

# Impact of Serum Pro-calcitonin Level Among SARS-CoV-2 Infected Patients: Emphasizing on A Medullary Thyroid Cancer Survivor in Kolkata, India

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## Abstract

The coronavirus that causes severe acute respiratory syndrome (SARS-CoV-2) is a positive sense single stranded RNA (ssRNA) virus that first appeared in China and has spread throughout the world since late 2019. The SARS-CoV-2 virus causes a mild to severe respiratory infection that affects not just the lungs but also pancreas and other endocrine glands, as well as responsible for ischemic stroke and sexual dysfunctions. Serum pro-calcitonin (PCT) levels have been linked to the severity of coronavirus disease (COVID-19) in several investigations. According to our studies, high PCT levels are linked to a greater risk of severe COVID-19 infection in patients, as well as its involvement and role in a COVID-19 infected cancer survivor. This is the first study we are aware of from India that shows COVID-19 infected people should have regular PCT screening may help clinicians to plan intensive care unit (ICU) placement and detect any recurrence of past illness if any.

**Keywords:** SARS-CoV-2; Pro-calcitonin; Medullary Thyroid Cancer; COVID-19.

## Introduction

SARS-CoV-2 is a newly discovered highly infectious single stranded RNA virus (ssRNA), spreading around the world since December 2019 from Wuhan City, China, and shares 79% and 50% amino acid homology with SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), respectively [10]. COVID-19 patients develop acute respiratory distress syndrome (ARDS), and they frequently necessitate hospitalization and critical care unit intervention. Numerous studies on the actual underlying pathophysiology of ARDS in these severe COVID-19 infection is under investigation [13, 14]. Many researchers have discovered that both hyperinflammation and immune thrombosis are important factors in the emergence of ARDS in COVID-19 [15]. Among other biomarkers, serum procalcitonin (PCT) is found to be associated with disease severity and was first reported as a bacterial infection marker in 1993, when large amounts of calcitonin (CTN) like immune reactivity were discovered in the blood with extra-thyroid illnesses and it is currently utilised in clinical practice as a biochemical diagnosis of sepsis [1]. Furthermore, greater PCT values have been linked with 5 times increased risk in severe SARS-CoV-2 infection, according to a meta-analysis [9, 11]. Thyroid parafollicular C-cells usually synthesise and release PCT, which is the 116-amino-acid precursor of the hormone CTN, a peptide that is formed during post-translational modification of PCT [6]. C-cells are the prime product of thyroid gland that operated to lower blood calcium. PCT measurement is the most sensitive diagnostic technique for detecting Medullary Thyroid Cancer (MTC) and C-cell hyperplasia till date [7, 9]. In MTC, it serves as a marker for residual or recurrent disease [2].

According to a Chinese case study in 2019, few biomarkers connected to sickness severity and fatality include ferritin, C-reactive protein, pro-calcitonin, Lactate dehydrogenase, D-dimer, and Interleukin-6. Increased levels of PCT [hazard ratios of 52.68] and C-reactive protein [hazard ratios of 5.47] were associated as potential danger for mortality in COVID-19 patients [3]. Medullary Thyroid Cancer (MTC) can be diagnosed as sporadic or familial using a blood test for rearranged during transfection (RET) proto-oncogene [4, 8]. Our research investigates the role of variations in serum PCT levels in COVID-19 infected patients in determining disease severity among symptomatic and asymptomatic patients. In order to improve diagnosis and better predict prognosis in cancer patients, we demonstrated a connection between disease severity and serum PCT levels in an MTC survivor. This is the first study to examine the effect of serum calcitonin levels in disease severity in COVID-19 infected patients from India, among symptomatic, asymptomatic, and cancer survivor.

