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Original Research Article

A Correlative Study of Serum CRP with Thyroid Dysfunction in Covid-19 Patients Admitted in a Rural Referral Hospital

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Conflict of interest: Nil

Abstract

Introduction: A novel coronavirus, also known as SARS-COV-2 was responsible for the COVID-19 global pandemic that began in December 2019. There seems to be a complex interplay between the causative agent and the inflammatory-immune responses occurring in the body in response to the infection. The triggered immune response is believed to affect multiple systems including endocrine system. Serum C-reactive protein (CRP) is one of the sensitive markers for inflammatory response.

Aim: To study the correlation between serum CRP values and possible thyroid dysfunction in Covid-19 positive patients.

Materials & Methods: A retrospective study was done on 50 patients who were admitted between May and October of 2021 with covid-19 infection at Government General Hospital, Ananthapuramu. The data regarding serum CRP and Thyroid parameters (Total T_3, Total T_4, TSH) was collected and analyzed for correlation between them by Pearson correlation using SPSS-25.

Results: The study showed correlation coefficient (r) values between thyroid parameters and CRP as:

Total T_3 values are positively correlated with serum CRP levels in Covid-19 patients with a correlation coefficient, $r=0.525$ ($p < 0.01$). Total T_4 values are positively correlated with serum CRP levels in Covid-19 patients with a correlation coefficient, $r=0.9$ ($p<0.01$).

TSH values are negatively correlated with serum CRP levels in Covid-19 patients with a correlation coefficient, $r = -0.475$($p<0.01$)

Conclusion: There is a significant positive correlation between Total T_3 & T_4 values with CRP and a significant negative correlation was seen between TSH and the bio-inflammatory marker, CRP.

Keywords: SARS-COV-2, COVID-19, CRP, Total T_3, T_4 and TSH.

Introduction

Corona virus disease-2019 (COVID19) and its causative agent Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-Cov-2) both were reported initially in Wuhan, Hubei province, China in December 2019. The World Health Organization (WHO) declared Corona virus disease-2019 a pandemic on 11th March [1]. COVID-19 was spreading very rapidly and has very high human-to-human transmission and caused varying degrees of illness [2] . Severe Acute Respiratory Syndrome (SARS) is a disorder which leads to multiple organ injury (lung is the major target organ), it has been presumed that SARS could have a detrimental effect on the thyroid gland, as well [3]. However, only a few publications are there which reported data on clinical observations based on blood samples from SARS patients examined for thyroid function [3,4].

CRP is a type of protein produced by the liver that serves as an early marker of infection or inflammation [5]. CRP preferably binds to phosphocholine expressed highly on the surface of damaged cells [6]. CRP concentration increases with the increase in inflammation or tissue damage, making it a useful marker for monitoring disease severity.

The endocrine system can be affected by SARS-CoV-2 since both hypothalamus and pituitary,

which regulate the functioning of most endocrine glands, express angiotensin-converting enzyme 2 (ACE2), the main protein to which SARS-CoV-2 binds for its entry into the host cells [7,8]. ACE2 is a transmembrane protein consisting of carboxypeptidase activity, due to which angiotensin I is cleaved to angiotensin 1-9 and angiotensin II to angiotensin 1-7, by endopeptidases and oligopeptidases [9]. The viral envelope contains a spike glycoprotein, which interacts with ACE2 with high specificity and affinity, which contributes to the high transmissibility and infectivity of SARS-CoV-2. Then, the virus particle enters the host cell by endocytosis or by fusion of the viral envelope with the cell membrane [10] .SARS-CoV-2 uses ACE2 along with the transmembrane protease serine 2 (TMPRSS2) as the key molecular complex to infect the target host cells [11,12] .ACE2 and TMPRSS2 expression levels are high in the thyroid gland than lungs [13,14] .

There seems to be a complex interplay between the inflammatory-immune responses between the thyroid gland and severity of virus infection.

The thyroid gland is a vital gland. It plays a major role in the metabolism, growth and development of the human body. It regulates various body functions by releasing thyroid hormones into the bloodstream. There are 2 types of cells inside the thyroid gland. Follicular cells secrete T_3 and T_4,

whereas parafollicular cells secrete calcitonin.

