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Non-Thyroidal Illness Syndrome in A Pediatric Intensive Care Unit During COVID-19 Era

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Abstract

Background: Non-thyroidal illness syndrome (NTIS) is defined as a condition that occurs during acute illness. In this study, we evaluated thyroid function tests in pediatric patients with coronavirus disease 2019 (COVID-19) infection who were admitted to the pediatric intensive care unit (PICU) and compared them with children admitted to the PICU due to other disorders.

Materials and Methods: This was a cross-sectional study where all patients between the ages of 1 month and 16 years admitted to the COVID-19 referral Hospital PICUs were evaluated over a 6 month period. A checklist was used to gather patient information. Thyroid hormones evaluated included; measurements of free T3, T3, T4 and TSH on the first day of admission. Data was analyzed using the SPSS 21 statistical package.

Results: A total of 73 patients were evaluated during the 6 month study period. 40 (54.8%) of them were male and 53(45.2%) were female. The mean age of the study population was 5.9±4.3 years.13 patients were admitted due to SARS-Cov-19 infection.

Thyroid function consistent with Non thyroidal illness syndrome was observed in 25(34.2%) of these patients. The level of T3 and FT3 in patients with COVID-19 were significantly lower than in patients without COVID-19 infection (P<0.05). Body temperature in patients with abnormal thyroid tests was significantly higher than in patients with normal thyroid tests (P=0.040).

Conclusion: We found that one-third of children admitted to the PICU had NTIS. We suggest that FT3 can be a marker of COVID-19 patient severity, as its lower levels were observed in pediatric patients admitted to the PICU.

Key Words: COVID-19 infection, Non thyroidal illness syndrome, Pediatric.

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1- INTRODUCTION

Non-thyroidal illness syndrome (NTIS) is defined as a condition during acute illness characterized by changes in serum levels of thyroid hormones. NTIS is represented by low values of serum T3 and/or thyroxine (T4) without an elevated secretion of thyroid-stimulating hormone (TSH) (1).

Some investigations have shown that during critical illness, decreased levels of serum free T3 (FT3), are usually associated with the severity of the disease and poor prognosis (2,3).

Critical illnesses such as pneumonia, sepsis, surgery, burns, trauma, myocardial infarction, and malignancy can cause NTIS. However, it can also occur in healthy people under conditions such as fasting (4,5). The 2019 coronavirus can affect any part of the body, including the lungs, heart, brain, liver , kidneys, and gut. One of these organs is the thyroid gland (6).

Graves' disease, nonthyroidal illness syndrome, Hashimoto's thyroiditis, and subacute thyroiditis are the most common coronavirus disease 2019 (COVID-19) - related thyroid disorders reported so far (7). SARS-CoV-2 enters the body's tissues through angiotensin-converting–enzyme 2 (ACE2) receptors and can cause a wide range of symptoms, from asymptomatic and flu-like symptoms, to severe lung infection and multi-organ involvement (8,9). Acute respiratory distress syndrome (ARDS) and respiratory failure, sepsis, acute cardiac injury and heart failure are the most common critical complications of COVID-19 (10). Involvement of various organs in children caused by the coronavirus is defined as MIS-C, in which thyroid hormone disorders have also been reported (11).

Given that the ACE2 receptor is abundantly found in thyroid tissue, SARS-COV-2 infection may affect thyroid tissue and thus the production of thyroid hormones (12).

In this study, we evaluated thyroid function tests in pediatric patients with COVID-19 infection who were admitted to the pediatric intensive care unit (PICU) and compared them with children who were admitted to the PICU due to other disorders and tested negative for COVID-19 infection.

2- MATERIALS AND METHODS

This was a cross-sectional study. All patients between the ages of 1 month and 16 years admitted to the PICUs of Akbar Children's Hospital were evaluated during a 6 month period. This hospital is affiliated with Mashhad University of Medical Sciences and is the COVID 19 referral center in the north east of Iran. The study was approved by the medical ethics committee of Mashhad University of Medical Sciences prior to performance (IR.MUMS.MEDICAL.REC.1400.396). Informed consent was obtained from the patients parents or guardian.

A checklist was used for gathering patient information including demographic information, drug history, history of past illnesses, clinical parameters and vital signs, laboratory parameters and thyroid function tests, duration of hospitalization and PICU stay , mechanical ventilation, and patient outcomes.

