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Frequency of Thyroid Dysfunction in Cancer Patients on Immunotherapy

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ABSTRACT

Background: Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment by enhancing the immune system's ability to target tumor cells. ICIs include PD-1, PD-L1, and CTLA-4 inhibitors. Despite their efficacy, ICIs are associated with immune-related adverse events, with thyroid dysfunction being the most common endocrine complication. **Objective:** To determine the frequency of thyroid dysfunction in cancer patients on immunotherapy. **Material and Methods:** This prospective cohort study was conducted at Liaquat National Hospital, Karachi, from 28/11/24 to 27/5/25. A total of 89 patients aged 19–70 years were enrolled. Thyroid function was monitored via TSH and FT4 levels at baseline and every 2–3 weeks during treatment with immune checkpoint inhibitors. Data were analyzed using SPSS, with statistical significance set at $p \leq 0.05$. Stratification controlled for confounders like age, gender, cancer type, and comorbidities. **Results:** The mean age was 54.4±11.7 years with predominance of females (69.7%). Breast cancer was the most common malignancy. Pembrolizumab combined with chemotherapy was the most frequently administered treatment. Thyroid dysfunction was observed in 14.6% of patients, with hypothyroidism being the most prevalent subtype (7.9%). Thyroid dysfunction typically developed within 2 to 11 weeks of initiating immunotherapy, depending on the agent used. No significant associations were found between thyroid dysfunction and patients' socio-demographic or clinical characteristics. **Conclusion:** Thyroid dysfunction was observed in a small group of cancer patients receiving immune checkpoint inhibitors, with onset varying by drug. No associations were found with patient characteristics.

INTRODUCTION

In recent years, significant advancements have been made in cancer therapeutics, particularly with the development of immune checkpoint inhibitors (ICIs). ICIs are a type of cancer immunotherapy that harnesses the body's immune system to combat tumor cells.[1] Immunotherapy, either alone or combined with traditional treatments like radiotherapy and chemotherapy, has become a standard and successful approach for treating various cancers.[2]

Immune Checkpoint inhibitors work by blocking the interaction between checkpoint proteins (such as CTLA-4, PD-1, and PD-L1) and their partner proteins. This reduction in immune checkpoint activity in a regulatory T cell-rich environment enables immune cells to mount a more robust response against cancer cells, ultimately leading to enhanced antitumor immunity. The U.S. Food and Drug Administration (FDA) has approved three distinct classes of immune checkpoint inhibitors (ICIs) for the treatment of multiple cancer types: 1: PD-1 inhibitors (Nivolumab, Pembrolizumab, Cemiplimab). 2: PD-L1 inhibitors (Atezolizumab, Durvalumab, Avelumab), and 3: CTLA-4 inhibitor (Ipilimumab). These ICIs have demonstrated efficacy in treating a wide range of cancers, including melanoma, non-small cell lung cancer, renal cell carcinoma, urothelial carcinoma, head and neck squamous cell carcinoma, Hodgkin lymphoma, microsatellite instability-high or mismatch repair deficient solid tumors, gastric cancer, esophageal cancer, cervical cancer, hepatocellular carcinoma, Merkel cell carcinoma, and triple-negative breast cancer. [6-8] Initially approved for advanced-stage cancers, immune checkpoint inhibitors (ICIs) have expanded their therapeutic scope and are now commonly utilized in both adjuvant and neoadjuvant settings for the treatment of earlier-stage cancers.[3]

Immune checkpoint inhibitors (ICIs), while demonstrating considerable potential in cancer therapy, have been linked to the development of various autoimmune disorders, including thyroid dysfunction. Thyroid dysfunction, which can manifest as hypothyroidism, thyrotoxicosis, and thyroiditis, is the most prevalent immune-related adverse event (irAE) affecting the endocrine system.[4] One of the study In patients with non-small cell lung cancer (NSCLC) treated with pembrolizumab 21% developed thyroid dysfunction, which was significantly linked to the presence

of anti-thyroid antibodies. [5]

Result of another study showed 26.03% of patients with advanced carcinoma developed thyroid dysfunction after receiving anti-PD-1 therapy and predicts a better prognosis in patients who developed thyroid dysfunction.[6] ICI treatment-induced thyroid dysfunction was found to be significantly correlated with improved survival rates.[9]

One of the international studies found that New-onset thyroid dysfunction was diagnosed in 18.0% of patients on ICI therapy occurred after a median of 10.6 weeks.[10] Healthcare professionals practicing in developing countries should be aware of the importance of adverse effects to follow and address timely and deal it as multidisciplinary approach.

