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RESEARCH ARTICLE

Cerić et al: Thyroid irAEs & NSCLC outcomes

Impact of thyroid immune-related adverse events on clinical outcomes in non-small cell lung cancer (NSCLC) patients treated with checkpoint inhibitor therapy: A single center study

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ABSTRACT

Immune checkpoint inhibitors (ICIs) have transformed the treatment landscape for non-small cell lung carcinoma (NSCLC) but are associated with immune-related adverse events (irAEs), including thyroid dysfunction. This study examines the incidence and clinical impact of thyroid dysfunction in NSCLC patients receiving ICIs at the Clinic of Oncology, Clinical Center University of Sarajevo. In this retrospective cohort study of 50 patients with metastatic NSCLC treated with ICIs—either in combination with chemotherapy or as monotherapy for those with Programmed death-ligand 1 (PD-L1) expression ≥ 50%—we collected data on demographics, treatment regimens, thyroid function tests, and survival outcomes. Thyroid dysfunction occurred in 24 patients (48%), with 12 (24%) developing hypothyroidism, 4 (8%) developing hyperthyroidism, and 8 (16%) experiencing a transition from hyperthyroidism to hypothyroidism. The incidence of thyroid dysfunction was significantly higher in patients treated with atezolizumab compared to pembrolizumab (p = 0.04), with 87.5% of affected patients receiving atezolizumab. The median time to onset of thyroid dysfunction was 10 cycles (IQR: 5) for hypothyroidism and 6 cycles (IQR: 19) for hyperthyroidism. Progression-free survival (PFS) was significantly longer in patients who developed thyroid dysfunction, with the median PFS not reached, compared to a median PFS of 14 months (95% CI: 9.68–18.32) in patients without thyroid dysfunction (p = 0.038). No significant associations were found between thyroid dysfunction and patient age or gender. These findings suggest that thyroid dysfunction is a common irAE in patients with metastatic NSCLC receiving ICIs, particularly atezolizumab, and its development may be associated with improved PFS. Regular monitoring of thyroid function is recommended to promptly identify and manage thyroid abnormalities during ICI therapy, potentially improving patient outcomes.

Keywords: Non-small cell lung cancer; NSCLC; immunotherapy, immune checkpoint inhibitors; ICIs; thyroid dysfunction; immune-related adverse events; irAEs; atezolizumab, pembrolizumab; progression-free survival; PFS

INTRODUCTION

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases and remains a leading cause of cancer-related mortality worldwide (1). Despite advances in treatment modalities, the prognosis for patients with metastatic NSCLC remains poor, underscoring the need for more effective therapies (2).

The introduction of immune checkpoint inhibitors (ICIs) has revolutionized the treatment landscape of NSCLC. ICIs, such as pembrolizumab and atezolizumab, function by blocking inhibitory pathways like programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1), thereby enhancing T-cell–mediated anti-tumor responses (3, 4). Clinical trials have demonstrated that ICIs improve survival outcomes in patients with advanced NSCLC, either as monotherapy or in combination with chemotherapy, particularly in those with high PD-L1 expression (5–7).

However, by unleashing the immune system, ICIs can lead to immune-related adverse events (irAEs), which can affect any organ system. Endocrine irAEs are among the most common, with thyroid dysfunction being particularly prevalent (8, 9). Thyroid dysfunction manifests primarily as hypothyroidism or hyperthyroidism and can significantly impact patient quality of life and treatment adherence if not promptly identified and managed (10).

The pathogenesis of ICI-induced thyroid dysfunction is not fully understood. Proposed mechanisms include an immune-mediated destruction of thyroid cells, induction of thyroid autoantibodies, and cross-reactivity between tumor antigens and thyroid tissue (10-12). Genetic predisposition may also play a role, as suggested by associations with human leukocyte antigen (HLA) genotypes (13).

Interestingly, emerging evidence suggests that the development of irAEs, including thyroid dysfunction, may correlate with improved clinical outcomes in patients receiving ICIs (14, 15). This association raises the possibility that thyroid irAEs could serve as a biomarker for treatment efficacy, although findings have been inconsistent and require further investigation.

