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ASSOCIATION OF THYROID STIMULATING HORMONE IN SEVERITY OF COVID-19 FEVER: A REPORT FROM DISTRICT FAISALABAD AND OKARA, PAKISTAN

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Abstract

Background: *The COVID-19 pandemic, caused by SARS-CoV-2, has presented unprecedented global health challenge, prompting extensive research into multifaceted determinants of disease severity. While established risk factors like age and comorbidities influence the clinical course of COVID-19, emerging evidence suggesting endocrine dysfunction, particularly alterations in Thyroid Stimulating Hormone levels, may significantly impact disease progression.*

Objective: *This study investigated the association between TSH levels with age groups of COVID-19 patients in District Faisalabad and District Okara, Pakistan.*

Methodology: *This study utilized a Systematic Sampling Method to select 168 patients with COVID-19 and thyroid gland dysfunction. TSH levels were determined using the ichroma TSH method, which employs Fluorescence Immunoassay.*

Results: *This study analyzes clinical data, including thyroid function markers, disease progression, and patient outcomes, to elucidate the role of TSH in the pathophysiology of COVID-19 and its potential clinical implications. The Fisher's Exact Test yielded a p-value of 0.267, indicating no statistically significant association between Thyroid Stimulating Hormone levels and respondents' age groups at the 5% significance level. This suggests that TSH levels are independent of age.* ***Conclusion:*** *Identifying an association between TSH levels and COVID-19 severity has significant implications for risk stratification, clinical decision-making, and the development of targeted therapeutic*

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interventions. These findings highlight the importance of considering endocrine factors in the context of COVID-19 severity, contributing valuable insights to the evolving landscape of pandemic research. Further research is warranted to validate and expand upon these preliminary findings to enhance our understanding of the complex interplay between thyroid function and COVID-19 outcomes.

INTRODUCTION

The world's attention was drawn to an alarming outbreak of pneumonia-like pulmonary infections attributed to an enigmatic pathogenic agent in Wuhan, Hubei Province, China in December 2019[1]. By March 2020, the World Health Organization (WHO) had formally declared the inception of a global pandemic, wrought by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[2]. As of July 27, 2022, the tally of confirmed COVID-19 cases had reached a staggering 568,773,510, with 6,381,643 lives tragically claimed by the virus [3]. The unfolding pandemic found its way to Pakistan in February 2020, with Karachi marking the initial diagnosis of COVID-19 within the country. Since then, Pakistan has documented 1,532,153 cases of COVID-19 by February 2020.

While the world grappled with the escalating pandemic, a notable convergence of COVID-19 with various non-neoplastic thyroid disorders came to the fore. Conditions such as Hashimoto's Thyroiditis, numerous thyroid-stimulating thyroid diseases, and postpartum thyroids exhibited associations with COVID-19 [4,5]. This intersection prompted an exploration into the thyroid's role in the context of the virus. Among the family of viruses to which human coronaviruses belong, the benign nature of the majority contrasts starkly with three noteworthy exceptions: severe acute respiratory syndrome (SARS, 2002–2003), Middle East Respiratory Syndrome (MERS, 2012), and the ongoing COVID-19 pandemic (2019–present). These exceptions stand out due to their ability to provoke respiratory tract infections, ranging from mild to severe, often culminating in multi-organ damage and the development of acute respiratory distress syndrome (ARDS) [6].

The primary target of COVID-19 is the respiratory system, notably the lungs; however, the virus's versatility in infecting other vital organs like the kidneys, intestines, liver, pancreas, and heart has been documented [7,8,9]. The wide distribution of angiotensin-converting enzyme-2 receptors (ACE-2), serving as entry points for SARS-CoV-2 into human cells has facilitated its potential to infiltrate several organs [4]. Notably, studies have revealed higher ACE-2 expression in the thyroid gland compared to the lungs [10.11], with a notable presence in follicular cells, suggesting the thyroid as a possible target for viral infection.