2.5 milliliters of blood were drawn from all patients admitted to the PICU ward on the first day of admission and sent to the hospital's laboratory for evaluation of thyroid function tests. Electrochemiluminescence immunoassay (ECLIA) was used for thyroid function test measurements. Thyroid hormones evaluated included measurement of free T3, T3, T4 and TSH. The reference values were reported by the laboratory and were age dependent. NTIS was defined as low levels of free T3 or T4 in the absence of elevated TSH or mildly decreased TSH

levels in patients without a preexisting hypothalamic-pituitary-thyroid axis abnormality.

Diagnosis of COVID-19 infection was made based on clinical and laboratory findings and a positive polymerase chain reaction (PCR) from a nasopharyngeal swab.

Patients treated with drugs that might affect thyroid function, history of chemotherapy or radiotherapy in the last 6 months, and patients with underlying pituitary or hypothalamus disease were excluded from the study.

None of our patients had received the COVID-19 vaccine, and all thyroid tests were done before the patients started treatment.

Statistical Analysis:

Data were analyzed using the SPSS 21 statistical package. Categorical data were described as a percentage and frequency. Student's t-test was used for means and chi-square test for proportions. For all tests, the level of confidence was considered 95%.

3-RESULT

A total of 73 patients were evaluated during the 6 month study period. 40 (54.8%) of them were male and 53 (45.2%) were female. The mean age of the study population was 5.9±4.3 years.

Among these 73 patients admitted to the PICU, 13 were admitted due to SARS-COV19 infection.

Thyroid functions consistent with Non-thyroidal illness syndrome were observed in 25 (34.2%) of these patients.

Table 1 shows the mean blood levels of thyroid hormones in the study population.

Table-1. Mean blood levels of thyroid hormones in the study population.

Hormones	Mean±SD
TSH (mIU/L)	2.03±1.98
FT3 (pmol/L)	5.08±11.02
T3 (pmol/L)	83.39±71.19
T4 (pmol/L)	8.46±8.30

Table-2. Comparison of demographic characteristics and thyroid tests between patients with normal thyroid tests and NTIS.

Clinical characteristics	NTIS Mean±SD	Normal thyroid tests Mean±SD	P-value
Systolic blood pressure (mmHg)	97.43±14.19	94.43±13.42	0.415
diastolic blood pressure (mmHg)	62.75±17.28	58.84±9.30	0.355
Number of pulses per minute	124±29.09	122.5±23.17	0.825
Number of breaths per minute	37.89±13.80	35.07±13.65	0.466
Body temperature (Co)	37.49±0.75	37.10±0.43	0.040
Age (month)	54.92±62.44	50.81±58.49	0.779
Duration of hospitalization (days)	17.42±16.13	16.17±15.49	0.754

* Independent T-test was used to compare the two groups.

Evaluation of the thyroid function tests revealed that 25 (34.2%) patients had NTIS, 2 (2.7%) patients had subclinical hypothyroidism, and others had normal thyroid function upon admission to the PICU.

Figure 1 demonstrates the comparison of thyroid hormones and TSH levels between

patients with and without COVID-19. The levels of T3 and FT3 in patients with COVID-19 was significantly lower than in patients without COVID-19 infection.

Table 2 demonstrates the patient's clinical characteristics with normal and abnormal thyroid tests. The body temperature in patients with abnormal thyroid tests was significantly higher than in patients with normal thyroid tests (P=0.040).

Figure 2 compares the demographic and clinical characteristics of patients with abnormal thyroid tests and patients with normal thyroid tests. There were no significant differences between the two groups in any of the investigated cases (p>0.05).

