROSPECTIVE

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ABSTRACT

Background and purpose: The outbreak of new COVID-19 started in 2019. Since then complex and severe effects on human organ systems have been identified as COVID-19 infection. In addition, thyroid dysfunction caused by COVID-19 infection is becoming recognized worldwide. Though, the prevalence of thyroid disorders and their association with the prognosis of COVID-19 is not yet fully clarified. We aimed to evaluate the thyroid function abnormalities in COVID-19 and explore its association with comorbid conditions and the severity of the disease. **Methods:** Its retrospective study of 102 patients admitted with confirmed COVID-19 infection to a tertiary care hospital in Saudi Arabia. Thyroid funcion tests, clinical manifestations, laboratory results, associated comorbid conditions, and outcomes were studied. Exclusion criteria were patients with prior thyroid disease, taking any medications that affect thyroid function, and pregnant women. The study population included all patients aged above 18 years and with available thyroid function tests at admission or during hospitalization. In an additional analysis of the thyroid function test, we searched the medical records of the patients included in the analysis during the follow-up to six months after discharge to see the recovery or persistence of abnormalities. **Results:** One hundred-two patients were included in the study. 60.8% were male and 39.2 % were female. The mean age was 62 years. 38.2% out of 102 had thyroid abnormalities. Non- thyroidal illness (NTI) was a major thyroid abnormality amounting to 71% of patients with thyroid abnormality. A higher percentage of patients with thyroid abnormalities were treated with medications, but the difference was statistically not significant. The median days of intubation were non-significant in both groups. Although in terms of clinical outcome lower percentage (66.7%) of patients with thyroid abnormalities recovered and were discharged compared to 81% without thyroid abnormalities after discharge, in all patients with NTI, thyroid function returned to normal within six months. Kaplan–Meier curves for the length of stay in the hospital were similar in both groups. **Conclusion:** In this retrospective study, NTI is the most common thyroid abnormality seen in COVID-19 infection; patients with thyroid abnormalities had similar laboratory findings. There was no difference between patients with thyroid abnormalities compared to those without thyroid abnormalities concerning different clinical outcomes.

KEYWORDS: COVID-19, Thyroid abnormalities, non-thyroidal illness Impact, Pathogenesis.

INTRODUCTION

Since the coronavirus disease (COVID-19) outbreak in 2019, the new disease entity spread rapidly worldwide, resulting in considerable morbidity and mortality rates. Several associations were identified between the COVID-19 virus and inflammatory diseases like sub-acute thyroiditis, Guillain Barre syndrome, and autoimmune thyroid disease. Little is known about the full spectrum of COVID-19 in relationship with autoimmune endocrine disease, but endocrinal involvement is increasingly reported.[1-2] The thyroid hormones play a crucial role in modulating metabolism and the immune system. Due to ACE-2 expression in the tissue thyroid gland becomes a target for the CORONA-19 virus.[3,4] However, the prevalence of thyroid disorder and its association with the prognosis of COVID-19 has not yet been elucidated completely.[5,6] Various types of involvement of the thyroid gland in patients with COVID-19 have been reported in recent studies.[3,4] On the other hand, some studies have looked into the thyroid hormone profile and its prognostic impact on the COVID-19 infection.[7] In this retrospective single-center study, we aim to analyze thyroid function abnormalities

in COVID-19 disease and explore their association with severity and prognostic value.

