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Thyroid function analysis and other biochemical parameters in patients with moderate and severe COVID-19

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Abstract

Background and objective: The severe acute respiratory syndrome coronavirus 2 (SARS -CoV-2) is the cause of coronavirus disease-19 (COVID-19). The effects of COVID-19 on the thyroid axis remain uncertain. This study aimed to determine the occurrence of thyroid dysfunction, as previously demonstrated for SARS-CoV-1 infection, and to analyze electrolytes (sodium, potassium, and chloride) to determine the severity of the disease.

Methods: Blood samples were taken from patients who were admitted to Erbil hospitals from July to October 2021. Infection was detected by polymerase chain reaction (PCR). The 306 cases were labeled as moderate or severe. The samples were assessed for doing C-reactive protein (CRP), as a marker of systemic inflammation, thyroid-stimulating hormone (TSH), triiodothyronine (T3) and thyroxine (T4), and (sodium, potassium, and chloride) electrolytes.

Results: Patients comprised of 157 (51.3%) males and 149 (48.7%) females. The result revealed that 274 (89.5%), 278 (90.8%), 292 (95.4%) of patients had normal TSH, T3, T4 level respectively, 22 (7.2%), 23 (7.5%), 9 (2.9%) of patients had low TSH, T3, T4 level respectively, and 10 (3.3%), 5 (1.6%), 5 (1.6%), had high TSH, T3, T4 level respectively. There was no significant difference between moderate and severe cases in alterations of TSH, T3, T4 level. There was a significant difference between moderate and severe cases in sodium, potassium, and chloride electrolyte abnormality.

Conclusion: The occurrence of thyroid dysfunction in moderate and severe cases. The severity of the COVID-19 infection is associated with abnormalities in sodium, calcium, and chloride electrolytes.

Keywords: COVID-19; TSH; T3; T4, Sodium; Potassium; Chloride.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped RNA beta-coronavirus which is the causative agent of coronavirus disease-19 (COVID-19) ranging from asymptomatic cases to severe respiratory cases.[1,2] COVID-19 has become the most lethal pandemic and rapidly moving disease since the Spanish influenza of 1918-1920.[3] Initially Coronavirus disease -19 (COVID-19) was reported in China, in December 2019; and declared by the World Health Organization (WHO) on January 30, 2020 as Public Health Emergency of International Concern. Since 2021, variants of the virus have emerged, with the Delta, Alpha and Beta variants being the most virulent, on 7 October 2021 has affected nearly more than 236 million cases and 4.83 million deaths, making it one of the deadliest pandemics in history.[4,5]

The most common symptoms of COVID-19 include headache, fatigue, loss of smell and taste, nasal congestion and runny nose, dry cough, muscle pain, sore throat, fever, diarrhea, and breathing difficulties,[6,7] that can rapidly evolve toward respiratory

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failure and acute respiratory distress syndrome (ARDS), requiring intensive care support.[8]

The coronavirus covering by the spike proteins which is bind to receptors angiotensin-converting enzyme 2 (ACE2), regulators of the renin-angiotensin-aldosterone system (RAAS), which are present on the epithelial surface of human cells.[3,9] The novel virus has a predilection for multiorgan involvement in addition to the respiratory manifestations due to the widespread presence of angiotensin-converting enzyme 2 (ACE-2) receptors, an entry point for the virus.[10]

The ongoing global pandemic of coronavirus disease 2019 (COVID-19) has been found to have multiple long-ranging effects on the normal physiological balance of the human body. Mild and severe effects on human organ systems are being identified, including the respiratory, immune, gastric systems, neurological disorders (both central and peripheral), cardiac abnormalities, renal failure, liver disease, rhabdomyolysis, coagulopathy and thrombosis,[11,12] leading to multiple organ dysfunction and even death in subjects with high risk factors (i.e., old age, male gender, obesity, diabetes, and cardiovascular comorbidities).[1,13]

In fact, alterations of thyroid function reported in patients affected by SARS-CoV-1 and SARS-CoV-2.[14] Thyroid inflammation and damage may be the consequence of three main mechanisms in COVID-19 patients: (1) a direct effect of the SARS-CoV-2 virus on the gland, based on the recent evidence that SARS-CoV-2 RNA is present in the serum from COVID-19 patients, indicating episodes of viremia, and the virus receptor, the angiotensin-converting enzyme 2 (ACE2), is highly expressed in thyroid follicular cells; (2) an indirect effect of systemic inflammatory immune response; and (3) the so-called euthyroid sick syndrome (ESS), a nonspecific adaptive mechanism for illness and an indirect marker of disease severity in various condition rather than a true thyroid dysfunction.[14-17] In addition, ACE-2 receptors expression was demonstrated in thyroid follicular cells, making them a potential target for SARS-CoV-2 entry, or as a consequence of the systemic illness non-thyroidal-illness (NTI).[18]