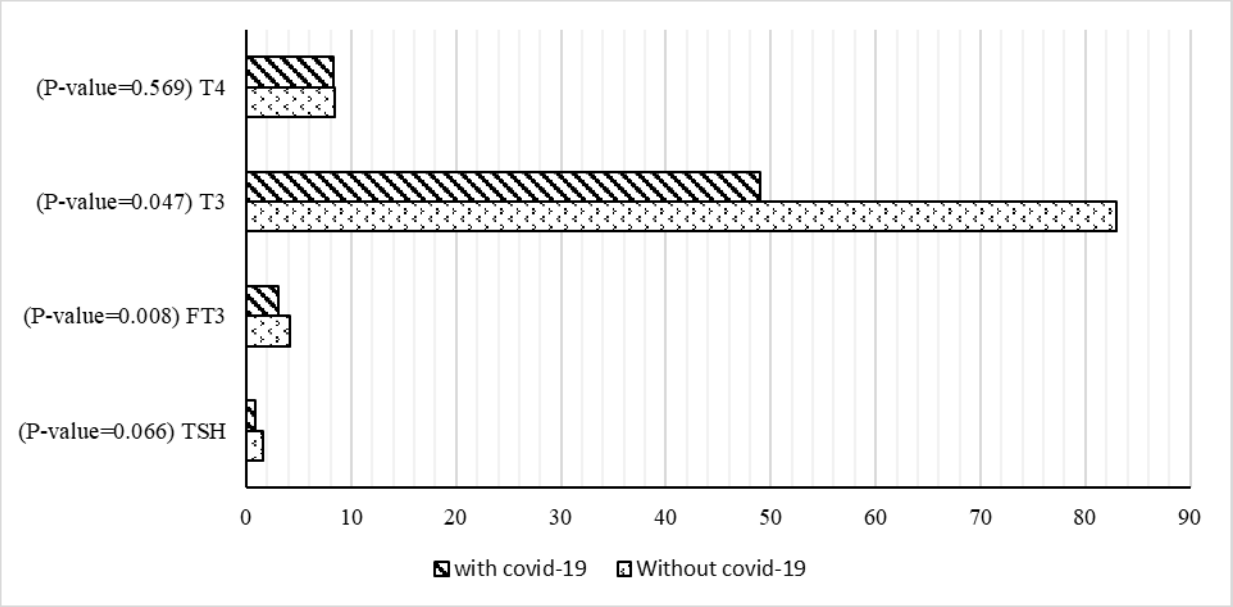

Figure-1: Comparison of thyroid test levels in patients with and without COVID-19.

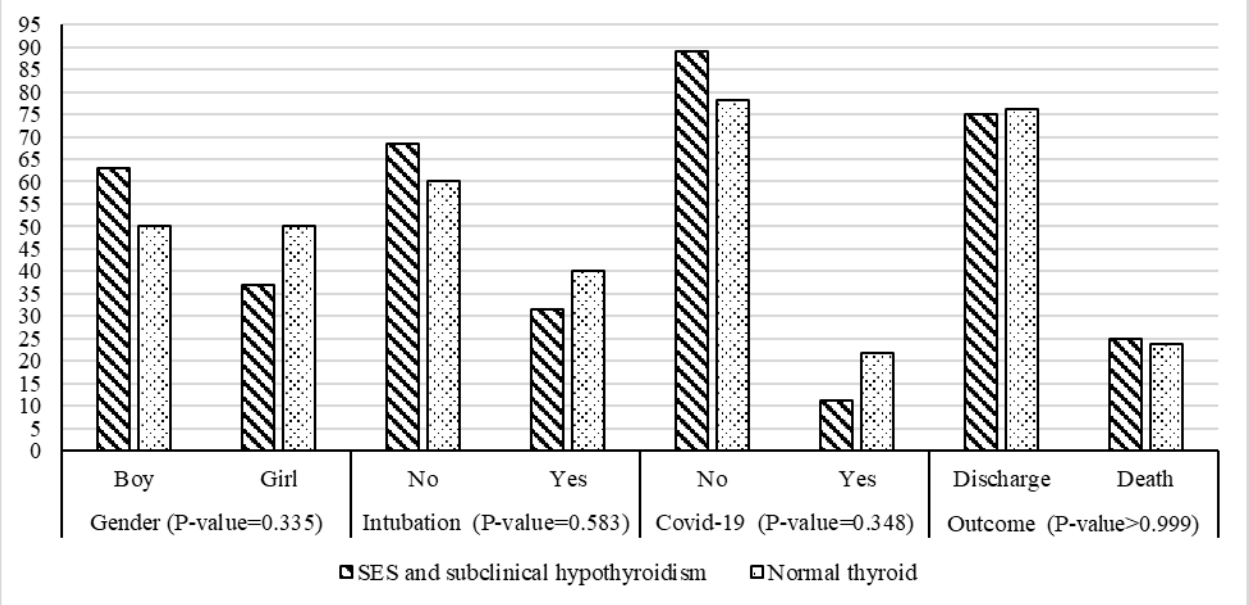

Figure-2: Compares the demographic and clinical characteristics of patients with abnormal thyroid tests and patients with normal thyroid tests (%).

4- DISCUSSION

In this study about a third of critically ill children admitted to our PICU had abnormalities in thyroid function tests consistent with NTIS. Previous studies have reported varying rates of this syndrome among critically ill pediatrics (13-15). It is presumed that NTIS is a form of adaptation to preserve energy during hypercatabolic states (16) and inflammatory cytokines play a role in it's pathogenesis, now considered an acute phase response (17).