#### Clinical histories of the study participants (Case-A to E):

The study included five COVID-19 infected patients: one asymptomatic (Case-A), one moderate (Case-B), one severe (Case-C), one critical (Case-D), and one MTC surviving symptomatic patient (Case-E). After being diagnosed with SARS-CoV-2 in December 2020, the asymptomatic patient was placed in home isolation for 14 days, while the rest of the patients were admitted to ID & BG Hospital in Kolkata for treatment of COVID-19, with moderate to critical illness during hospitalized, and they were cured and discharged depending upon the severity of their diseases and improvement quality of the each participants. Case-A doesn't showed any symptoms related to COVID-19, he visited the hospital to get tested for the COVID-19 RT-PCR as he was about to fly to another state and got positive to SARS-CoV-2. Fever, loss of appetite, headache and burning sensation in eyes were the symptoms initially felt by the Case-B, C and E (Table 1). Blood sugar, oxygen saturation, blood pressure and heart rate were all within safe limits for Case-A, B, C and E. However, due to unavailability of SARS-CoV-2 vaccines in December 2020, all enrolled patients received their Covishield<sup>a</sup> vaccine with the first and second doses by June and December 2021, respectively. Except for the significant variations in serum calcitonin concentrations, quantitative and qualitative blood counts were normal, and other biochemicals indicators were likewise normal among all the contributors included in this study. Only Case-D and Case-E affirmed that they have alcohol consumption and smoking habit, respectively. Except Case-E, none of the enrolled participants have any past clinical histories and comorbidities (Table 2).

**Table 1:** Socio-demographic Characteristics of the Enrolled Patients.

Particulars	Case-A	Case-B	Case-C	Case-D	Case-E
Age (Year)	40	25	49	32	34
Gender	Male	Male	Male	Male	Male
Height (cm)	172	169	171	167	166
Weight (kg)	85 <sup>‡</sup>	59 <sup>‡</sup>	72 <sup>‡</sup>	81 <sup>‡</sup>	82 <sup>‡</sup>
*BMI (kg/m <sup>2</sup> )	28.7	20.7	24.6	29	29.8
Marital Status	Married	Unmarried	Married	Unmarried	Unmarried
Occupation	Em- ployed	Employed	Employed	Employed	Employed
Locality Area	Urban	Urban	Urban	Urban	Rural
Average Monthly Income (INR)	Rs. 25000	Rs. 20000	Rs. 26000	Rs. 70000	Rs. 15000
Educational Status	Graduate	Post- graduate	Graduate	Doctorate	Graduate
Household Condition	Hygienic	Hygienic	Hygienic	Hygienic	Unhygienic
Extra Activities (if any)	-	Footballer	Musician	Motorcy- clist	-
Smoking Habits	-	-	-	-	+
Alcohol Consumption	-	-	-	+	-
Previous Cancer History (if any)	-	-	-	-	**
Steroidal Medication Use (if any)	-	-	-	-	+

\*BMI: Body Mass Index

‡ Overweight

‡ Normal

- Absent

+ Present

**Table 2:** Routine Biochemical Analysis and Clinical Manifestation of the Enrolled Patients.

Parameters	Case-A	Case-B	Case-C	Case-D	Case-E
<b>Biochemical parameters</b>					
Heart Rate (Beats/Minute)	81	62	75	70	85
SPO2 Saturation (mmHg)	98	96	90	84	95
Blood Pressure: SP/DP (mmHg)	130/85	110/75	115/80	122/79	130/80
Random Blood Glucose Level (mg/dL)	120	90	95	115	110
RBC Count (trillion cells/L)	4.56	5.11	4.71	5.22	4.92
WBC Count (billion cells/L)	6.8	7.6	6.3	5.9	4.4
Hemoglobin (grams/dL)	14.3	13.5	14	17.2	13.2
Hematocrit (%)	42.1	40.5	38.4	43.7	48.3
Platelet Count (billion/L)	198	213	226	185	176
C-Reactive Protein Test (mg/L)	3.5	3.1	3.7	3.6	3.9
<b>Clinical parameters</b>					
Fever	-	+	++	++	+
Dry Cough	-	-	+	-	+
Runny Nose	-	-	-	-	+
Tiredness/Fatigue	-	+	+	++	+
Loss of Taste or Smell	-	+	+	-	+
Sore Throat	-	-	+	+	+
Headache	-	+	+	+	++
Diarrhoea	-	-	-	-	-
Photosensitivity	-	+	+	+	+
Red or Irritated eyes	-	+	+	-	+
Chest Pain	-	-	-	-	-
Loss of Speech or Mobility, or Confusion	-	-	-	-	-
Difficulty Breathing or Shortness of Breath	-	-	-	+++	-