Furthermore, the link between COVID-19 infection and Th1/Th17 hyperactivity has surfaced, potentially instigating inflammatory responses that may give rise to autoimmune diseases [12]. Given the thyroid gland's vulnerability to inflammation and its involvement during COVID-19, it becomes imperative to explore the potential interplay between these two phenomena. While factors such as age, comorbidities, and immune status have been established as determinants of COVID-19 severity [8,9], emerging evidence points toward endocrine dysfunction, specifically variations in hormone levels, as potentially influential in the clinical trajectory of COVID-19. In this context, Thyroid Stimulating Hormone (TSH), a master regulator of thyroid gland activity, has emerged as a compelling subject of investigation.

The thyroid gland plays a pivotal role in regulating crucial physiological processes including metabolism, immune function, and cardiovascular health. TSH, originating from the anterior pituitary gland, orchestrates this intricate equilibrium by stimulating the release of thyroxine (T4) and triiodothyronine (T3) from the thyroid. Disturbances in this finely tuned balance may trigger a cascade of physiological alterations, potentially affecting the body's defense mechanisms against viral intruders, including the formidable SARS-CoV-2.

As the relentless impact of COVID-19 continues, particularly in regions such as District Faisalabad and District Okara in Pakistan, unraveling the potential

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correlation between TSH levels and the severity of COVID-19 fever emerges as a paramount endeavor. Elucidating plausible links between thyroid function and COVID-19 outcomes not only aids in risk stratification for patients but also provides a robust foundation for clinical decision-making and the development of targeted therapeutic strategies [13,14]. Additionally, insights into the complex interplay between thyroid function and COVID-19 pathogenesis contribute to a broader understanding of the multifaceted mechanisms underpinning the variable severity of COVID-19 [15,16].

This study of COVID-19 and its multifaceted interactions with thyroid disorders culminated in the recent documentation of Subacute Thyroiditis (SAT) following SARS-CoV-2 infection. SAT, an inflammatory disorder, presents with mild fever, neck pain, general malaise, and thyroid dysfunction [17]. Typically, thyrotoxicosis accompanies the initial stages of SAT, followed by a phase of hypothyroidism post-resolution, spanning several weeks or months Remarkably, individuals who tested positive for SARS-CoV-2 displayed slightly elevated heart rates and experienced discomfort, particularly among young women [18,19]. This study embarks on a rigorous investigation into the association between Thyroid Stimulating Hormone (TSH) levels and the severity of COVID-19 fever among individuals residing in District Faisalabad and District Okara, Pakistan. Employing a meticulous analysis of clinical data encompassing thyroid function markers, disease progression, and patient outcomes, this research endeavor seeks to shed light on the role played by TSH in the pathophysiology of COVID-19 and its potential implications for clinical practice.

Material and Methods

Study duration

This retrospective study aimed to investigate the relationship between Thyroid Stimulating Hormone (TSH) levels and the severity of COVID-19 fever among patients in District Faisalabad and District Okara, Punjab, Pakistan. The study period spanned from February 2021 to June 2022.The design study is based on human data, the ethical committee approval letter (No. UO/ERC/2021/04A) is provided as supplementary data.

Patient's selection

The study population comprised individuals who had tested positive for COVID-19 and exhibited abnormalities in TSH or thyroid hormones, indicating thyroid illness. Blood samples were collected from two sources: Al Kabeer International Diagnostic and Research Laboratory, Faisalabad, Punjab, Pakistan, and Al-Noor Medical Lab and Diagnostic Center, Renala Khurd, District Okara, Punjab, Pakistan.

Study samples collection

The study employed a systematic random sampling technique to select a total of 169 patients who met the criteria of having COVID-19 and thyroid gland dysfunction. Among these patients, 99 samples were collected from Faisalabad, including 28 male patients and 71 female patients. Additionally, 70 samples were collected from Okara, consisting of 35 male patients and 34 female patients. The inclusion criteria for patients were those aged 6 years or above with confirmed COVID-19 diagnosis through laboratory testing.