We found that the levels of T3 and freeT3 in patients with COVID-19 hospitalized in the PICU were significantly lower than in patients without COVID-19 admitted to the PICU.

One of the most important manifestations of COVID-19 disease may be changes in thyroid tests. Evidence has shown that COVID-19 disease is associated with the induction of thyroid disease, an increase in existing dysfunction or an autoimmune process (18).

Michele Fastiggi et al. reported that most MIS-C patients had NTIS and low levels of Ft3.They considered the level of fT3 as an independent risk factor for the severity of MIS-C (19). The results of this study are consistent with ours, but these investigations were specifically conducted in MIS-C patients. A lower level of Ft3 was reported with an increased probability of hospitalization in the ICU. However, in our study, we did not separately evaluate patients with MIS-C among those who had COVID-19 disease.

Some studies have shown that serum levels of TSH and TT3 were lower in patients with pneumonia caused by COVID-19 than in healthy cases and non-COVID-19 pneumonia (20-21). Although our findings showed a lower serum TSH level in patients with COVID-19, it was not significant.

A systematic review reported that the level of serum TSH in 44-94% of COVID-19 patients was normal, but a low level of TSH was mentioned in 15% up to 56% of them (22). Perhaps the difference in the studies evaluated in this systematic review was in terms of the severity of the COVID-19 disease, which increased the range of serum TSH changes. It seems that the report of low TSH levels in our study was related to the hospitalization of our patients with COVID-19 in the ICU and the severity of the disease.

Chen et al, like our study, showed that TSH levels were lower in patients with severe and critical COVID-19 disease (23).

One of the features of this study was the evaluation of thyroid hormones in all critically ill patients admitted to the pediatric intensive care unit. Our results indicated that the thyroid hormones TSH, FT3, and T3 in patients with COVID-19, who were hospitalized according to the severity of symptoms in the ICU were lower than in patients hospitalized with other causes in the ICU. The results of our study were in line with Michael Llamas's meta-analysis, but they only mentioned free T3 as a simple tool to predict the severity of COVID-19 disease (24). In the present study, TSH and T3 levels were also reported to be low in these patients.

We did not find a significant relationship between COVID -19 and NTIS but some studies indicated NTIS was significantly associated with the severity of COVID-19 disease (20).

In fact, our results showed that the prevalence of NTIS in patients with and without COVID-19 is not significantly different from each other. Perhaps this was due to the fact that all the patients studied in this research were hospitalized in the PICU.

An interesting finding observed in this study was that the average body temperature at the time of admission was

higher in patients who suffered from NTIS than in other patients. To the extent of our investigations, this result was not found in other studies.

Comparing the outcome of patients hospitalized in the PICU with and without NTIS, it showed that nearly a quarter of the patients in each group had died, and there was no difference between the two groups.

Consistent with our results, Muhammad Said El-Mekkawy and his colleagues did not find an association between NTIS and increased mortality (5). However some studies of critically ill children reported that a reduction in the level of T3 and T4 increased the risk of death by 30 times (25,26). This discrepancy could be due to the hospitalization of critically ill patients with various underlying diseases in our intensive care unit.

We showed that the need for ventilation in patients with NTIS is not more than in patients with normal thyroid function. Some other studies also confirmed this result, as Runmei Zou reported that between the two groups (NTIS, NON NTIS) in terms of the need for ventilation, there is no significant difference (20).

One of the limitations of our study was the lack of patient follow-up after discharge from the hospital. Therefore, to more accurately evaluate the effects of COVID-19 disease, it is necessary to follow up the patients for a longer period after the diagnosis of NTIS. Also, due to the high cost of T3RU in our country, we could not check this test in our patients.

It should be noted that none of the patients diagnosed with NTIS were treated with levothyroxine. Therefore, studies with a larger volume are necessary to investigate the need to treat critical patients in the ICU.

5- CONCLUSION

NTIS was a common disorder in critically ill patients. Our study revealed that one-third of children admitted to the PICU had NTIS. We propose that FT3 can serve as a marker of COVID-19 patient severity, as lower levels were observed in pediatric patients admitted to the PICU.

6-ACKNOWLEDGMENTS

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7- CONFLICT OF INTERESTS

The authors declare no conflict of interest.

8- FUNDING

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9- DATA AVAILABILITY

All data generated or analyzed during this study are included in this published article.

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