On the other hand, the occurrence of a “cytokine storm” that would, in turn, induce a “non-thyroidal illness” (NTI) syndrome. Some specific cytokines and chemokines appear to have a direct role on the hypothalamus–pituitary–thyroid axis, and some authors have observed an increased incidence of a destructive thyroiditis, either subacute or painless, in patients with COVID-19.[19] Furthermore, changes in thyroid function parameters, which are commonly referred to as “non thyroidal illness” (or sick euthyroid syndrome, or low T3 syndrome), can be detected in many severe clinical conditions, both acute and chronic, including COVID-19, and represents an adaptive mechanism rather than a true thyroid dysfunction. The alteration is a decrease in serum T3 level, that can be accompanied, or not, by a slight decrease in TSH level and, as the severity and length of the non-thyroidal illness syndrome increases, also in total T4.[19-22]

Recent researches report a frequency of subacute or painless thyroiditis in COVID-19 patients, as well as the onset of autoimmune hyperthyroidism or Graves’ disease.[18]

A systemic inflammatory response is observed in coronavirus disease 2019 (COVID-19). Elevated serum levels of C-reactive protein (CRP), a marker of systemic inflammation, high sensitivity and standard laboratory parameters, are associated with severe disease in bacterial or viral infections.[21,23]

Most frequent forms of renal involvement in COVID-19 are acute kidney injury, proteinuria, hematuria and electrolyte imbalances (Sodium, Potassium, and Chloride).[24-25] Evidence has been provided that electrolyte disorders may also be

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present, including sodium, potassium, and chloride abnormalities.[1,13,25] Nearly, three-quarters of hospitalized patients with COVID-19 had some renal involvement during the disease,[24,26] in an analysis, lower concentrations of sodium, and potassium were related to severe disease. Such determine of electrolyte disturbances have important implications for patient management.[25]

Researchers have sought that among the many extra-pulmonary alterations possible occurrence of thyroid dysfunctions may occur. Up to now, very few studies have tackled this issue. This study aimed to determine thyroid function alterations in patients with COVID-19, and determine electrolyte disorders and comparing sodium, potassium, and chloride serum concentrations between patients with severe disease versus those with moderate less severe disease, to enhance our current understanding of electrolyte imbalance in COVID-19.

Methods

Blood samples were taken from patients without history of thyroid disease who were admitted to Erbil hospitals from July to October 2021. SARS-CoV-2 infection was demonstrated by reverse transcriptase-polymerase chain reaction (RT-PCR) assay of oropharyngeal and nasopharyngeal swabs to detect the presence of viral RNA in all patients.

The 306 cases were classified as moderate or severe. Moderate disease was defined as presence of dyspnea with respiratory rate more than 24/min or SpO_2 between 90 and 94% in room air,[27,28] severe disease was classified as having pneumonia, respiratory rate of ≥ 30 breaths/min, and oxygen saturation ≤ 90% at rest.[12] Seven laboratory parameters were examined in 306 patients with COVID-19 infection, serum levels of C-reactive protein (CRP), as a marker of systemic inflammation. Biochemical parameters such as thyroid-stimulating hormone (TSH), triiodothyronine (T3) and thyroxine (T4), electrolytes (sodium, potassium, and chloride) were analyzed. Data included demographic variables, age and gender of patients.

Microsoft Excel and SPSS (version 23) were used for data summarization and the data analysis purposes. The Chi square test was used to investigate the association between different categorical variables, while Pearson Correlation Coefficient test was used to investigate the association between a number of numerical variables. A *P*-value of equal or less than 0.05 was considered to be statistically significant.

Results

SARS-CoV-2 infection was detected by reverse transcriptase- polymerase chain reaction (RT-PCR) in 306 patients. Patients with COVID-19 infection comprised of 157 (51.3%) males and 149 (48.7%) females, about half (51.3%) of patients were males. The age of patients was ranging from 23 to 89 years, with the mean ± SD of 56.7±16.2, and 79 (25.8%) of them were at age 60-69 years as depicted in Table 1.