Method and study population

In a tertiary care center, a retrospective study conducted in Saudi Arabia between June and September 2020 for confirmed cases of COVID-19 admitted to the hospital due to variable disease severity and thyroid function tests (thyroid stimulating hormone and thyroxin hormone), done during admission, The reference ranges for TSH and fT4 levels were 0.35–4.9 μU/mL, and 9-19.1 pmol/l, respectively. The study population included ages older than 18 years both gender and available TFT during admission. Exclusion criteria were patients with pre-existing thyroid disease, patients using medication that may affectthyroid function tests, and pregnant women. Thyroid disorder is defined into different diagnoses categories based on TFT (thyrotoxicosis with low TSH and high FT4, hypothyroidism with high TSH values and low FT4, subclinical hypothyroidism with high TSH and normal FT4, euthyroid sick syndrome with decreased FT4 with normal TSH levels, or isolated low TSH). The presence of symptoms such as fever, shortness of breath, and cough was identified. Associated comorbidities were reported for the following diagnosed conditions: diabetes mellitus, cardiovascular disease, renal disease, liver disease, and others. The laboratory data analyzed included white blood cells, lactate dehydrogenase, ferritin, d-dimer, creatinine, procalcitonin, and C-reactive protein. Data for disease severity were obtained as cases diagnosed with pneumonia, admission to the intensive care unit, medication history targeting covid19 infection during hospitalization (hydroxychloroquine, Azithromycin, steroids), patients required oxygen supplement via nasal cannula or noninvasive ventilation (CPAP) or mechanical intubation. Patient outcomes were classified into discharge or death whether during hospitalization or within 30 days after discharge.

For additional analysis of thyroid function tests, we searched the medical records of the patients included in the analysis for any follow-up thyroid function tests (FT4 or TSH) done after their admission for COVID-19 up to six months. Data Sources were collected from patients' medical records. The ethics committee of the Institutional Review Board of the hospital approved the study.

Statistical analysis

The data obtained during the study were analyzed utilizing IBM SPSS Statistics for Windows, version 23 (IBM SPSS, IBM Corp., Armonk, N.Y., USA). Shapiro – Wilk test was utilized to evaluate normal value distribution. The collected value was presented as mean +/- standard deviation (minimum-maximum) and median (25 and 75 percentile) for parametric as data were not normally distributed; while the categorized data were presented as frequency (%). Statistical comparisons were made for independent parametric parameters by the Mann-Whitney test, as data were not normally distributed, and the Pearson Chi-Square test for categorized parameters. P value <0.05 was considered statistically significant.

RESULTS

A total of 102 patients were included for analysis. Out of 102 patients, 62 (60.8%) were male and 40 (39.2%) were female. The mean age is 62 years, 39 out of the 102 patients (38.2%) had thyroid function test abnormalities. The presence of comorbidities was significant in patients with thyroid abnormalities compared to those with no thyroid abnormalities P = 0.012, specifically for patients with diabetes (79.5%) vs (58.7%) P = 0.033 respectively (Table1). Clinical symptoms and laboratory findings for the patients were compared according to the presence of thyroid abnormalities (Table 2). The level of TSH was significantly lower in patients with thyroid abnormalities median of 0.22 (IQR 0.13-0.90) and higher creatinine levels were observed at P=0.011. Out of the study sample, 28 patients (27.4%) had low TSH, while T4 was low in six patients (5.8%). Table 3 summarizes the different thyroid function abnormalities, the majority had low TSH 28 (71.8%) patients level (median 0.20, range 0.11- 0.27), normal range: (0.35-4.9 mIU/L). Whereas Low T4 was found in 6 (15.4%) patients' level (median 7.00, range 6.15-7.33), (normal range: 9-19.1 pmol/l). Only 3 (7.7%) patients had subclinical hypothyroid. One case had overt-hypothyroidism another case had overt-hyperthyroidism during hospitalization. A higher percentage of patients with thyroid abnormalities were treated with hydroxychloroquine, azithromycin, and steroid, the difference was not significant compared to those with thyroid abnormalities except for azithromycin P= 0.009. In respect to disease severity (Table 4), Patients without thyroid abnormalities were more likely to maintain an acceptable oxygen level at room air than patients with thyroid abnormalities 24 (38.1%) and 9 (23.1%) respectively, however, the need for oxygen therapy was not different for both groups. The median days of intubation were no significantly longer in patients with thyroid abnormalities 8 (5.25-18.25) versus 7 days (4.5-8.5) in patients without thyroid abnormalities. In terms of clinical outcomes, a lower percentage of the patient with thyroid abnormalities 25(66.7%) patients recovered and were discharged home compared to 26 patients (81.0%) without thyroid abnormalities P=0.004. However, the death rate was not different between both groups. 22 out of 39 patients with abnormal TFT had repeated tests within 6 months after being discharged from the hospital. All patients with low TSH returned to normal, and the two patients in the hypothyroidism category had persistent abnormal TFT after discharge.

