

# The Interrelationship between COVID-19 and Thyroid Carcinomas: Impacts, Mechanisms, and Management Challenges during the Pandemic

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## Abstract

The subsiding of the COVID-19 pandemic and the various effects it could have on the health of infected patients in the long term have prompted researchers to conduct studies in this field. One of the most notable issues is the finding of a relationship between SARS-CoV-2 infection and the development of cancer in human organs. Since thyroid carcinomas have increased in the past two decades, especially after the COVID-19 pandemic, we decided to review the relevant literature and encourage further studies. So far, findings regarding the effects of SARS-CoV-2 on the development of thyroid disorders, flare up of the pre-existing diseases, and neoplastic changes through the induction of cytokine storms, gene mutations and chromosomal rearrangements have been obtained, which requires further evidence. On the other hand, the effects of medical treatment for thyroid carcinoma patients during COVID-19 should also be considered.

**Keywords:** COVID-19; Pandemic; Thyroid; SARS-CoV-2

**Abbreviations:** COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; TMPRSS2: Transmembrane serine protease 2; CLEC4M: C-Type Lectin Domain Family 4 Member M; DPP4: Dipeptidyl Peptidase 4; CRP: C - reactive protein

## Introduction

Nowadays, considering the post-COVID-19 transition period and the significant effects of the pandemic on people's health, researchers have decided to conduct various studies on the effects of COVID-19 on a variety of diseases. In the meantime, the possible relationship between COVID-19 and some types of cancers, including thyroid carcinomas (TCs), has attracted a lot of attention due to the increase in TCs and the challenges caused by the pandemic as a result of the limitation of medical services during the quarantine and pandemic declaration period (from March 2020 to May 2023) [1-6]. Depending on whether the cancer cells originate from the follicular (approximately 95% of cases) or parafollicular (5% of cases) part of the thyroid gland, they can present different pathological features and prognoses; in this regard, papillary and follicular cell carcinoma, anaplastic cell carcinoma, and poorly differentiated thyroid carcinoma occur in the follicular part. Medullary thyroid carcinoma and squamous cell thyroid carcinoma are specific to the parafollicular part. However, there are also cases that can occur in both parts of the thyroid gland, including primary thyroid lymphoma, malignant thyroid teratoma, primary thyroid sarcoma, and metastases from cancers in other areas of the body [7]. Our aim in reviewing the present literature is to compile a summary of the research conducted on the relationship between COVID-19 and TCs and to look at the possible biological mechanisms, mutual consequences, and changes in the therapeutic approach to TCs during the pandemic.

## Overview of Thyroid Carcinoma

TC is one of the most common endocrine malignancies, with a significant increase in incidence over the past two decades. According to the World Health Organization (WHO), the female-to-male ratio is estimated to be approximately 3:1 [8]. In 2020, slightly more than 500,000 new cases of TCs were reported worldwide [9]. The most common types are papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), which originate from thyroid follicular cells. The pathogenesis of TC could be due to one or more genetic mutations, chromosomal rearrangements, and changes in the tumor environment resulting from exposure to environmental factors such as chemicals or viruses, as it has been shown that inflammation of thyrocytes leads to increased cytokine release and factors such as interleukin-6 and interferon- $\alpha$ , which would lead to TCs, indicating that the immune system response is of great importance in this regard [7].

## COVID-19 and Thyroid Dysfunction

Existing evidence suggests that COVID-19 may have effects on thyroid function, so that several cases of hyperthyroidism and hypothyroidism have been reported [10, 11]. Epidemiological research showed that patients with COVID-19 could potentially exacerbate pre-existing autoimmune thyroid disease. One study found that interleukin-6 and thyroid stimulating hormone (TSH) levels were correlated in COVID-19 patients, with high interleukin-6 levels associated with low TSH levels, increasing the risk of hyperthyroidism. The mechanisms underlying these changes may include a viral-induced inflammatory response that could even lead to thyroiditis and subsequent changes in thyroid hormone levels (such as seen in hypothyroidism) [7]. Several studies have shown that in the acute phase of SARS-CoV-19 infection, TSH levels are often normal 3 months after hospitalization, and thyroiditis appears to be transient in most cases [12-16]. Besides, another study found that abnormal thyroid findings due to COVID-19 were transient, lasting no more than a year at most [17].