Despite the clinical significance of thyroid dysfunction during ICI therapy, data on its incidence and impact in patients with NSCLC, particularly in relation to specific ICIs like pembrolizumab and atezolizumab, remain limited. Understanding the incidence, timing, and clinical implications of thyroid irAEs is crucial for optimizing patient management, improving outcomes, and informing monitoring strategies during treatment.

Therefore, this study aims to investigate the incidence and clinical impact of thyroid dysfunction in patients with metastatic NSCLC treated with ICIs at the Clinic of Oncology, Clinical Center University of Sarajevo. By examining the association between thyroid dysfunction and clinical outcomes such as progression-free survival (PFS), this research seeks to enhance the understanding of thyroid irAEs in this patient population and contribute to the development of evidence-based management guidelines.

MATERIALS AND METHODS

Study design and setting

This retrospective cohort study was conducted at the Clinic of Oncology, Clinical Center University of Sarajevo, a tertiary care hospital serving a diverse patient population in Bosnia and Herzegovina. We retrospectively identified all patients initiating ICI therapy at our institution between January 2020 and January 2022. Data collection continued until April 2023, which served as the final analysis cutoff. During this interval, the median follow-up (time from ICI initiation to last contact or censoring) was 10.6 months (IQR: 4.1). Some patients treated early in the study period had substantially longer follow-up times.

Patient selection

The inclusion criteria for this study were as follows: patients had to be at least 18 years of age at the time of therapy initiation, with a histologically or cytologically confirmed diagnosis of metastatic non-small cell lung cancer (NSCLC). They were required to have started first-line immune checkpoint inhibitor (ICI) therapy, either alone or in combination with chemotherapy, and to have available baseline and follow-up thyroid function tests (TFTs). Additionally, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 was necessary for eligibility.

Exclusion criteria included any prior treatment with ICIs or participation in clinical trials involving ICIs. Patients with pre-existing thyroid dysfunction or other major endocrine disorders were not eligible, nor were those with concurrent malignancies or other significant comorbidities that could affect survival. Lastly, individuals with incomplete medical records or those lost to follow-up before the first response evaluation were excluded from the study.

Treatment regimens

Patients received ICIs in accordance with institutional protocols and national guidelines. Treatment options included pembrolizumab, administered as monotherapy for patients with

PD-L1 expression ≥50%, those with <50% PD-L1 received atezolizumab, usually in combination with chemotherapy. In some instances, treating oncologists could opt for atezolizumab monotherapy based on patient comorbidities or treatment intolerance. Atezolizumab was administered at a dose of 1200 mg every 3 weeks, while pembrolizumab was given at a dose of 200 mg every 3 weeks. Chemotherapy regimens, typically platinum-based doublets, were selected according to standard practice.

Data collection

Data were extracted from electronic medical records using a standardized data collection form by trained oncology residents or attending physicians. Accuracy was ensured by cross-referencing this information with laboratory and pharmacy records.

The variables collected encompassed a wide range of patient and treatment details. Demographic data included age, gender, smoking status, and body mass index (BMI). Clinical characteristics covered histological subtype, tumor stage (TNM), PD-L1 expression level, ECOG performance status, comorbidities, and, where available, tumor grade. Treatment details encompassed the type of immune checkpoint inhibitor (ICI), dosing schedules, number of cycles, and any concomitant medications. Thyroid function was monitored by measuring TSH, FT4, and FT3 at baseline and before each treatment cycle. Immune-related adverse events (irAEs) were documented and graded according to CTCAE v5.0. Outcomes included progression-free survival (PFS), overall survival (OS), and tumor response as determined by RECIST v1.1.