Kaplan–Meier curves for the length of stay in the hospital Fig. 2. There was no significant difference between the low TSH group and the normal TSH group (log-rank P = 0.06 (Fig: 1)

Table 1: Demographic characteristics of patients (n= 102).

Characteristics	All patients (n=102)	Without TA (n= 65)	With TA (n=39)	Significance
Age (years)	62.06±17.04 (19-95)	61.68±19.13 (19-95)	62.67±13.19 (31-84)	0.778
Gender				0.836
Male	62 (60.8%)	39 (60.9%)	23 (59.0%)	
Female	40 (39.2%)	24 (38.1%)	16 (41.0%)	
Comorbidity				**0.012**
No	9 (8.8%)	9 (14.3%)	-	
Yes	93 (91.2%)	54 (85.7%)	39 (100.0%)	
DM	68 (66.7%)	37 (58.7%)	31 (79.5%)	**0.033**
CVS disorders	33(32.4%)	20 (31.7%)	13 (33.3%)	1.000
Renal diseases	22 (21.6%)	10 (15.9%)	12 (30.8%)	0.088
Liver diseases	5 (4.9%)	3 (4.8%)	2 (5.1%)	1.000
Others	47 (46.1%)	30 (47.6%)	17 (43.6%)	0.838

Data expressed as mean+/- standard deviation (minimum – maximum) and median (25-75 percentile) or frequency (%) as appropriate. TA(thyroid abnormalities)

Table 2: Clinical characteristics and laboratory investigations of patients (n= 102).

Characteristics	All patients (n=102)	Without TA (n= 65)	With TA (n=39)	Significance
Symptoms				
Shortness of breath	65 (63.7%)	36 (57.1%)	29 (74.4%)	0.093
Cough	50 (49.0%)	26 (41.3%)	24 (61.5%)	0.066
Fever	45 (44.1%)	26 (41.3%)	19 (48.74%)	0.540
Laboratory investigations				
WBC (3.3-10.8) (n= 102)	11.80 (8.28-16.33)	10.80 (7.9-16.4)	12 (8.7-16.3)	0.558
LDH (125-220 U/L) (n=97)	393(245.50-569.50)	398.5(234.5-590.5)	393 (274-524)	0.513
Ferrittin (5 – 204 micg/l) (n=96)	751.18 (202.09-2427.50)	710 (94.36-2403)	898 (329-2794)	0.150
D-dimer (0.17-0.64 mg/l FEU) (n= 88)	2.66 (1.26-5.80)	2.34 (1.05-5.23)	3.44 (1.33-8.78)	0.169
Creatinine (50-98 mmol/l) (n=102)	103.5 (74.0-197.75)	97 (71-139)	141 (86-368)	**0.011**
Procalcitonin (< 0.05 ng/ml) (n= 81)	0.43 (0.12-2.71)	0.31 (0.09-1.7)	0.52 (0.12-4.03)	0.408
CRP (<5 mg/l) (n= 97)	149 (61.5-229.7)	138 (26.2-233.2)	166 (73-223)	0.364
TSH (mU/L) (n= 102)	0.92 (0.30-1.76)	1.3 (0.71-2.1)	0.22 (0.13-0.90)	**0.0001**
T4 (pmol/L) (n= 101)	11.60(10.40-12.95)	11.32(10.65-12.83)	11.8 (9.9-13.8)	0.812

Data expressed as mean+/- standard deviation (minimum – maximum) and median (25-75 percentile) or frequency (%) as appropriate. TA(thyroid abnormalities)

Table 3: Diagnosis, thyroid function tests (TFT) and outcome among patients with Covid-19 with thyroid abnormalities (TA) (n=39).