## Covid-19 and Thyroid Carcinoma

The relationship between COVID-19 and cancers, especially TCs, is complicated. The immune response to SARS-CoV-2 may influence tumor behavior and patient outcomes. The SPIKE protein of this virus, by recognizing the ACE2 (Angiotensin Converting Enzyme type 2) receptor located on the host cell membrane (such as thyrocytes, lung epithelia, heart muscles, and renal

vessels), penetrates into cells, replicates, and possibly causes disparate clinical manifestations by causing mutations in the genes encoding proteins involved in multiple metabolic pathways. In addition, other studies have shown that significant changes in the expression of some genes observed in TC tissue, such as TMPRSS2, CLEC4M, and DPP4 would interact with SARS-CoV-2. SARS-CoV-2 enters cells by binding to the receptor derived from the ACE2 gene. This process is supported by the receptor derived from the TMPRSS2 gene as a cofactor, which exposes the fusion peptide to further the fusion of SARS-CoV-2 and the host cell membrane and enhances cell entry and infectivity by degrading the SARS-CoV-2 spike [18-20]. CLEC4M is another gene-derived receptor that would act like ACE2 for the entry of SARS-CoV-2 into the cells. CLEC4M has the potential to play a role in the cells where ACE2 is not expressed, acting as a facilitator of virus entry into the cells, although further studies are needed to confirm this function [21]. Dipeptidyl peptidase 4 (DPP4) is the other cell membrane protein with various functions in controlling plasma glucose, cell migration and proliferation, and the immune system. It acts as a cell membrane receptor for SARS-CoV-2 and the development of severe acute pulmonary infection [22]. It is believed that this facilitation of viral entry into thyroid gland cells may lead to neoplastic changes through cytokine storms, immune system changes such as T lymphocyte suppression, and chromosomal rearrangements [7]. Studies have shown that in the period following the onset of the COVID-19 pandemic, in addition to an increase in TC patients, especially in the elderly and men, the diagnosis of invasive tumors such as follicular, medullary, and anaplastic TCs has also increased [23]; the patients with cancers, including TCs, showed different immune responses to COVID-19, and this infection would be associated with a weakened immune system and poor prognosis [24].

## Implications of the Covid-19 Pandemic on Thyroid Carcinoma Management

Although the COVID-19 pandemic significantly disrupted healthcare systems worldwide and caused delays in the management of TC patients, some researchers represented that mortality from TCs did not increase within 2 years before and 2 years after the pandemic [7]; however, delays in the diagnosis and treatment due to quarantine and limited patient access to the healthcare facilities have raised concerns about the possibility of disease progression in the patients with TCs [25]. One study showed that the patients with TCs experienced delays in the surgical interventions during the pandemic, leading to increased anxiety and stress, which could have negative effects on the TC patients' physical and mental health [26]. These psychological factors could also negatively impact adherence to treatment and overall quality of life, emphasizing the need for comprehensive supportive protocols for those patients. In addition, the psychological stress alongside the COVID-19 pandemic would exacerbate pre-existing thyroid diseases, especially in individuals with autoimmune thyroid disorders [27]. In addition to these points, it was shown that measuring the inflammatory factors in the COVID-19 patients (especially in association with normal CRP and elevated procalcitonin) could help in the early diagnosis of TCs, especially the medullary type, since procalcitonin is a precursor of the calcitonin hormone, which originates from the parafollicular part of the thyroid gland. Furthermore, some studies examined the effects of the drugs used in the treatment of TC on COVID-19; for example, thyroxine (T4) could increase the entry of SARS-CoV-2 into the patients' cells, and multi-kinase inhibitors, which are used in the treatment of some types of TCs, prevent the replication of this virus and improve the function of T cells. It should be noted that radioactive iodine did not poor the prognosis of COVID-19 infection [7]. So far, extensive research has been conducted on the relationship between COVID-19 and TCs, but there are still some uncertainties. Longitudinal studies are needed to assess the long-term effects of COVID-19 on TC outcomes, including recurrence rates and overall survival. In addition, further studies on the biological effects of SARS-CoV-2 infection on the body cells and the development of malignancies such as TCs are needed to guide targeted interventions for effective prevention and treatment, and understanding the interaction between COVID-19 and TC will be essential for developing effective management strategies and improving the patients' outcome in the post-pandemic era. Consequently, the relationship between COVID-19 and TCs is an emerging area of research that requires further investigation. This pandemic has not only highlighted the vulnerability of cancer patients, but also the importance of integrating multidisciplinary approaches for the effective management of TCs. As the world continues to grapple with the challenges posed by COVID-19, it is impera-

tive that studies aimed at understanding and addressing the complex association between the current viral infections, cancers, and ultimately advancing the management of the patients with TCs receive special attention.

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