Data Collection

Demographic data, including age and gender, comorbidities (hypertension, diabetes, cardiovascular disease, respiratory disease, and other diseases), clinical symptoms (fever, general symptoms, respiratory symptoms, ear, nose, and throat symptoms, and digestive symptoms), and clinical outcomes (disease severity and death), were collected. Laboratory tests on admission included a complete blood count, blood chemistry, and biomarkers, including platelet counts, T3 (triiodothyronine) levels, T4 (thyroxine) levels, and Thyroid Stimulating Hormone (TSH) levels. The severity of COVID-19 was classified according to the clinical classification of the WHO Interim Guidelines, with patients categorized as mild, moderate, severe, or asymptomatic, following the Pakistan protocol of the Ministry of Health.

Fluorescence Immunoassay (FIA) for Thyroid Stimulating Hormone levels

Thyroid Stimulating Hormone (TSH) levels were determined using the ichroma TSH method, which employs Fluorescence Immunoassay (FIA) to assess

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TSH levels in human serum/plasma. This method was used for the quantitative measurement of TSH in accordance with established protocols by the WHO.

Statistical analysis

The collected data were analyzed using MS Excel 2010 software, including frequency distributions, percentages, and graphs, were utilized to describe the data and its results. The Chi-square test was employed to assess associations between variables of interest, to determine the significance of the results. A p-value of less than 0.05 was considered statistically significant, providing evidence to support the alternative hypothesis. Conversely, a p-value exceeding the significance level of 0.05 led to the retention of the null hypothesis, indicating insufficient evidence to support the alternative hypothesis.

Results

Clinical characteristics of patients with COVID-19

A total of 168 patients participated in the study that underwent thyroid function testing. The mean and standard deviation of their age was found 33.26 ±13.41. In this study the number of female's patients were more than male patients.

Age distributions and level of thyroid stimulating hormone

Table 1 presents the mean, standard deviation and the TSH range observed across different age groups of COVID-19 patients. Mean and standard deviation of TSH values represent the average concentration of TSH within each age category. In males the Mean± Stdev of TSH level for patients aged 10-20 years was determined to be 2.04±1.44 mIU/L. In the 21-30 age group, patients exhibited a notably higher mean TSH level of 1.78±1.19mIU/L. Patients aged 31-40 years displayed a mean TSH level of 2.13±1.12 mIU/L, indicating a relatively lower average TSH concentration. The mean TSH level for patients between 41 and 50 years was 1.73±1.21 mIU/L, signifying a moderate average TSH concentration. Patients above the age of 50 exhibited a mean TSH level of 2.56±1.47 mIU/L, which was notably higher than several other age groups, while in females the values obtained were 1.29±0.85, 2.29±1.68, 1.88±1.19, 1.77±1.58, 2.15±1.19 among different age groups respectively. Notably, the "21-30" age group displayed the highest mean TSH level, while the "41-50" age group exhibited the lowest mean TSH level. These findings highlight the variations among varying age group.

Table 1: TSH Levels by Age Group in COVID_19 patients

Age group	Gender		Age	TSH Range (mIU/L) Mean± Stdev	
	Male	Female	Mean± Stdev	Male	Female
10-20	9	16	12.5±3.5	2.04±1.44	1.29±0.85
20-30	25	36	30.5±5.5	1.78±1.19	2.29±1.68
31-40	9	28	18.5±9.5	2.13±1.12	1.88±1.19
41-50	11	16	13.5±2.5	1.73±1.21	1.77±1.58
Above 50	9	9	9±0	2.56±1.47	2.15±1.19

Chi square analysis

The chi square test was performed on the observed patients with different age groups. The p-values show significance and non-significance of the patients under study. The degree of freedom on all age groups was observed 1. The patients with age group 10-20 shows non-significant, with 20-30 also show non-significance. The patients with age group 30-40 and 41-50 shows significance, while the patients above 50 years of age show non-significance. These can be seen in table 2.