Table 1 Socio-demographic criteria

Variable		Frequency	Percent %
Sex	Males	157	51.3
	Females	149	48.7
Age of groups	≤39	56	18.3
	40-49	61	19.9
	50-59	43	14.1
	60-69	**79**	**25.8**
	≥70	67	21.9
	Total	**306**	**100.0**

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Out of 306 patients with COVID-19 infection, 56 (18.3%) patients were categorized as non severe moderate cases and 250 (81.7%) as severe cases on admission. Significantly elevated serum levels of C-reactive protein (CRP), as a marker of systemic inflammation are associated with viral infections, is observed in (94.4%) of patients. There were no deaths in cases of moderate infection, but the mortality rate in severe cases were 43.8%, as shown in Figure 1.

The severity of the disease was non-significantly more in males, but the mortality rate was significantly (*P* = 0.044) more in females, as shown in Table 2.

The study showed that there was a significant statistical association (*P* <0.001) between age and severity of disease. Almost 97% of those aged 70 years and more were severe cases compared to 87.3% for those aged 60-69 years and 88.4% for those aged 50-59 years. There was also a significant statistical association between age and mortality rate. The mortality rate among those aged 70 years and more was 61.2% compared to 44.3% for those aged 60-69 years and 53.5% for those aged 50-59 years as shown in Table 3.

Table 2 The association of Gender with severity and mortality rate in patients

	Males No. (%)	Females No. (%)	Total No. (%)	*P* value
Severity				
Moderate	28 (17.8)	28 (18.8)	56 (18.3)	0.824
Severe	129 (82.2)	121 (81.2)	250 (81.7)	
Mortality				
Alive	97 (61.8)	75 (50.3)	172 (56.2)	0.044
Dead	60 (38.2)	74 (49.7)	134 (43.8)	
Total	157 (100.0)	149 (100.0)	306 (100.0)	

Table 3 The association of age with severity and mortality rate in patients

Age	≤39 No. (%)	40-49 No. (%)	50-59 No. (%)	60-69 No. (%)	≥70 No. (%)	Total No. (%)	*P* value
Severity							
Moderate	19 (33.9)	20 (32.8)	5 (11.6)	10 (12.7)	2 (3.0)	56 (18.3)	< 0.001
Severe	37 (66.1)	41 (67.2)	38 (88.4)	69 (87.3)	65 (97.0)	250 (81.7)	
Mortality							
Alive	39 (69.6)	43 (70.5)	20 (46.5)	44 (55.7)	26 (38.8)	172 (56.2)	< 0.001
Dead	17 (30.4)	18 (29.5)	23 (53.5)	35 (44.3)	41 (61.2)	134 (43.8)	
Total	56 (18.3)	61 (19.9)	43 (14.1)	79 (25.8)	67 (21.9)	306 (100)	

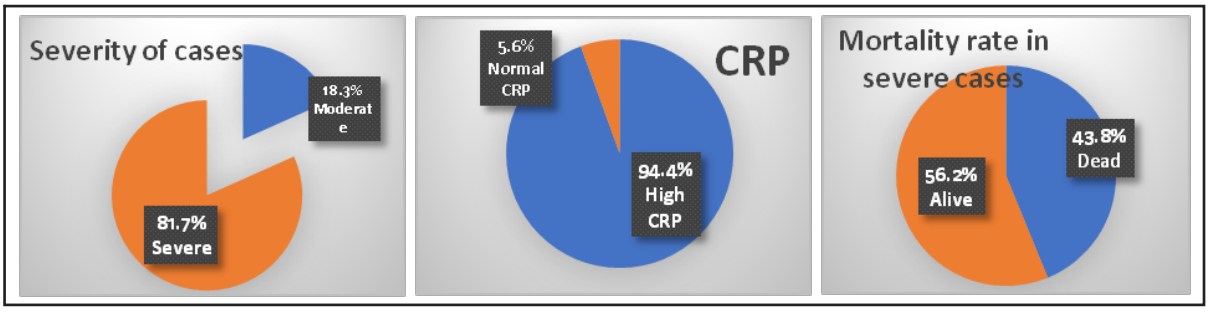

Figure 1 Elevated C-reactive protein (CRP) in patients with COVID-19 infection and mortality rate in severe cases

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Elevated serum levels of C-reactive protein (CRP) were observed in (99.6%) of patients with severe cases, as a marker of systemic inflammation, and it was significantly more than moderate cases, at (*P* <0.001).

The results revealed that 274 (89.5%), 278 (90.8%), 292 (95.4%) of the patients had normal TSH, T3, T4 level respectively, 22 (7.2%), 23 (7.5%), 9 (2.9%) of patients had low TSH, T3, T4 level respectively, and 10 (3.3%), 5 (1.6%), 5 (1.6%), had high TSH, T3, T4 level respectively. There was no significant difference between moderate and severe cases in alterations of TSH, T3, T4 level.