T_3 and T_4 increases basal metabolic rate. The functions are

- Increases body temperature.
- Breaks down the energy stored in the liver and muscles.
- Helps in brain tissue growth.
- Promotes growth in children.
- Activation of the nervous system.

Calcitonin helps in calcium and bone metabolism.

Aim & Objectives:

To study and determine the correlation between serum CRP and thyroid functional status (Total T_3, Total T_4 & TSH levels) in covid-19 infected patients.

Materials and Methods:

50 Patients admitted in covid ward of Government General Hospital, Ananthapuramu, Andhra Pradesh, infected with COVID-19 during the study period from May 2021 to September 2021were studied. This study was approved by Institutional Ethics Committee.

The cases of the study included a total of 50 COVID-19 infected patients who were positive to Reverse Transcriptase- Polymerase Chain Reaction (Ct value between 24-34) between the age group of 18-45 years. A detailed history was obtained from the patient or relative. The blood investigations, radiological investigations and bedside tests were studied. From the data, correlation between thyroid function and serum C-reactive protein were assessed. The correlation coefficient is *a statistical measure of the strength of a linear relationship between two variables*. Its values can range from -1 to 1.

Inclusion Criteria:

- Patients admitted in the hospital (In-patients) consenting for research.
- Age group between 18-45 years.
- Covid-19 RT-PCR test result positive.
- Patients not on thyroid medication prior to study.

Exclusion Criteria:

- Patients not giving consent for research.
- Age group less than 18 years and more than 45 years.
- Outpatients.
- Patient with thyroid disease or thyroid medication prior to study.

Sample Collection:

SARS-CoV-2 infection was confirmed by real-time reverse transcriptase–polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swab.

Fasting blood sample was collected in vacutainers. Serum was separated and analyzed for T_3, T_4, TSH and CRP. The tests were done on Access 2 Immunoassay Analyzer of Beckmann Coulter using kits MAGLUMI T_3, MAGLUMI T_4 and MAGLUMI TSH.

Principle of CLIA - When a complementary antigen and antibody are present, the paratope of antibody binds to the epitope of the antigen and this forms antigen-antibody complex also known as immune complex. Estimating the levels of immune complexes by using labelled antibodies is principle used in CLIA.

RT-PCR – Nasopharyngeal /oropharyngeal swabs from patients were collected in VTM (Viral Transport Medium) and stored at a temperature of -20° C ±5° C. Samples were transported with refrigerant packs in sealed Styrofoam box or Ice pack. The kit used for RT-PCR testing is **Meril COVID-19 One-step RT-PCR kit.**

Real time-Polymerase Chain Reaction is used for diagnosis of patients with COVID-19**.**

Steps in RT-PCR:

1. Reagent preparation.

2. Sample adding.

3. PCR Amplification – a) Reverse transcription – 50 ˚C

b) Denaturation – 95 ˚C

c) Annealing – 55 ˚C

d) Extension – 72 ˚C

4. Result Interpretation.

5. Quality control.

Statistical analysis:

All data were collected, tabulated and analysed using Microsoft excel software. The associations between thyroid function and inflammatory biomarker C-reactive protein were analyzed using Pearson correlation co-efficient. 'r' value and 'P' value were calculated using SPSS-25.

Results:

The mean ± SD of various parameters studied and results obtained are tabulated in Table no-1 below.

Table 1: Mean and Standard Deviation of various parameters of the study.

Parameter	Mean ± S.D or n%
Age group	34.6±8.37
Gender	
Female	29(58%)
Male	21(42%)
Total T_3	2.14±0.63
Total T_4	14.62±4.07
TSH	0.96±1.45
CRP	32.04±10.51

The COVID-19 patients had a mean age of years 34.6±8.37 old, out of which 58% (29/50) were females and 42% (21/50) were males. The mean and Standard Deviation (SD) values of various parameters in the current study were as follows. Total T_3 was 2.14±0.63, Total T_4 was 14.62±4.07, TSH = 0.96±1.45 and CRP was 32.04±10.51.