- Absent

+ Mild

++ Moderate

+++ Severe

**Previous clinical histories of the MTC patient (Only Case-E):**

As we underline the link between blood calcitonin levels in a MTC survivor COVID-19 infected patient, the elaborative preceding clinical histories noted from the personal medical records of Case-E. He was admitted to IPGME&R, SSKM hospital in Kolkata, India, in 2014 at the age of 26 years with high serum PCT value along with anxiety, palpitation, headache, excessive sweating, and stomach pain, despite having a normal C-reactive protein level. He underwent a full body evaluation, including a PET/CT scan with Gallium (Ga)-68-DOTA-NOC and urinal metanephrine and non-metanephrine tests. The patient's MTC were verified by a nuclear radiologist, and he underwent bilateral adrenalectomy and full thyroidectomy in the same year he was admitted. The patient has been receiving post-operative therapy and yearly follow-up ongoing at the All India Institute of Medical Sciences (AIIMS) in New Delhi, India, since 2015. According to the post-surgery follow up investigation, tracer avid nodule noted in left Paratracheal region (9x6mm, previously 9x7mm) noted in thyroid bed region abutting trachea.

Tracer avid enlarged left supraclavicular (13x10mm, previously 13x9 mm) and left cervical level II lymph nodes with increased tracer uptake noted. Soft tissue thickening noted in thyroid bed region (maximum thickness in right thyroid bed is 5mm, previously it was 11mm) with minimal tracer uptake. Mildly tracer avid sub-centimetric bilateral cervical level IA, left para vertebral (at D2/D3 vertebral level) lymph nodes noted. Thyroid gland is not visualized, status post surgery normal radiotracer uptake is seen in the pituitary gland. Thyroid gland is not visualised III defined soft tissue thickening noted with increased tracer uptake in thyroid bed region-11m. Sub-centimetric left paratracheal (level VI) node with increased tracer uptake noted. Left supraclavicular lymph node measuring 12 x 11 mm with increased radiotracer uptake. Multiple Endocrine Neoplasia Type 2 (MEN2A) RET gene mutation- no further details in the report of thyroidectomy. Normal range for serum calcitonin (thyrocalcitonin) between 5.0-18.2 pg/mL.

**Table 3:** Serum Procalcitonin Levels and Vaccination details of the Enrolled Patients.

Particulars	Case-A	Case-B	Case-C	Case-D	Case-E
<b>Serum PCT Levels (in pg/mL)</b>					
December-20	50	76	191	447	813
June-21	23	25	52	58	779
December-21	19	22	33	23	798
June-22	16	18	19	18	812
<b>Vaccination Against SARS-CoV-2</b>					
December-20	NA	NA	NA	NA	NA
June-21	π	π	π	π	π
December-21	π̄	π̄	π̄	π̄	π̄
June-22	⊕	⊕	⊕	⊕	⊕