The study also showed that most of patients had an electrolyte abnormality at baseline. Hyponatremia was the most frequent electrolyte abnormality 105 (34.3%), but hypokalemia and hypochloremia was found to be 36 (11.8%), 11 (3.6%) respectively. Lastly, 38 (12.4%), 35 (11.4%), 23 (7.5%) of patients had hyperkalemia, hypernatremia, and hyperchloremia respectively. There was a significant difference between moderate and severe cases in sodium, potassium, and chloride electrolyte abnormality, at (*P* = 0.01, *P* = 0.004, *P* = 0.040 respectively), as depicted in Table (4).

Table 4 CRP, TSH, T3, T4levels, Sodium, Potassium, Chloride electrolyte in moderate and severe cases

Parameters		Severity			*P* value
		Moderate No. (%)	Severe No. (%)	Total No. (%)	
CRP	Normal	16 (28.6)	1 (0.4)	17 (5.6)	< 0.001
	High	40 (71.4)	249 (99.6)	289 (94.4)	
	Total	56 (100)	250 (100)	306 (100)	
TSH	Low	5 (8.9)	17 (6.8)	22 (7.2)	0.0687
	Normal	50 (89.3)	224 (89.6)	274 (89.5)	
	High	1 (1.8)	9 (3.6)	10 (3.3)	
	Total	56 (100)	250 (100)	306 (100)	
T3	Low	5 (8.9)	18 (7.2)	23 (7.5)	0.09
	Normal	50 (89.3)	228 (91.2)	278 (90.8)	
	High	1 (1.8)	4 (1.6)	5 (1.6)	
	Total	56 (100)	250 (100)	306 (100)	
T4	Low	1 (1.8)	8 (3.2)	9 (2.9)	0.849
	Normal	54 (96.4)	238 (95.2)	292 (95.4)	
	High	1 (1.8)	4 (1.6)	5 (1.6)	
	Total	56 (100)	250 (100)	306 (100)	
Sodium electrolyte	Low	16 (28.6)	89 (35.6)	105 (34.3)	0.01
	Normal	39 (69.6)	127 (50.8)	166 (54.2)	
	High	1 (1.8)	34 (13.6)	35 (11.4)	
	Total	56 (100)	250 (100)	306 (100)	
Potassium electrolyte	Low	5 (8.9)	31 (12.4)	36 (11.8)	0.004
	Normal	51 (91.1)	181 (72.4)	232 (75.8)	
	High	0 (0)	38 (15.2)	38 (12.4)	
	Total	56 (100)	250 (100)	306 (100)	
Chloride electrolyte	Low	1 (1.8)	10 (4)	11 (3.6)	0.040
	Normal	55 (98.2)	217 (86.8)	272 (88.9)	
	High	0 (0)	23 (9.2)	23 (7.5)	
	Total	56 (100)	250 (100)	306 (100)	

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The significant and non-significant correlations between seven parameters PCR, TSH, T3,T4, sodium, potassium, and chloride, in this study depicted in Table 5. There was highly significant relation between TSH with T3, and T4. There was a significant relation between sodium and chloride electrolyte abnormality, There was also a significant relation between potassium and chloride electrolyte abnormality. But there was no significant relation between sodium and potassium electrolyte abnormality.

Table 5 The significant and non-significant relation between seven parameters (CRP, TSH, T3, T4, sodium, potassium, and chloride)

		CRP	TSH	T3	T4	Sodium	Potassium	Chloride
CRP	Pearson Correlations	1	-.044	.097	.010	.070	.085	.132*
	Sig. (2-tailed)		.439	.090	.856	.221	.136	.021
	N	306	306	306	306	306	306	306
TSH	Pearson Correlations	-.044	1	.367**	.354**	.055	.056	.061
	Sig. (2-tailed)	.439		.000	.000	.336	.327	.288
	N	306	306	306	306	306	306	306
T3	Pearson Correlations	.097	.367**	1	.343**	.106	.012	.048
	Sig. (2-tailed)	.090	.000		.000	.063	.829	.401
	N	306	306	306	306	306	306	306
T4	Pearson Correlations	.010	.354**	.343**	1	.079	.025	.026
	Sig. (2-tailed)	.856	.000	.000		.167	.658	.653
	N	306	306	306	306	306	306	306
Sodium	Pearson Correlations	.070	.055	.106	.079	1	-.041	.398**
	Sig. (2-tailed)	.221	.336	.063	.167		.477	.000
	N	306	306	306	306	306	306	306
Potassium	Pearson Correlations	.085	.056	.012	.025	-.041	1	.171**
	Sig. (2-tailed)	.136	.327	.829	.658	.477		.003
	N	306	306	306	306	306	306	306
Chloride	Pearson Correlations	.132*	.061	.048	.026	.398**	.171**	1
	Sig. (2-tailed)	.021	.288	.401	.653	.000	.003	
	N	306	306	306	306	306	306	306

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is highly significant at the 0.01 level (2-tailed).