The comparison of mean ± SD of T_3, T_4, TSH and CRP among different age groups is tabulated in Table no-2 below.

Table 2: Comparison of mean and standard deviation of Total T_3, Total T_4, TSH and CRP values among different age groups of COVID-19 infected patients.

AGE (in years)	n	T_3 (Mean ± SD)	T_4 (Mean ± SD)	TSH (Mean ± SD)	CRP (Mean ± SD)
18-24	09	1.22 ± 0.47	14.97 ± 4.05	1.96 ± 2.64	31.3 ± 10.57
25-31	07	1.86 ± 0.45	13.35 ± 5.51	0.58 ± 0.62	30.71 ± 11.61
32-38	10	1.99± 0.65	14.61 ± 3.37	0.72 ± 0.80	32.6 ± 11.31
39-45	24	2.66 ± 0.32	14.79 ± 4.17	0.75 ± 0.95	32.45 ± 10.55

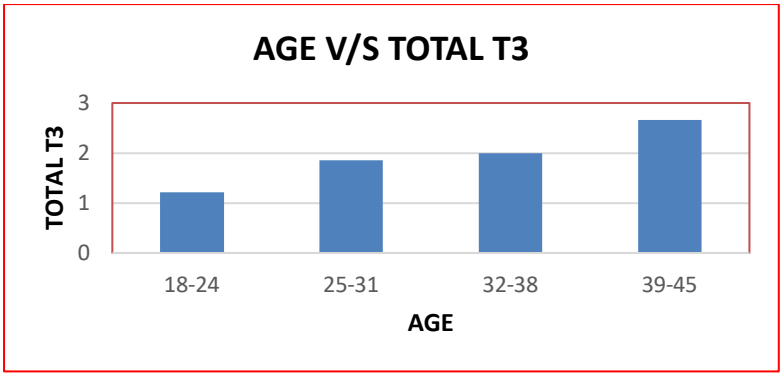
Out of 50 patients studied, 09 were in the age group of 18-24. The group Mean ± SD of T_3,T_4, TSH and CRP was 1.22 ± 0.47, 14.97 ± 4.05, 1.96 ± 2.64 and 31.3 ± 10.57, respectively.

Out of 50 patients studied, 07 were in the age group of 25-31. The group Mean ± SD of T_3,T_4, TSH and CRP was 1.86 ± 0.45, 13.35 ± 5.51, 0.58 ± 0.62 and 30.71 ± 11.61 respectively.

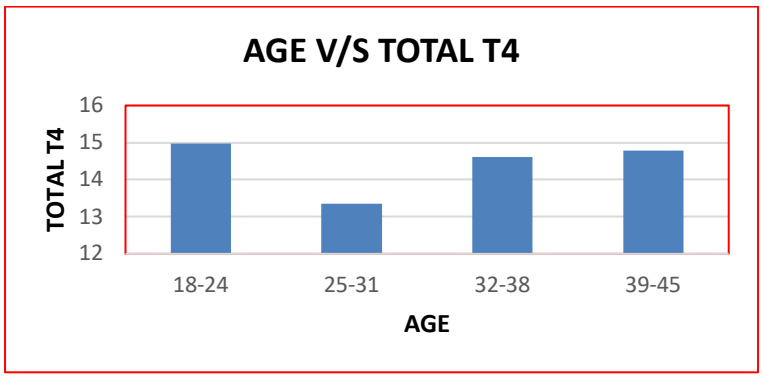
Out of 50 patients studied, 10 were in the age group of 32-38. The group Mean ± SD of T_3,T_4, TSH and CRP was 1.99± 0.65, 14.61 ± 3.37, 0.72 ± 0.80 and 32.6 ± 11.31 respectively.

Out of 50 patients studied, 24 were in the age group of 39-45. The group Mean ± SD of T_3,T_4, TSH and CRP was 2.66 ± 0.32, 14.79 ± 4.17, 0.75 ± 0.95 and 32.45 ± 10.55 respectively.