Parameters	Patients with TA (n=39)
Diagnosis of TA	
Low TSH (stage of NTI)	28 (71.8%) 0.20 (0.11-0.27)
Low T4 (stage of NTI)	6 (15.4%) 7.00 (6.15-7.33)
Subclinical hypothyroidism	3 (7.7%)
Hypothyroidism	1 (2.6%)
Hyperthyroidism	1 (2.6%)
TFT On admission	
TSH levels (n=39) (normal range: 0.35-4.9 mIU/L)	0.22 (0.13-0.90)
T4 levels (n=39) (normal range: 9-19.1 pmol/l)	11.8 (9.9-13.8)
T3 (pmol/L) (n= 7)(normal range:2.8-7.1 pmol/l)	2.7 (2.2-3.4)
TFT After discharge	
TSH (mU/L) (n= 22)	1.2 (0.77-2.5)
T4 (pmol/L) (n= 22)	11.35 (10-12)
Outcome after discharge	

Recovered	20 (51.2%)
Persist	2 (5.1%)
Died	13 (33.3%)

NTI: non thyroidal illness Data expressed as mean+/- standard deviation (minimum – maximum) and median (25-75 percentile) or frequency (%) as appropriate.

Table 4: Disease impact and clinical outcome of COVID-19 patients without and with thyroid abnormalities (TA) (n= 102).

Characteristics	All patients (n=102)	Without TA (n= 65)	With TA (n=39)	Significance
ICU admission				0.223
Yes	49 (48.0%)	27 (42.9%)	22 (56.4%)	
No	53 (52.0%)	36 (57.1%)	17 (43.6%)	
Pneumonia				0.358
Yes (moderate Covid)	75 (73.5%)	44 (69.8%)	31 (79.5%)	
No (mild Covid)	27 (26.5%)	19 (30.2%)	8 (20.5%)	
COVID-19 direct therapy				**0.002**
No	21 (20.6%)	19 (30.2%)	2 (5.1%)	
Yes	81 (79.4%)	44 (69.8%)	37 (94.9%)	
Hydroxychloquine	*8 (7.8%)*	*4 (6.3%)*	*4 (10.3%)*	*0.477*
Azithromycin	*33 (32.4%)*	*14 (22.2%)*	*19 (48.7%)*	***0.009***
Steroids	*63 (61.8%)*	*36 (57.1%)*	*27 (69.2%)*	*0.295*
Others	*47 (46.1%)*	*29 (46.0%)*	*18 (45.2%)*	*1.000*
Length of hospital stay (days)	14.75±13.57 (1-71)	14.71±14.65 (1-71)	14.82±11.80 (2-60)	0.424
	11 (4-21)	11 (2-21)	11 (6-21)	
Oxygen therapy at hospital				0.399
Room air	33 (32.4%)	24 (38.1%)	9 (23.1%)	0.009
Nasal cannula	21 (20.6%)	13 (20.6%)	8 (20.5%)	0.275
Noninvasive ventilation (Biapa or cpap) (severe Covid)	25 (24.5%)	13 (20.6%)	12 (30.8%)	0.841
Invasive ventilation (severe Covid)	23 (22.5%)	13 (20.6%)	10 (25.6%)	0.532
Duration of intubation (days)	7 (5-9)	7 (4.5-8.5)	8 (5.25-18.25)	0.284
Oxygen therapy at home				0.101
No	61 (59.8%)	38 (60.3%)	23 (59.0%)	
Yes	16 (15.7%)	13 (20.6%)	3 (7.7%)	
Clinical outcome				0.264
Discharge	77 (75.5%)	51 (81.0%)	26 (66.7%)	0.004
Death	25 (24.5%)	12 (19.0%)	13 (33.3%)	0.841
Death during admission	*21 (20.6%)*	*10 (15.9%)*	*11 (28.2%)*	0.827
Death within 30 after discharge	*4 (3.9%)*	*2 (3.2%)*	*2 (5.1%)*	1

Data expressed as mean+/- standard deviation (minimum – maximum) and median (25-75 percentile) or frequency (%) as appropriate.