Definition, monitoring, and management of thyroid dysfunction

Thyroid dysfunction was diagnosed based on thyroid function tests (TFTs) and clinical evaluation, with hypothyroidism defined as TSH > 4.0 mIU/L accompanied by decreased or normal FT4, and hyperthyroidism (thyrotoxicosis) defined as TSH < 0.4 mIU/L with elevated FT4 and/or FT3. Thyroiditis progression was characterized by an initial presentation of hyperthyroidism followed by the development of hypothyroidism (painless thyroiditis). Patients with transient or subclinical TSH alterations (n = 3, 6%) were monitored closely but not classified as having thyroid dysfunction unless they met these criteria. TFTs were measured at baseline and every six weeks during ICI therapy, with additional testing if clinically indicated.

Management of hypothyroidism involved levothyroxine (starting at 25–50 μg/day), while hyperthyroidism was treated with beta-blockers and, if necessary, antithyroid medications.

All treatment approaches followed the European Thyroid Association (ETA) recommendations (16).

PD-L1 assessment

PD-L1 immunohistochemistry (IHC) was performed using either 22C3 pharmDx (Dako) or Ventana SP142/SP263 assays, following drug-specific requirements. For pembrolizumab, the Tumor Proportion Score (TPS) was determined using 22C3 pharmDx, while atezolizumab required the Ventana (SP142 or SP263) assays according to the manufacturer's instructions. In our analyses, PD-L1 expression was categorized as <1%, 1–49%, or ≥50% based on the TPS or the corresponding Ventana scoring guidelines.

Time-dependent covariate analysis for lead-time bias

To address potential lead-time (immortal time) bias—where patients developing thyroid dysfunction may have inherently longer treatment exposure—we conducted a time-dependent covariate analysis. In this approach, patients were considered in the "no dysfunction" group until the time thyroid dysfunction was first diagnosed.

Outcome measures

Progression-Free Survival (PFS) was defined as the time from the initiation of immune checkpoint inhibitor (ICI) therapy to disease progression (per RECIST 1.1) or death. Overall Survival (OS) was defined as the time from ICI initiation to death from any cause, with censoring at the last follow-up. Radiologic assessments were performed every 12 weeks using computed tomography (CT) scans, and treatment responses were categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD).

Data handling and missing data

Patients with missing or incomplete data were reviewed individually. Multiple imputation methods were used when appropriate, and sensitivity analyses were conducted to assess the robustness of findings. Discrepancies in data were resolved by consensus among independent reviewers.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY), and a two-sided p-value <0.05 was considered statistically significant. Descriptive statistics were used to summarize baseline variables. Group comparisons, such as between patients with and without thyroid dysfunction, employed Student's t-test or the

Mann-Whitney U test for continuous variables, and chi-square or Fisher's exact test for categorical variables. Survival analyses for progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method, with differences between groups assessed by the log-rank test. Multivariate analysis using Cox proportional hazards models was conducted to adjust for potential confounders (e.g., age, gender, ECOG performance status, PD-L1 expression), and Schoenfeld residuals confirmed the proportional hazards assumption. Finally, a time-dependent covariate for thyroid dysfunction was introduced to minimize immortal time bias.

Ethical statement

All procedures were conducted in accordance with the Declaration of Helsinki and institutional guidelines to ensure patient confidentiality and data protection.

RESULTS

Patient characteristics

A total of 50 patients with metastatic NSCLC and an ECOG performance status of 2 or lower met the inclusion criteria. The median follow-up duration was 10.6 months (IQR: 4.1 months), and by the time of data cutoff, 9 patients (18%) had died. Table 1 summarizes the baseline characteristics, which include a median age of 68 years (range: 59–82), with 27 male (54%) and 23 female (46%) patients. The cohort comprised adenocarcinoma and squamous-cell carcinoma histological subtypes, and TNM staging was documented for all patients, demonstrating that most (86%) had stage IV disease at diagnosis. Tumor grade information was available for 22 individuals; among these, 14 were classified as G2 and 8 as G3.

Treatment regimens

Regarding the treatment regimens, 13 patients (26%) received pembrolizumab monotherapy for tumors with PD-L1 expression ≥50%, whereas 37 patients (74%) were treated with atezolizumab, either alone or in combination with chemotherapy. The median number of immune checkpoint inhibitor (ICI) therapy cycles administered was 19.5 (IQR: 19).