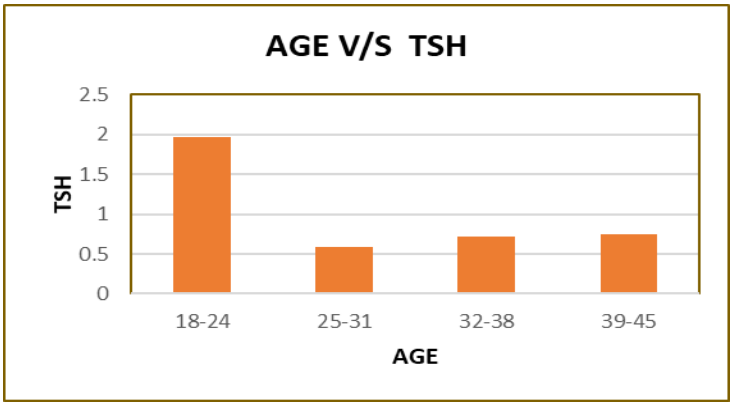
The comparison of T_3, T_4, TSH and CRP values in different age groups are depicted in Graph-1, Graph-2, Graph-3 and Graph-4 below.



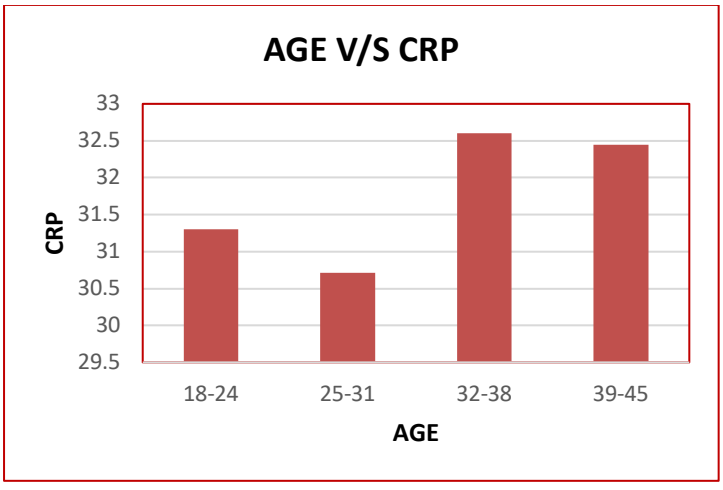
Graph-1: Comparison of Total T_3 values among different age groups with COVID-19 infection.



Graph-2: Comparison of Total T_4 values among different age groups with COVID-19 infection.



Graph-3: Comparison of TSH levels among different age groups with COVID-19 infection.



Graph-4: Comparison of CRP values among different age groups with COVID-19 infection.

The correlation of thyroid function parameters T3, T4 and TSH with CRP of 50 Covid-19 infected patients were depicted in Figure 1 below.

Total T_3 values of 50 patients showed weak positive correlation with serum CRP levels in Covid-19 patients with a correlation coefficient, r=0.525 ($p < 0.01$) (Figure -1)

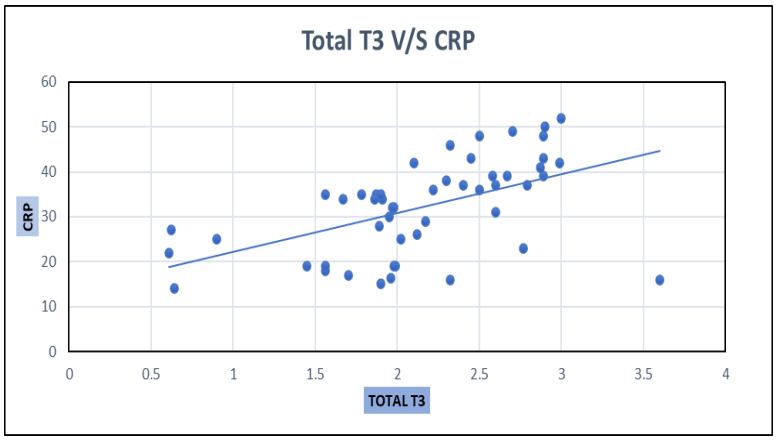


Figure 1: Correlation between Total T_3 and serum CRP values of 50 COVID-19 infected patients.