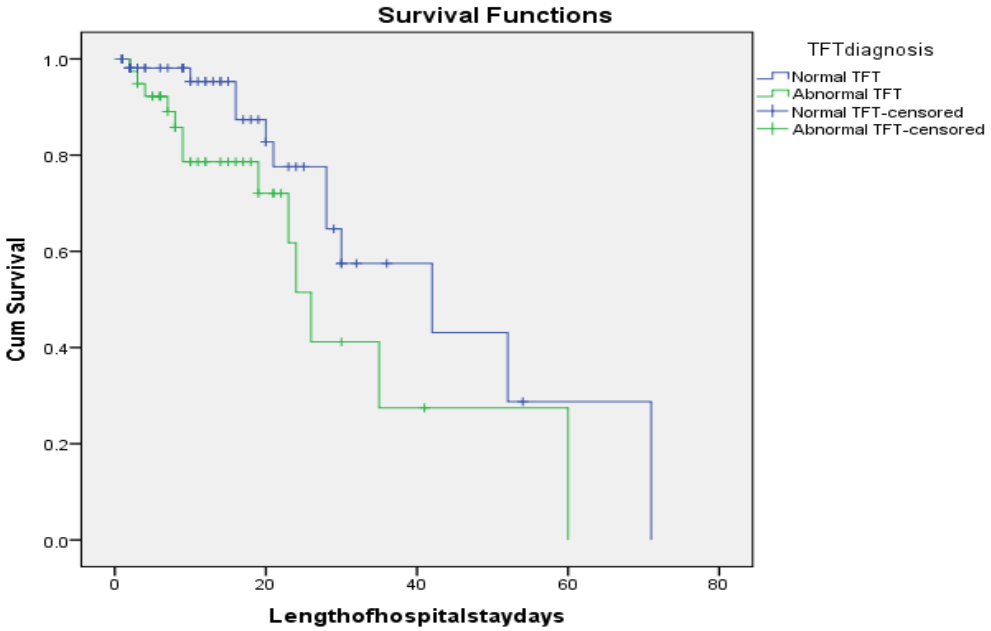

Fig no: 1 Kaplan-Meier Curve for mortality in COVID-19 patients with thyroid abnormalities (TA) or those without TA.

DISCUSSION

In 2019 coronavirus infection (COVID-19) appeared suddenly and started to spread all over the world. It was a highly infectious virus causing mortality and morbidity.[8] Over the past 2.5 years the effect of COVID-19 infection on thyroid function and the thyroid hormone profile and its prognostic impact on COVID-19 continues to be unclear. A large number of research studies have been published, predominantly retrospective studies, to enhance our knowledge about the pathogeneses and clinical spectrum of COVID-19 and thyroid abnormalities. The COVID-19 infection may lead to multi-organ dysfunction in several ways.