Incidence of thyroid dysfunction

Thyroid dysfunction was observed in 24 of the 50 patients (48%), presenting as hypothyroidism (12 patients, 24%), hyperthyroidism (4 patients, 8%), or a hyperthyroid-to-hypothyroid transition consistent with thyroiditis progression (8 patients, 16%). The median time to the onset of hypothyroidism was 10 treatment cycles (IQR: 5), whereas hyperthyroidism typically appeared earlier, at 6 cycles (IQR: 19). Additionally, three patients

(6%) experienced transient or subclinical alterations in TSH, which normalized without pharmacological intervention.

Association with treatment type

Among the 24 patients who developed thyroid dysfunction, 21 (87.5%) were receiving atezolizumab, and 3 (12.5%) were on pembrolizumab. Thyroid dysfunction was significantly more frequent in atezolizumab-treated patients than in pembrolizumab-treated patients ($p = 0.04$).

Association with demographic and clinical factors

No significant association was found between the development of thyroid dysfunction and patient age (68.8 ± 4.5 vs. 66.6 ± 5.7 years; $p = 0.06$) or gender (males: 13/27 vs. females: 11/23; $p = 0.98$). PD-L1 expression as a continuous variable did not differ significantly between groups, but categorically, most patients in both groups had PD-L1 $\geq$1%.

Management of thyroid dysfunction

Among the 24 patients who developed thyroid dysfunction, 16 (66.7%) required pharmacological management. All 12 patients with hypothyroidism received levothyroxine. Among those who experienced transient hyperthyroidism, four were managed with beta-blockers alone, and no antithyroid drugs were necessary. Patients who transitioned from hyperthyroidism to hypothyroidism were monitored closely and initiated on levothyroxine therapy when indicated.

Progression-free survival

At a median follow-up of 10.6 months, the overall cohort had a median PFS of 21 months (95% CI: 11.6–30.4). Patients who developed thyroid dysfunction experienced a significantly longer PFS (median not reached) compared to those without dysfunction (14 months; 95% CI: 9.68–18.32), $p = 0.038$ by log-rank test (Figure 1). This association remained significant in a time-dependent covariate analysis, which accounted for the varying onset of thyroid dysfunction; patients transitioning to thyroid dysfunction continued to show improved PFS compared to those who never developed it.

Despite a median follow-up of 10.6 months (IQR: 4.1) for the entire cohort, the overall Kaplan–Meier–estimated median PFS was 21 months (95% CI: 11.6–30.4). This is not contradictory as time-to-event analyses reflect only the subset of patients who either progressed or had adequate long-term follow-up by the analysis cutoff. Some individuals enrolled early in the study period and remained progression-free for more than two years,

thereby influencing the median PFS estimate. In contrast, patients enrolled late had fewer months of follow-up and were censored if they had not yet progressed.

Overall survival

OS data were immature at the time of this analysis, with the median OS not reached in either group. Further follow-up is required to determine whether the PFS benefit in patients with thyroid dysfunction translates to an OS advantage.

Multivariate analysis

A Cox proportional hazards model adjusted for age, gender, ECOG performance status, PD-L1 expression (categorized), and presence of other irAEs identified PD-L1 expression as the only independent predictor of improved PFS (HR: 0.98, 95% CI: 0.969–0.997, p = 0.02). Neither age nor gender nor the presence of thyroid dysfunction remained independently significant after controlling for PD-L1, although thyroid dysfunction trended toward a favorable hazard ratio.

Subgroup analysis

In the subgroup analysis, among the 37 patients treated with atezolizumab, those who developed thyroid dysfunction exhibited a significantly longer median progression-free survival (PFS) (not reached vs. 13 months; p = 0.006). By contrast, in the pembrolizumab cohort, only 3 of the 13 patients experienced thyroid dysfunction, thereby limiting the statistical power for a robust comparison.

Safety and tolerability

Overall, ICI therapy was well tolerated. Grade ≥3 adverse events occurred in 3 patients (6%) but were not thyroid-related. No patients discontinued ICI therapy due to thyroid dysfunction.