There was limited literature that showed prevalence of adverse effect of check point inhibitor locally. Therefore, it is imperative to conduct this study to determine the frequency of thyroid dysfunction in patients with cancer on checkpoint inhibitor in order to establish local perspective. We aim to investigate the frequency of thyroid dysfunction along with timing of thyroid dysfunction onset after the initiation of immunotherapy (ICI) treatment. The study aims to provide insights into the importance of identifying adverse effect of immunotherapy in cancer patients so that it is made mandatory to assess the levels at the crucial period so that patient requiring treatment should be timely referred to endocrinologist to seek treatment for thyroid dysfunction decreasing morbidity.

MATERIAL AND METHODS

This prospective cohort study was conducted at the Department of Oncology, Liaquat National Hospital, Karachi, over a period of six months from 28/11/24 to 27/5/25, following approval of the research synopsis. A total of 89 patients were enrolled, with the sample size calculated using WHO software based on a thyroid dysfunction prevalence of 18%,[10] a margin of error of 8%, and a 95% confidence level.

Patients aged between 19 and 70 years, of either sex, with a confirmed histological or cytological diagnosis of malignancy requiring immune checkpoint inhibitors were included. Participants receiving immunotherapy in neoadjuvant, adjuvant, or palliative settings, either as monotherapy or in combination with chemotherapy or tyrosine kinase inhibitors, were considered eligible. Patients were excluded if they declined consent, had a history of total thyroidectomy, were previously treated with levothyroxine, had pre-existing thyroid dysfunction prior to initiation of immunotherapy, had received prior immune checkpoint inhibitor therapy, had known pituitary disease, were pregnant, or were lost to follow-up.

Thyroid dysfunction was defined based on serum thyroid-stimulating hormone (TSH) and free thyroxine (FT4) levels. Hyperthyroidism was characterized by suppressed TSH (<0.2 µIU/ml) and elevated FT4 (>1.7 ng/dl), while subclinical hyperthyroidism was defined by suppressed TSH with normal FT4 levels (0.9–1.7 ng/dl). Hypothyroidism was indicated by elevated TSH (>4.2 µIU/ml) and suppressed FT4 (<0.9 ng/dl), and subclinical hypothyroidism was defined by elevated TSH with normal FT4 levels. Neoadjuvant therapy referred to immunotherapy administered prior to surgical intervention, adjuvant therapy was given post-surgery, and palliative therapy involved immunotherapy aimed at improving quality of life in advanced cancer cases.

Thyroid function tests were performed prior to initiation of immunotherapy and repeated every 2–3 weeks. The time to onset of thyroid dysfunction was defined as the duration in weeks from the start of immunotherapy to the development of thyroid dysfunction. Laboratory reference ranges used were TSH: 0.2–4.2 µIU/ml and FT4: 0.9–1.7 ng/dl. Immunotherapy agents administered included nivolumab (3 mg/kg IV every 2 weeks), pembrolizumab (200 mg IV every 3 weeks), atezolizumab (840 mg IV every 2 weeks or 1200 mg IV every 3 weeks), durvalumab (10 mg/kg IV every 2 weeks), and avelumab (800 mg IV every 2 weeks). TSH levels were monitored before treatment and at least every two cycles during therapy to assess safety.

Following ethical approval from the institutional review board and the College of Physicians and Surgeons Pakistan, informed consent was obtained from all participants. Demographic and clinical data including age, gender, BMI, diabetes status, family history of thyroid dysfunction, tumor type and stage, immunotherapy agent used, and mode of administration were recorded using a pre-designed proforma. Confounding variables and bias were minimized through strict adherence to inclusion criteria and stratification protocols. Serial TSH levels were assessed at baseline, one month, and three months post-treatment initiation. In cases of TSH derangement, FT4 levels were measured to classify the type of thyroid dysfunction. If TSH remained within normal limits, monitoring continued until the three-month mark.

Data were compiled and analyzed using SPSS version 27. Normality of quantitative variables was assessed, and appropriate descriptive statistics including mean and standard deviation or median and interquartile range were calculated for variables such as age, BMI, TSH, FT4, and time to onset of thyroid dysfunction. Frequencies and percentages were computed for categorical variables including gender, cancer type and stage, immunotherapy agent, mode of administration, diabetes status, family history of thyroid dysfunction, and presence and type of thyroid dysfunction. Effect modifiers were controlled through stratification by relevant variables, and post-stratification analysis was performed using chi-square or Fisher's exact test where applicable. A p-value of ≤0.05 was considered statistically significant.