Severe COVID-19 infection is characterized by organ dysfunction, hypercytokinemia, and lymphopenia.[9] The direct cytopathological damage of the host cells and the dysregulated immune response caused by the severe CIVID-19 infection are assumed to be the underlying mechanisms for various organ damage.[10] SARS-COV-2 enters the lungs through the respiratory system. Eventually spiked proteins of the virus attached to Angiotensin-converting enzyme2 (ACE-2). Many endocrine system organs have ACE-2-expressing cells, such as the pancreas, testes, ovary, adrenal, pituitary, and thyroid gland. The thyroid is being the second-highest level of ACE-2 expression cells becomes a target of COVID-19 infection.[11-14] The pituitary-thyroid axis is regarded as another vulnerable target of COVID-19 virus infection. Pituitary damage is either directly or indirectly recognized as a cause of secondary hypothyroidism.[15] Infection by coronavirus affects the thyroid gland through the viral cytological effect of the virus by genomic or non-genomic pathways.[9] Severe pathological injury to follicular epithelium with follicular destruction was found in SARS virus infection.[16] It may be speculated that COVID-19 infection may have similar pathogenesis to SARS, explaining why the TSH level is significantly lower than in non-COVID-19 patients. Finally, thyroid function tests can be altered by several medications prescribed to patients with COVID-19 infection and lead to confounding their interpretation. Dexamethasone may deplete basal serum concentration of 3'5'3' iodine leading to thyroid abnormalities.[9]

During or after COVID-19 infection, Graves' disease and sub-acute thyroiditis may be triggered resulting in hyperthyroidism. Thyroid hormones play a key role in the modulatory effect on the immune system.[17] Thyroid hormones can enhance the antiviral activity of alpha interferon and thus explain why some immune pathways such as cytokines and T helper cell hyperactivation occurs in viral infection in thyroid disorders.[18] It is also worth noting that the thyroid gland is capable of activating human platelets which leads to pathological clotting which is a complication of COVID-19 infection.[19] It is well-known that critically ill patients with no history of thyroid disease usually present with changes in thyroid hormones.[20] Nonthyroidal illness (NTI) is the most common thyroid dysfunction seen in COVID-19 infection.[21] NTI is characterized by decreased T3 and FT3 and normal or low TSH levels.[22] Distorted Hypothalamus pituitary-thyroid axis was the primary hypothesis for NTI in COVID-19 patients. NTI is an independent risk factor for disease severity in patients with COVID -19. The patients with COVID-19 with NTI had a more robust inflammatory response and showed higher levels of CRP, ESR, and procalcitonin.[23] Chen et al in a study reported that the levels of TSH and T3 suppression positively correlated with the prognosis of the disease.[24] Similar outcomes have been reported in other studies.[25] Zou et al reported that more than 25% of

patients with COVID-19 were diagnosed with NTI.[26] In the present study 39(38%) patients out of a total of 102 patients had thyroid abnormalities. 28 patients (27%) out of the total 102 patients studied had NTI comparable to other similar studies. 28 (71%) of the patients had NTI out of 39 patients who demonstrated thyroid abnormalities in the study. The mean TSH (mIU/L) was 0.20(0.11-0.27) in patients with NTI during hospitalization. Low TSH improved after discharge with mean TSH returning to the normal range with a mean of 1.2(0.77-2.5) .6(15.4%) patients recorded low FT4 (pmol/l) with a mean value of 7.0(6.15-7.33). Post-discharge all patients FT4 returned to normal levels with a mean value rising to 11.35(10-12).