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Table 2: Analysis of Chi-Square showing p-values

Age group	Frequency	Degree of freedom	P-values
10-20	14.88	1	0.45
20-30	36.31	1	0.07
31-40	22.02	1	0.04
41-50	16.07	1	0.01
Above 50	10.71	1	0.09

TSH in Male patients in district Faisalabad

In the 10-20 year age group, there were 4 patients, with 14.3% of total male patients. There have not been any patients in this age group. In the 21-30 year age group, there have 7 patients who have 25% of the total male patients. One patient has an abnormal TSH test and a high value from the standard TSH test value. In the 31-40 year age group, 5 patients, 17.8%, were male. One patient was positive TSH value. In the 40-50 year age group, there have 8 patients who have 28.5% of total male patients. There has not been any male patient in this age group who has been affected by Thyroid Stimulating Hormone. And above 50 years, there have been 4 patients, with 14.3% of total male patients having COVID-19 positive, but thyroid stimulating hormones have not been affected. Further, it is shown in Figure 1.

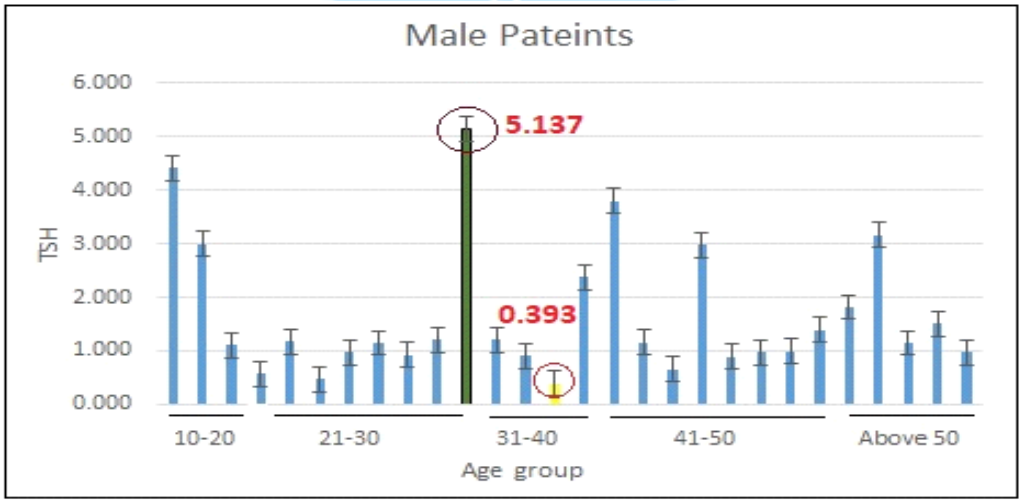

Figure 1: The Figure shows the male patients with COVID-19 based on Age group

Female patients in district Faisalabad

There were 71 female patients in 98 patients. It was 71.7% of the total patients. There have been 3 patients reported who have thyroid stimulating hormone abnormal with the severity of COVID-19 fever (shown in Figure 2). Sixty-eight patients had normal TSH test values, 95.8% of the total female patients. Only 4.2% of patients have reported a TSH value abnormal with the severity of COVID-19 fever. Based on the age group, there have not been any patients in 0-10 years, so that age group has not been included. 11-20 year age group total of 8 female patients included, with 11.3% total female patients. There were not any patients have reported TSH test abnormal values in this age group. In the 21-30 year age group, there were 24 female patients reported, which is 33.8% of the total female patients. In this age group, one patient had a high TSH test value with severity of COVID-19 fever. In the 31-40 year age group, 25 female patients have been reported, 35.2%. There was one patent that had a low-value TSH test normal value. In the 41-50 year age group, 10 patients have been reported, 14.1% of total

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female patients. Only one patient reported an abnormal value of thyroid hormone; the TSH test had a low result compared to the standard value. Of the above 50-year patients, 4 female patients have been reported, which is 5.6% of total female patients. There has not been any patient-reported which TSH test was abnormal value with the severity of COVID-19 fever. Further, Figure 2 is shown below.