Total T_4 values showed strong positive correlation with serum CRP levels in Covid-19 patients with a correlation coefficient, r=0.9 ($p < 0.01$). (Figure -2)

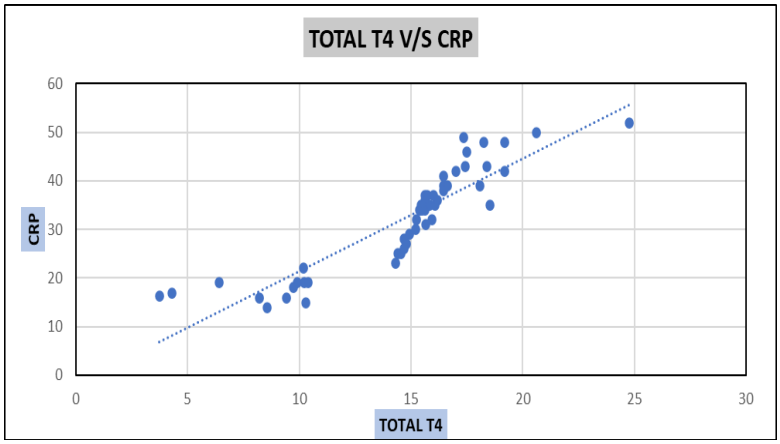


Figure 2: Correlation between Total T_4 and serum CRP.

TSH values are negatively correlated with serum CRP levels in Covid-19 patients with a correlation coefficient, r = -0.475($p < 0.01$) (Figure-3)

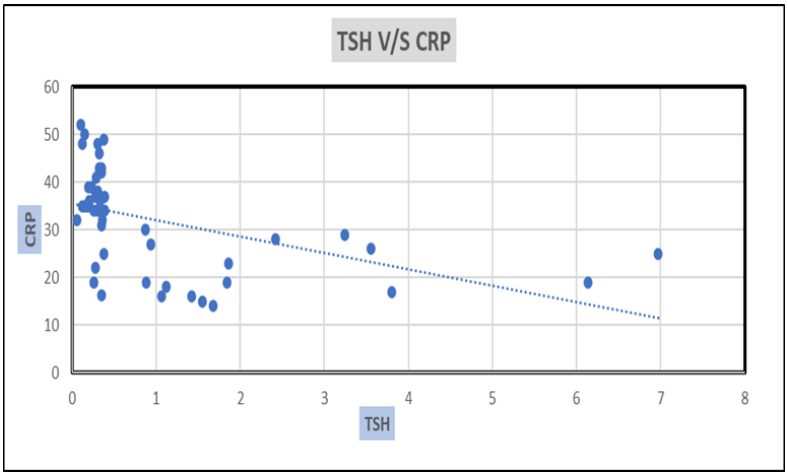


Figure 3: Correlation between TSH and serum CRP.

Discussion:

COVID-19 is an infectious illness that has caused a pandemic worldwide. As a novel type of disease which has high infectivity and mortality, the pathophysiology of COVID-19 has not been fully studied. CRP is pentameric protein synthesized by liver, and its levels rise with response to inflammation. Severe acute respiratory syndrome (SARS), is very severe infectious illness, which is a systemic disease which has extensive effects on multiple organ systems. Coronaviruses infection has wide spectrum of severity in clinical presentation, ranging from asymptomatic cases and common cold to more severe and even fatal respiratory damage [15]. CRP is an acute-phase reactant protein that is primarily induced by the IL-6 action on the gene responsible for the transcription of CRP during the acute phase of an inflammatory or infectious diseases. Post-acute COVID-19 syndrome seems to have affected thyroid hormone balance. Thyroid gland undergo various changes during the acute and recovery stages of any viral infection like SARS COVID-19 infection. This condition is known as "Sick Euthyroid Syndrome" or "Non-Thyroid Illness".