NA: Not Available

π: Covishield 1st Dose Taken

π̄: Covishield 2nd Dose Taken

⊕: Covishield Booster Dose Taken

⊖: Covishield Booster Dose Not Taken

## Discussion

The severe impact of the COVID-19 pandemic overloads healthcare facility, potentially leading to burnout among over-worked health-care workers. Enrolled all of the five patients detected and confirmed SARS-CoV-2 infection at the Virus Research and Diagnostic Laboratory, R. G. Kar Medical College and Hospital in Kolkata, India, with a mean cycle of threshold (Ct) value of  $23 \pm 5$  using one of the Indian Council of Medical Research (ICMR) approved RT-PCR kit manufactured by Angstrom Biotech Pvt Ltd, Rajasthan, India. The findings revealed that average serum PCT values in severe patients were three times higher than in moderate/asymptomatic participants, and seven times higher in critical patients than in moderate/asymptomatic participants. Serum PCT levels are linked to various bacterial co-infections [5]. Blood, urinalysis, sputum cultures, and pneumococcal and listeria monocytogenes antigen tests all showed up negative, indicating that the patients had no bacterial co-infection. Furthermore, a latest study suggested that a steady rise in PCT values could indicate worse disease condition [12]. The hormonal investigation revealed that all of the recruited patients had high serum PCT levels and were all discharged from the ID & BG Hospital in Kolkata, India, with no deaths reported so far. The mean duration of hospitalization was  $17.8 \pm 9.8$  days. Post recovery, serum PCT levels dropped in all four recovered individuals except the cancer survivor. As directed by endocrinologist, the cancer survivor should routinely monitor his serum PCT levels to know the status of recurrence of the MTC, if any. Post operative serum calcitonin levels for 6 years (2015-2020) were within or approximately 200 pg/mL.

In 2014, when he diagnosed with MTC his serum PCT level was 1853 pg/mL, which is considered as baseline for that particular person. Endocrinologist stated that if the PCT values cross the 50% of baseline PCT levels at any time, it is important to recognize that MTC can recur at any time and to seek medical assistance as soon as feasible. During latest follow up it has been noticed that the average values of the serum procalcitonin post COVID-19 infection suddenly raised to 796 pg/mL and 805 pg/mL in the year 2021 and 2022, respectively. Serum PCT levels, on the other hand, increased and then dropped within 6 months in all the COVID-19 infected recovered patients except Case-E. Case-E, on the other hand, has not yet reached 50% of the baseline PCT levels, which is concerning, given that it is close to reaching 50% of the baseline PCT levels. Our result indicates that a cancer survivor infected with COVID-19 experience and settled into elevated PCT levels, but the other patients' PCT levels reverted to normal (Table 3). In the last 2 years, no decrease in PCT levels has been observed in the MTC patient though the rationale behind the settling in higher PCT levels in MTC survivor is unknown. Our study result provides enough evidences still based on the outcomes of one patient, we cannot conclude that COVID-19 infection can cause MTC recurrence in a survivor until the survivor reaches 50% of his baseline PCT levels and is diagnosed with MTC again, or any other cancer. Individuals with comorbidities or other background clinical histories, particularly those who have recovered from cancer and become infected with COVID-19, should have their serum PCT levels monitored in a serial manner to rule out any recurrence of past infections, if any.

## Conclusion

This study shows that serum PCT can help determine the severity of COVID-19 patients by serving as an indicator of disease severity. It's critical to be able to identify COVID-19 affected patients who are at high risk of developing a severe infection, as and when they present to the emergency unit. More intensive management or early ICU admission may be advantageous for these patients. Despite the fact that single MTC recovered COVID-19 patient has been reported with elevated serum PCT level, further investigation into the relation in between SARS-CoV-2 infection and cancer recurrence is warranted in order to better understand the underlying mechanism between serum PCT production and SARS-CoV-2 infection which might ease-up the diagnosis and contribute to the development of treatment procedures.

## Statement and Declarations

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### Disclosure

The authors declare that they have no competing interests.

### Availability of data and material

Data and materials are available upon request to the corresponding author

### Consent to participate and publish

Well informed permission was acquired from discrete contributor included in this study. Written consent to publish has been received from the participant.

### Ethics approval

This study was approved by the Institutional Ethical Committee.

### Author Contributions

RRG and RPC contributed to the conception and design of the study. RPC, SS made the required analysis. RPC, SC, and AC performed the data interpretation. RPC, SC, SS, and DB drafted the report. TM, NM, BP, and BD contributed to manuscript preparation and review of the manuscript. All authors have read and approved the final report.

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