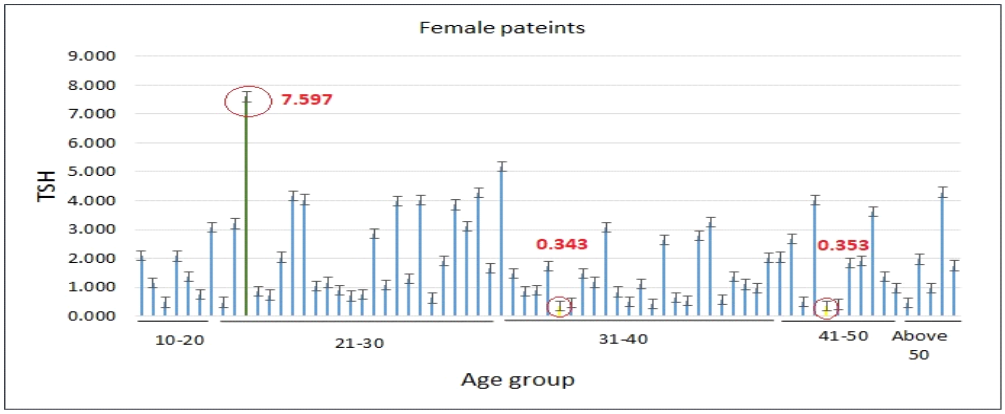

Figure 2: The Figure shows the female patients with COVID-19 based on Age group

TSH test ratio in District Okara

The population of district Okara was 3.040 million in which 1.564 million was male and 1.476 million has female. There were 70 patients who have a report in the Okara district; those patients affected with thyroid hormone with the severity of COVID-19 fever have performed TSH tests. In 70 patients of district Okara, there have 07 patients which abnormal TSH test values. It means that COVID-19 has been more affected in district Okara as compared the Faisalabad. In the district, Okara COVID-19 patients were affected by 10% of thyroid-stimulating hormones.

Male Patients in District Okara

In district Okara based on age group, male patients have been described in five groups. There have not been any child patients whose ages are between 1- 10 years. So, this age group has yet to be described in figure 3. In the 10-20 year age group, there were 4 patients, with 13.8% of total male patients. There have not been any patients in this age group. In the 21-30 year age group, there have 18 patients who have 50% of the total male patients. There have not been any patients in this age group. In the 31-40 year age group, 7 patients, 19.4%, were male. One patient was high TSH value. In the 40-50 year age group, there have 4 patients who have 11.2% of total male patients. There has not been any male patient in this age group who has been affected by Thyroid Stimulating Hormone. And above 50 years, there have been 2 patients, with 5.6% of total male patients having recorded, and one patient was high TSH value. It is shown in Figure 3.

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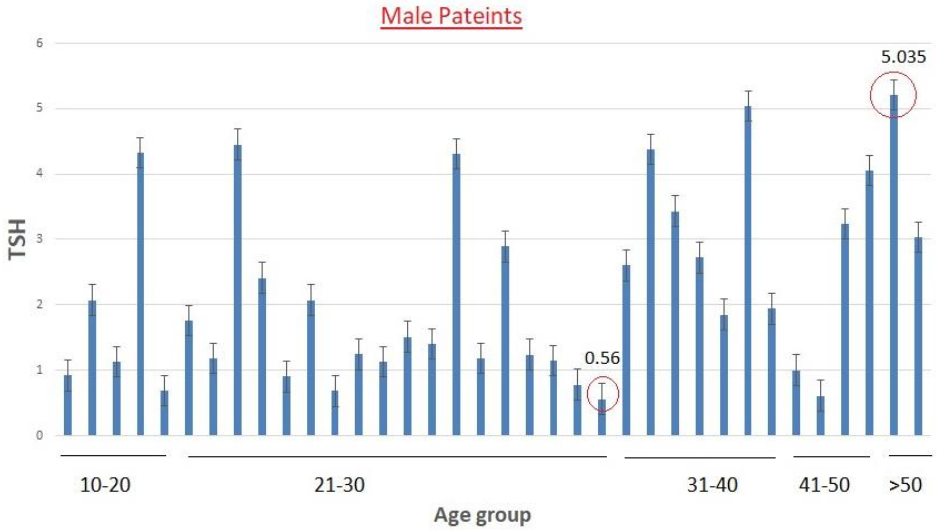