In our study, the Total T_3 values were increasing with increase in the age group of Covid-19 infected patients which means, patients of age group 39-45 years had high Total T_3 values. Total T_4 values did not show significant increase with increase in the age group. TSH values decreased with increase in the age group of patients. High CRP values were observed in age groups of both 39-45 years and 32-38 years

A study reported that the thyroid glands of patients with SARS were significantly affected by extensive injury to the follicular epithelial and parafollicular cells [16]. Another study showed that the TT_3, TT_4, and TSH levels of patients with SARS were considerably lower than those of controls in both the progression and recovery phases [17]. Our study shows that there can be an influence of COVID-19 induced inflammatory response on thyroid function. In this study, we studied the correlation of the disease severity of Covid-19, based on the inflammatory bio-marker CRP with the thyroid function test values of the patients, which means patients with raised CRP may have thyroiditis with increased Total T_3 & T_4 levels and decreased TSH levels. The degree of decrease in TSH was positive correlated with the severity of the disease, measured by increased CRP values. In COVID-19 patients, a profile of cytokines, such as IL-2, IL-6, IL-7, IFN-γ, and TNF-α, is associated with disease severity and mortality of patients [18,19,20,21] . Our results also showed that thyroid dysfunction was associated with increased inflammation biomarkers including CRP, initiating inflammatory reaction which would have played an important role in thyroid dysfunction in COVID-19. The following studies published about Thyroid function status in COVID-19 patients were studied for similarity with our study.

Our study shows that T_3 and T_4 were positively correlated with CRP. Our study correlated with similar results obtained in the studies of Chen et al. reported an altered thyroid function in Covid-19 infected patients [22]. Okwor et al showed that plasma levels of FT_3 and TSH were significantly higher in COVID-19 patients compared to healthy controls [23], while Gao et al. informed that reduced FT_3 independently predicted cause of mortality of patients with severe COVID-19 [24]. Min chen et al study was comparison of thyroid function among COVID-19 infected and non-covid healthy people and results are lower TSH and Total T_3 values are reported in COVID-19 patients [25] . Khoo et al compared the levels of T4 and TSH at admission and after COVID-19 recovery with the patient-matched baseline level assayed in 2019 (i.e., before the pandemic) and confirmed that after recovery serum hormone levels returned to baseline [26]. Wang et al - TT3 and TSH levels were significantly lower in COVID-19 patients. Thyroid dysfunction was more commonly found in critical than in mild/moderate cases and also had an increased level of leukocytes, neutrophils, CRP and decreased level of lymphocytes. Ahn J et al studied that patient who had severe to critical COVID-19 disease had lower TSH and T3 levels compared with those with non-severe disease. T3 was negatively correlated with CRP [27]

Gender showed no effects on the severity of COVID-19 patient. SARS-CoV-2 infection can cause both pulmonary and systemic inflammation, determining multi-organ dysfunction in patients with high risk factors (Elderly age groups, severe hypertension and various other comorbidities like CVS diseases and diabetes) [28,29].

Acute respiratory distress syndrome (ARDS) and respiratory failure, sepsis, acute cardiac injury, and heart failure are considered the most common critical complications of COVID-19 [30]. Both direct (i. e. caused by the virus infection of the target cells) and indirect injury (i. e. by abnormal inflammatory immune responses to virus infection in the body which involves coagulation, cytokine and complement systems) have been linked to the wide clinical expression spectrum and multisystem organ failure of COVID-19 and SARS.

Respiratory infections could potentially precipitate a thyroid storm in patients with decompensated hyperthyroidism, which in turn may favour the infection-related mortality risk [31] . It is also important to note that T_4 is known to activate human platelets and this could sustain pathological clotting encountered as a complication of virus infections. These and other remarks warrant an improved

knowledge of the relationship between COVID-19 and thyroid.

Conclusion:

It is found that there is a positive correlation between Total T_3 & T_4 levels with serum C-reactive protein values in covid-19 patients. There is a negative correlation between TSH and the bio-inflammatory marker, C-reactive protein. Although the cellular and molecular mechanisms are not completely understood, this correlation may be due to "cytokine storm" which is an important identified pathology in this disease. In our study of 50 patients, we found that there is increase in T_3, T_4 levels with CRP values of > 14. There could be an interesting factor in relation to thyroid hormones in management of Covid-19. As the sample size was only 50 further studies with greater sample size are required to confirm our study The hyperthyroid state observed needs to be evaluated for the possible etiology and probable consequences in relation to severity of disease, morbidity and mortality due to covid -19.

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