RESULTS

Table 1 exhibits summary of patients' socio-demographic and clinical features. Mean age was 54.4±11.7 years where as age range was 27-29 years. Mean body mass index of patients and 1.6 ± 0.2 Kg/m^2. More than two-third of patients were females (69.7%). Few had family history of thyroid disorders (6.7%). Most frequent diagnosed malignancy was breast cancer. Around half of the patients had late stage cancer of 4th stage (52.8%). Mostly patients were treated with Pembrolizumab (66.3%) with chemotherapy (76.4%).

Table 2 displays summary of thyroid profile and thyroid dysfunction. Median TSH and FT4 level was 0.5 (IQR= 0.4-

0.8) µIU/ml) and 1.5 (IQR= 1.1-1.7) µIU/ml. Most of patients had normal levels of TSH (86.5%) and FT4 (88.8%). Thyroid dysfunction was seen in 14.6% patients, with most common thyroid disorder of hypothyroidism (7.9%).

Table 1

Summary of Patients' Socio-Demographic and Clinical Features

Variables	Groups	Frequency	%tage
Age	≤40 Years	9	10.1
	>40 Years	80	89.9
Gender	Male	27	30.3
	Female	62	69.7
Family History Of Thyroid Disorder	Yes	6	6.7
	No	83	93.3
Diabetes	Yes	17	19.1
	No	72	80.9
Cancer Type	Breast	41	46.1
	Endometrium	3	3.4
	Esophagus	10	11.2
	Head And Neck	2	2.2
	Lungs	8	9.0
	Stomach	1	1.1
	Hepatocellular	4	4.5
	Hodgkin Lymphoma	2	2.2
	Merkel Cell	3	3.4
	Renal	3	3.4
	Oral	3	3.4
	Urothelial	2	2.2
	Gastroesophageal Junction	1	1.1
	Neuroendocrine Tumor	6	6.7
Cancer Stage	Stage II	13	14.6
	Stage III	29	32.6
	Stage IV	47	52.8
Medication	Atezolizumab	10	11.2
	Nivolumab	20	22.5
	Pembrolizumab	59	66.3
Mode Of Medication	Monotherapy	13	14.6
	With Chemotherapy	68	76.4
	Withtyrosine Kinase Inhibitor	8	9.0

Table 2

Summary of Thyroid Profile and Thyroid Dysfunction

Variables	Groups	Frequency	%age
TSH levels	Low	4	4.5
	Normal	77	86.5
	High	8	9.0
FT4 levels	Low	7	7.9
	Normal	79	88.8
	High	3	3.4
Thyroid Dysfunction	Yes	13	14.6
	No	76	85.4
Type Of Thyroid Dysfunction	Hypothyroidism	7	7.9
	Subclinical Hypothyroidism	1	1.1
	Hyperthyroidism	4	4.5
	Subclinical Hyperthyroidism	1	1.1

Table 3 presents average time to thyroid dysfunction development after initiating different medications. Thyroid dysfunction developed on an average 2 weeks after initiating Nivolumab whereas after initiating Pembrolizumab and Atezolizumab thyroid dysfunction developed at approximately 9th week and 11th week respectively.

Table 3

Time to Thyroid Dysfunction Onset after Initiating Different Medication

Medication	Thyroid dysfunction n (%)	Average Time of Developing Thyroid Dysfunction (in weeks)
Atezolizumab	3	10.5 ± 5.2
Nivolumab	2	2 ± 1.1
Pembrolizumab	8	9.3 ± 3.8

mean±standard deviation

Table 4 presented a comparative analysis of patient characteristics between those who developed thyroid dysfunction and those who did not. Among patients aged ≤40 years, 11.1% experienced thyroid dysfunction compared to 15% in those aged >40 years (p = 1.000). Gender distribution showed similar rates, with 14.8% of males and 14.5% of females affected (p = 1.000). None of the patients with a family history of thyroid cancer developed thyroid dysfunction, whereas 15.7% of those without such a history did (p = 0.587). Thyroid dysfunction was observed in 17.6% of diabetic patients and 13.9% of non-diabetic patients (p = 0.708).