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Discussion

The study showed that in 306 patients with COVID-19 infection, an approximately 1:1 ratio of males (51.3%) and females (48.7%) was found, and the age range was 23-89 years. There was a significant statistical association between age and severity of disease. All patients were community-acquired cases. Significantly elevated serum levels of C-reactive protein (CRP), as a marker of systemic inflammation associated with viral infections, was observed in 94.4% of patients with COVID-19 infection.

Other studies reported that, females were from (28-49%) and increased values of CRP (75–93% of cases).[29] Female (28%), increased C reactive protein CRP (93%).[30] Females (32%), Males (68%), increased C reactive protein (86%). Age range 21-82 was ≤39 (10%), 40-49 (22%), 50-59 (30%), 60-69 (22%), ≥71 (15%).[31] Female (49%), increased C reactive protein (91%).[32]

The results clearly showed alterations of thyroid function during COVID-19 disease as a consequence of direct or indirect effects of SARS-CoV-2 infection on the gland or as a consequence of the systemic illness non-thyroidal-illness (NTI).[18] The results revealed that 274 (89.5%), 278 (90.8%), 292 (95.4%) of the patients had normal TSH, T3, T4 level respectively. There was no significant difference between moderate and severe cases in alterations of TSH, T3, T4 level.

The results of this study were consistent to those reported by Khoo and coworkers (2021) in London, UK, they reported that most patients (86.6%) presenting with COVID-19 were euthyroid, with none presenting with overt thyrotoxicosis.[33]

In seven studies, low TSH levels were reported from 5% up to 54% of COVID-19 patients, and high TSH levels were reported from 0% up to 8% of COVID-19 patients.[2,16,22,34-37] Several studies are contrary to our results, they reported that the lower TSH and T3 levels, with statistical significance ($P < 0.001$), were observed in patients with severe COVID-19 disease. The thyroxine (T4) level of the patients with COVID-19 was not significantly different.[37] Similar studies reported that (35%) of COVID-19 patients had one or more abnormality in the thyroid function, low TSH level being the most common (18.33%), but only (9.1%) of patients had characteristic pattern of thyroiditis. There was no significant difference in any of the parameters between mild, moderate, and severe groups.[38] In another study in Turkey, they reported that (34.1%) of the patients were euthyroid.[39]

Lower T3 serum levels were observed in intensive care unit (ICU) than in non-ICU patients and in non-survivors than survivors, respectively. T3 may become a simple tool for management of patients with severe COVID-19.[40] Mateu-Salat and Colleagues in 2020 detected two cases of autoimmune hyperthyroidism, Graves' disease, occurring after SARS-CoV-2 infection.[41]

This fluctuation in the results might be attributed to the number of cases taken, difference in geographic region, endocrinology, religious activities, or social activities.

This study also showed that most of the patients had an electrolytes abnormality at baseline. Hyponatremia was the most frequent electrolyte abnormality. There was a significant difference between moderate and severe cases in sodium, potassium, and chloride electrolyte abnormality. These results match with the finding of a similar study, they found that (55.8%) of patients had an electrolyte abnormality at baseline. Hyponatremia were the most frequent electrolyte abnormality (35.8%), but hypokalemia and hypochloremia was found in (6.8%) of patients. Lastly, (1.7%) of the participants had hyperkalemia. None of patients had hypernatremia, or hyperchloremia at baseline.[26]

In five studies with 1415 COVID-19 patients, they all reported that sodium and potassium electrolytes were significantly lower in patients with severe COVID-19, and non-significant difference for chloride

level was observed between patients with severe and non-severe COVID-19.[1,13,25,42,43] Gheorghe and colleagues in 2021 found that the clinical manifestations of hyponatremia may be the first to appear in some cases.[44] Electrolytes should be measured at initial presentation during hospitalization because the severity of COVID-19 infection is associated with abnormalities in electrolytes

Conclusion

The occurrence of thyroid dysfunction in moderate and severe cases. The severity of the COVID-19 infection is associated with abnormalities in sodium, potassium, and chloride electrolytes. In our opinion, assessment of thyroid function should be considered in COVID-19 patients. Electrolytes should be also measured at initial presentation during hospitalization in order to establish timely and appropriate corrective actions.

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Competing interests

The author declares that he has no competing interests.

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