Figure 3: The graph shows the male patients with COVID-19 based on Age group

Female Patients in district Okara

There were 34 female patients in 70 patients. It was 48.5% of the total patients. There have been 5 patients reported who have thyroid stimulating hormone abnormal with the severity of COVID-19 fever (shown in graph 4). 14.7% patients had normal TSH test values, 85.3% have normal TSH value with severity of COVID-19 fever. Based on the age group, there have not been any patients in 0-10 years, so that age group has not been included. 11-20 year age group total of 4 female patients included, with 11.2% total female patients. There were 01 patients have reported TSH test abnormal values in this age group. In the 21-30 year age group, there were 11 female patients reported, which is 32.3% of the total female patients. In this age group, one patient had a high TSH test value with severity of COVID-19 fever. In the 31-40 year age group, 10 female patients have been reported, 29.4%. There was one patent that had a low-value TSH test normal value. In the 41-50 year age group, 05 patients have been reported, 14.7% of total female patients. There were 02 patient reported an abnormal value of thyroid stimulating hormone (TSH). Of the above 50-year patients, 04 female patients have been reported, which is 11.8% of total female patients. There has not been any patient-reported which TSH test was abnormal value with the severity of COVID-19 fever. Further, Figure 4 is shown below.

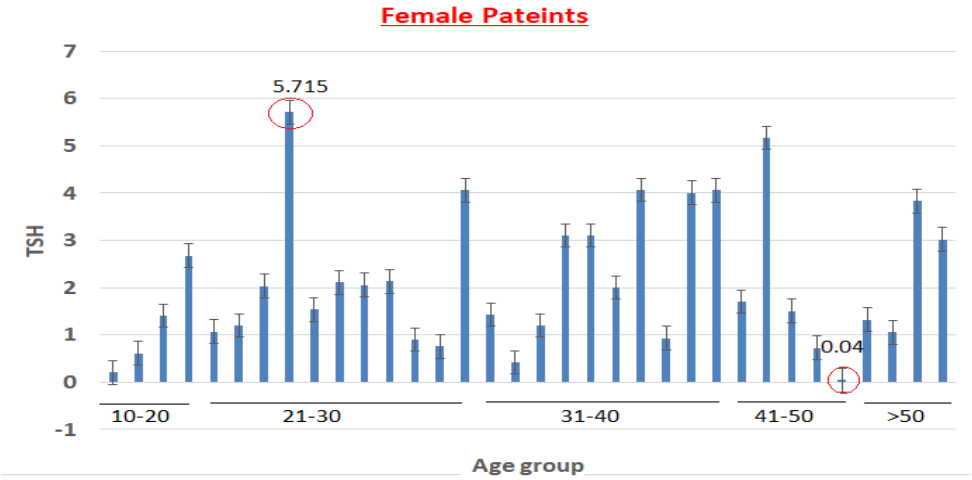

Figure 4: The graph shows the female patients with COVID-19 based on Age group.

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The patients have more records in the district of Faisalabad. Because Faisalabad is a large city with more population compared to the district of Okara, so more patient data and samples were collected compared to Okara. The district Okara is a small city with a low population compared to the district Faisalabad, so there is a low chance of COVID-19 patients.

Discussion

The ongoing COVID-19 pandemic has brought about an unprecedented global health crisis, prompting extensive research into the diverse clinical manifestations and consequences of this novel coronavirus infection[6,9,13]. Among the many facets of this research, the relationship between COVID-19 and thyroid function has emerged as an intriguing area of investigation. In our study, "Association of Thyroid Stimulating Hormone in Severity of COVID-19 Fever: A Report from District Faisalabad and District Okara, Pakistan," we delved into this crucial aspect by examining the potential associations between Thyroid Stimulating Hormone (TSH) levels and the severity of COVID-19 fever in patients from these regions in Pakistan [20].