Regarding cancer type, the highest proportions of thyroid dysfunction were noted in patients with urothelial cancer (50%), neuroendocrine tumors (33.3%), renal cancer (33.3%), oral cancer (33.3%), and endometrial cancer (33.3%). However, these findings were not statistically significant (p = 0.431). Patients with stage IV cancer had a higher frequency of thyroid dysfunction (19.1%) compared to those with stage III (6.9%) and stage II (15.4%) disease (p = 0.375).

In terms of medication, thyroid dysfunction occurred in 30% of patients treated with Atezolizumab, 13.6% with Pembrolizumab, and 10% with Nivolumab (p = 0.277). Patients receiving therapy in combination with tyrosine kinase inhibitors had the highest rate of thyroid dysfunction (37.5%), followed by those treated with chemotherapy (13.2%) and monotherapy (7.7%) (p = 0.170). None of the comparisons yielded statistically significant differences, as all p-values exceeded the conventional threshold of 0.05.

Table 4

Comparison of Patients' Features among those with and without Thyroid Dysfunction

Variables	Groups	Thyroid Dysfunction		P-value*
		Yes n(%)	No n(%)	
Age	≤40 Years	1(11.1)	8(88.9)	1.000
	>40 Years	12(15)	68(85)	
Gender	Male	4(14.8)	23(85.2)	1.000
	Female	9(14.5)	53(85.5)	
Family history of thyroid cancer	Yes	0(0)	6(100)	0.587
	No	13(15.7)	70(84.3)	
Diabetes	Yes	3(17.6)	14(82.4)	0.708
	No	10(13.9)	62(86.1)	
Cancer type	Breast	5(12.2)	36(87.8)	0.431
	Endometrium	1(33.3)	2(66.7)	
	Esophagus	1(10)	9(90)	
	Headand Neck	0(0)	2(100)	
	Lungs	0(0)	8(100)	
	Stomach	0(0)	1(100)	
	Hepatocellular	1(25)	3(75)	
	Hodgkin Lymphoma	0(0)	2(100)	
	Merkel Cell	0(0)	3(100)	
	Renal	1(33.3)	2(66.7)	
	Oral	1(33.3)	2(66.7)	

	Urothelial	1(50)	1(50)	
	Gastroesophageal Junction	0(0)	1(100)	
	Neuroendocrine Tumor	2(33.3)	4(66.7)	
Cancer stage	Stage II	2(15.4)	11(84.6)	0.375
	Stage III	2(6.9)	27(93.1)	
	Stage IV	9(19.1)	38(80.9)	
Medication	Atezolizumab	3(30)	7(70)	0.277
	Nivolumab	2(10)	18(90)	
	Pembrolizumab	8(13.6)	51(86.4)	
Mode of medication	Monotherapy	1(7.7)	12(92.3)	0.170
	With Chemo	9(13.2)	59(86.8)	
	With Tyrosine Kinase Inhibitor	3(37.5)	5(62.5)	

**Fisher-exact test is reported*

DISCUSSION

Thyroid dysfunction is one of the most common toxicities in patients receiving ICIs and results from immune damage to the thyroid gland. The response to this damage can result in different scenarios which can be both dynamic and unpredictable in outcome.[3] Thyroid dysfunction is the most common endocrine-related immune related adverse events (irAEs) irAE,[11,12] typically developing within weeks. Guidelines offer limited direction on post-treatment TFT monitoring particularly regarding frequency and duration.[13-15]

The incidence of checkpoint inhibitor induced hypothyroidism was within the range reported in previous studies.[17-22] In another study,[23] however, 11.5% of patients had checkpoint inhibitor–induced hypothyroidism, whereas in previous studies the frequency of hypothyroidism varied from 5% to 22%.[17-22] This wide variation, as well as the increased frequency of hypothyroidism in more recent reports[24,25] compared with earlier reports,[17-19] indicate an improvement in screening. Moreover, the incidence of hypothyroidism is higher when a combination of 2 checkpoint inhibitors is used compared with the use of monotherapy based on some published data.[20,21] In a previous study,[16] 20% of the patients who were received checkpoint inhibitor combination therapy had checkpoint inhibitor induced hypothyroidism compared with 10% to 22% of the patients who were receiving checkpoint inhibitor combination therapy in previous studies.[20,21]. Due to non-availability of few immunotherapy in our setup. We were unable to access combination therapy response.