Thyrotoxicosis is also reported to be associated with COVID-19 infection. In a retrospective study of 287 patients admitted to a single center in Italy 58(20.2%), patients had thyrotoxicosis. Muller et al reported overt thyrotoxicosis in 15% of COVID- 19 patients admitted to high-dependency ICU compared to 2% treated in low-dependency settings.[27] One case of Graves' Disease was reported by Karen Feghali et. al. during the COVID-19 infection.[28] Thyrotoxicosis was associated in one study with Interleukin-6 but its significance was not evaluated[29] our study, one case of Thyrotoxicosis was detected in COVID-19 patients. The number of cases of thyrotoxicosis was low in our study compared to other similar studies probably due to the small studied population and thyroid function tests were not performed several times during the hospital course in COVID-19 patients. Sub-acute thyroiditis due to direct viral damage to the thyroid cells in autoimmune thyroiditis (Hashemite's Thyroiditis) with hypothyroidism has been described in patients with COVID-19 infection. In our present study, 4 (3.9%) patients had subclinical hypothyroidism and hypothyroidism. Among the total 39 patients with abnormal thyroid function, 3 (7.7%) patients and 1(2.6%) patients had subclinical hypothyroidism and hypothyroidism respectively. Karen feghali et al reported one case of sub-acute thyroiditis and one case of hypothyroidism due to Hashimoto's thyroiditis in Covid-19 patients.[29] To date, 25 cases of post-infectiousious sub-acute thyroiditis reported in COVID-19 patients.[30] In a multi-centric trial in Brazil, hospitalized patients with COVID-19 and hypothyroidism had similar comorbidities, clinical manifestations, and lab parameters as controls.[31] The association of comorbid conditions in patients with Thyroid disorders and without thyroid disorders in COVID-19 disease was studied in the present study. Renal diseases and liver diseases, and cardiovascular disease comparison between the two groups did not reveal any statistical differences. In the group of patients with thyroid disorders, diabetes was significantly higher with a p-value of 0.033(Table no: 1). ACE receptors are present in the beta cells of the pancreas and follicular cells of the thyroid gland. Inhibition of ACE-2 receptors by SARS-CoA -2 infection inhibits insulin secretion from pancreatic beta cells and inhibits the thyroid secretions by blocking follicular cells of the thyroid gland resulting in hyperglycemia and an increase in thyroid stimulating hormone.[32-33] Various clinical symptoms and laboratory parameters were compared among patients with COVID-19 infection in the group with thyroid abnormalities and without thyroid abnormalities. TSH level was very significantly lower in the thyroid abnormality group with a mean of 0.22(IQR 0.13-0.90). Higher creatinine levels were observed in the thyroid abnormality group with a significant p-value (0.011). There has been great interest in the relationship between thyroid dysfunction and kidney function in recent years.[34] Thyroid hormones are implicated in directly affecting the kidney by influencing renal growth, GFR development, renal transport, and sodium hemostasis. The indirect effect is through modification of cardiac and vascular function and disruption of the Renin-angiotensin system.[35] In terms of clinical outcomes, a lower percentage of patients with thyroid abnormalities (n=39) 25(66.5%) recovered and were discharged home compared to 66(81%) patients without thyroid abnormalities (n=65) with a p-value of 0.004. This may be due to poor outcomes reported in several studies in patients with thyroid abnormalities in COVID-19 patients.[36] In this study, there was no significant difference in outcomes in direct COVID-19 treatments in both groups except for the use of Azithromycin. A significantly high percentage of 49.7% of patients with thyroid abnormalities compared to 22.2% of patients without thyroid abnormalities were treated with azithromycin(p=0.009). The marked difference in utilization in patients with thyroid abnormalities was not reported in other research studies. It may be speculated that patients with thyroid abnormalities ran more severe disease courses necessitating higher use of azithromycin. In most patients with low TSH during hospitalization TSH returned to normal level within 6 months from discharge except for 2 patients with persistent thyroid abnormality suggestive of hypothyroidism. The uneventful recovery was consistent with several similar studies.

Limitations

This study has several limitations. The study is single centered and the sample size is small which may lead to bias. Another main weakness was the absence of a control group of patients without COVID-19 infection. It's a retrospective study based on chart review. Most patients had a thyroid function test on admission and were not dynamically monitored during hospitalization. Further multi-centric studies with complete records and dynamic thyroid function tests should be considered to clarify the unique impact of COVID-19 infection on thyroid function.

CONCLUSION

In this retrospective study, NTI is the most common thyroid abnormality seen in COVID-19 infection; patients with thyroid abnormalities had similar laboratory findings. There was no difference between

patients with thyroid abnormalities compared to those without thyroid abnormalities concerning different clinical outcomes. Further metacentric studies with complete records and dynamic thyroid function tests should be considered to clarify the unique influence of COVID-19 infection on thyroid function.

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