Our findings align with a growing body of evidence that suggests a connection between COVID-19 and thyroid function. Several key observations and previously reported data warrant discussion: In line with our study, existing research, such as that conducted in Chinese patients without pre-existing thyroid conditions, has highlighted deviations in thyroid function among COVID-19 patients. These deviations extend to Thyroid Hormones (THs), with notably lower levels observed in COVID-19 patients when compared to healthy individuals and even patients with pneumonia of similar severity. These findings emphasize the need for a more comprehensive understanding of the impact of COVID-19 on thyroid function [21].

COVID-19 presents a myriad of clinical challenges, including respiratory failure and cardiovascular complications. The severity of the disease can vary significantly, and our study, as well as previous research, suggests a correlation between the severity of COVID-19 and thyroid dysfunction. This association raises important questions about the mechanistic links between COVID-19 and thyroid alterations. While the exact pathways remain to be elucidated, it is evident that thyroid function deviations are not merely incidental but may be related to the disease's progression. The complexity of COVID-19 is further underscored by its association with various co-morbidities, including autoimmune disorders such as Guillain-Barre's syndrome, autoimmune hemolytic anemia, and autoimmune thrombocytopenic purpura. These coexisting conditions, known to be linked to COVID-19, highlight the multifaceted nature of the disease and its potential to impact various physiological systems [11.22].

Understanding the relationship between COVID-19 and thyroid function has clinical implications, particularly in the management of patients. Our study found that COVID-19 patients did not receive thyroid hormones (THs) and showed no significant differences in various thyroid parameters after recovering from COVID-19. This underscores the importance of cautious interpretation of hormone levels, especially in small patient cohorts. The observed reduction in TSH levels in some cases could be attributed to non-thyroidal illness syndrome, likely induced by systemic changes and cytokine responses [16]. Emerging evidence, including data from studies comparing COVID-19 patients in high-intensity care units (HICU) in different years, indicates a subset of COVID-19 patients displaying characteristics akin to subacute thyroiditis (SAT) and thyrotoxicosis. This subset often exhibits low TSH levels and thyrotoxicosis, suggesting a possible link between SARS-CoV-2 infection and thyroid dysfunction. The need for routine thyroid function testing in COVID-19 patients requiring high-intensity care is underscored, as they may commonly manifest thyrotoxicosis associated with subacute thyroiditis induced by SARS-CoV-2 [20.23].

In conclusion, our study contributes to the ongoing discourse on the relationship between TSH levels and the severity of COVID-19 fever. While further research is necessary to elucidate the precise mechanisms underlying these associations, our findings support the growing body of evidence suggesting that COVID-19 can impact thyroid function. This knowledge has implications for clinical practice, emphasizing the importance of monitoring thyroid function in COVID-19 patients,

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especially those with severe disease. The multifaceted nature of COVID-19 and its potential to affect various physiological systems necessitate ongoing research to provide a comprehensive understanding of the virus's impact on thyroid health [22,24].

Conclusion

In conclusion the emergence of SARS-CoV-2 in December 2019 initiated a global pandemic of coronavirus disease (COVID-19). Rapidly spreading across numerous countries and territories, COVID-19 posed a significant public health challenge. Yet, many aspects of how COVID-19 affects thyroid function remain unclear. The severity classification of COVID-19 cases demonstrated significant insights into the overall clinical picture of the 168 individuals studied. It is evident that thyroid abnormalities in COVID-19 patients are not merely a coincidental occurrence but rather a clinically relevant manifestation that accompanies varying degrees of disease severity. The relationship between COVID-19 and thyroid function remains complex and necessitates further investigation to elucidate the precise mechanisms underlying these alterations. This study found the association between COVID-19 and thyroid function, shedding light on the potential implications for patient care.

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Author's contribution

All authors contributed equally in the manuscript

Conflict of interest

None

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