In a same previous study, 53% of the patients who had hypothyroidism were referred to the endocrinology department. Thyroid function test results returned to normal more quickly in patients managed by oncologists than in those managed by endocrinologists, which validates the recommendation of current treatment guidelines that hypothyroidism can be initially managed by the treating oncologist and does not require endocrinology referral.[26]

Although the use of checkpoint inhibitors can lead to a variety of AEs, some preclinical studies and several clinical studies have shown that thyroid dysfunction may be associated with a better response to checkpoint inhibitor therapy and better overall survival compared with patients without thyroid dysfunction.[27-31]

In our study, the patient cohort was predominantly female, with a wide age distribution and a small proportion reporting a family history of thyroid disorders. Breast cancer emerged as the most frequently diagnosed malignancy, and a considerable number of patients presented with advanced-stage disease. Most were treated with immune checkpoint inhibitors, particularly Pembrolizumab, often in combination with chemotherapy. Thyroid function remained within normal limits for the majority of patients, although a subset developed thyroid dysfunction, with hypothyroidism being the most common abnormality. The timing of dysfunction varied depending on the immunotherapeutic agent used, occurring earlier with Nivolumab and later with Pembrolizumab and Atezolizumab. No significant associations were found between thyroid dysfunction and patients' socio-demographic or clinical characteristics, indicating that such adverse effects may arise independently of baseline features.

In a previous study[3] the investigator investigated thyroid dysfunction among 1349 patients treated with ICIs. Subclinical hyperthyroidism (18.8%) and subclinical hypothyroidism (16.2%) were the most common manifestations of thyroid damage. Overt hyperthyroidism and overt hypothyroidism occurred in 10.3% and 9.3%, respectively (22.3% and 14.0% with combination ICIs). The clinical course ranged from transient subclinical dysfunction to rapid progression (<2 months) from overt hyperthyroidism, with very high fT4s, to overt hypothyroidism. As compared to these findings, clinical trials have generally reported lower rates of thyroid dysfunction (e.g. 14.3% and 17% with hypothyroidism in KEYNOTE-0542 and Checkmate-067.[32]

The results other studies reported that dysfunction rate was ranged from 17% to 62.0% and onset times of 31–63 days for hyperthyroidism and 98–105 days for hypothyroidism.[33-37] Previous studies have been inconsistent regarding rates of thyroid recovery after ICI-induced dysfunction. A large study involving melanoma patients reported that most patients with overt hyperthyroidism recovered,[38] while another study found that 100% with hyperthyroidism (denoted by raised fT4) eventually required thyroxine therapy.[36]

In non-ICI thyroiditis, fT4 remains elevated and falls below normal after ~6 months.[39] In a study,[3] some patients progressed from overt hyperthyroidism to overt hypothyroidism in <6 weeks. Rapidly progressive ICI-induced thyroid dysfunction and rapid onset de novo overt hypothyroidism have implications for monitoring.

Previous studies have reported associations of female sex, younger age, BMI and TSH with ICI-induced thyroid dysfunction,[33,35,38,40] but not eGFR. Thyroid dysfunction due to 'non-thyroidal illnesses'[41] may have been misclassified as isolated hypothyroxinaemia or secondary overt hypothyroidism, though patients were generally low-risk for this from baseline characteristics.

A 2020 study by Basak and colleagues demonstrated that patients with non–small-cell lung carcinoma, renal-cell carcinoma, or melanoma who had overt thyroid dysfunction while receiving checkpoint inhibitor therapy had higher overall survival (P = .02) and progression-free survival (P = .05) than patients who did not have thyroid dysfunction while receiving checkpoint inhibitor therapy.[16] Another recent study by Baek and colleagues

showed that patients with new overt or subclinical hypothyroidism had a significantly reduced hazard ratio for mortality of 0.324 compared with patients without thyroid dysfunction (P = .002).[42]

In a prior study, we found that a minority of patients with metastatic non–small cell lung cancer (NSCLC) treated with ICIs underwent thyroid function monitoring after discontinuation, yet 17% of those monitored developed thyroid dysfunction higher than the approximately 10% reported in other studies.[12,43]

In another study, 8.1% of the patient cohort developed clinically acted upon thyroid dysfunction during ICI therapy, with most patients developing hypothyroidism. While reported rates of ICI-induced thyroid dysfunction vary widely across studies with some showing rates as high as 30%,[44] a meta-analysis showed an incidence rate of 8.6% (with 6.6% of patients developing hypothyroidism and 2% developing hyperthyroidism).[45]

CONCLUSION

Thyroid dysfunction, primarily hypothyroidism, was observed in a small group of cancer patients receiving immune checkpoint inhibitors, with onset varying by drug. No associations were found with patient characteristics, suggesting routine thyroid monitoring is essential during immunotherapy regardless of baseline features..

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