DISCUSSION

In this retrospective cohort study, we examined the incidence and clinical impact of thyroid dysfunction among patients with metastatic NSCLC receiving ICI therapy at our institution. Thyroid dysfunction occurred in nearly half of the patients (48%), consistent with higher-end estimates reported in the literature (11, 17). Notably, the majority of patients who experienced thyroid dysfunction were on atezolizumab, suggesting that PD-L1 blockade may pose a higher risk of thyroid irAEs than PD-1 blockade, as has been observed elsewhere (11, 26).

An important finding was the association between thyroid dysfunction and prolonged PFS, a relationship that has been proposed in prior studies (14, 15, 25). While the exact biological

mechanisms remain uncertain, it is hypothesized that the same augmented immune response contributing to thyroid autoimmunity may also enhance anti-tumor efficacy (20, 21). Our time-dependent covariate analysis further supported this association by reducing lead-time bias, indicating that the timing of thyroid dysfunction during therapy remains relevant to patient outcomes. It is important to note that although the median PFS is 21 months, the estimate is based on the subset of patients who had sufficient follow-up (primarily early enrollees). Ongoing follow-up will better refine this estimate, and our current 95% CI of 11.6–30.4 months reflects the limited number of events at later time points.

We did not observe a direct link between the severity of thyroid dysfunction (as judged by TSH, FT4, or FT3 levels) and clinical benefit—only the occurrence of dysfunction itself appeared to matter. This observation aligns with reports that even subclinical or mild thyroid abnormalities can reflect broader immune activation (18). No significant relationship was found with age or gender, suggesting that all patients on ICIs, regardless of demographic factors, require vigilant thyroid monitoring.

Only ~30% of patients with advanced cancer derive benefit from immune checkpoint inhibitor therapy (22), highlighting the need for improved predictive biomarkers to guide treatment. Tumor PD-L1 expression determined by IHC is currently the most widely used criterion for selecting patients, but it has limited predictive power on its own (22). Accordingly, emerging evidence indicates that baseline and dynamic changes in systemic inflammatory and nutritional indices—such as the HALP (hemoglobin, albumin, lymphocyte, and platelet) score, as well as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR)—correlate with immunotherapy efficacy and can effectively predict outcomes in advanced NSCLC (23). In particular, patients with low HALP combined with high NLR/PLR have significantly poorer prognoses, suggesting that these readily available markers could serve as valuable tools for patient stratification in the immunotherapy setting (23).

Our study has several limitations. The retrospective, single-center design limits generalizability and introduces potential selection bias. The sample size, although reflective of our institution’s experience, is relatively small, particularly for subgroup analyses. We also lacked comprehensive data on thyroid autoantibodies, which could yield mechanistic insights into ICI-induced thyroiditis (19). Additionally, OS data remain immature, and extended follow-up is needed to confirm whether PFS advantages translate into a survival benefit.

Future research should focus on prospective, multicenter trials with larger cohorts, incorporating routine measurements of thyroid autoantibodies and other immunological markers (e.g., cytokine profiles). Studies investigating the impact of early detection and management of thyroid irAEs on clinical outcomes would also be beneficial. Moreover, refining PD-L1 assessment—potentially in combination with other biomarkers—could help identify patients at higher risk of thyroid irAEs and perhaps better responders to ICI therapy (27).

Clinically, our findings underscore the necessity of regular thyroid function testing in patients receiving ICIs, especially with atezolizumab. Prompt identification and treatment of thyroid dysfunction are crucial for maintaining quality of life and preventing therapy interruptions. The potential role of thyroid dysfunction as a biomarker for ICI response, although not yet definitive, is an area of active interest and warrants further investigation.

CONCLUSION

Thyroid dysfunction is a common immune-related adverse event in patients with metastatic NSCLC receiving ICIs—particularly atezolizumab—and may correlate with improved PFS. These observations highlight the importance of systematic thyroid monitoring in this population and raise the possibility that thyroid dysfunction could serve as a surrogate marker of enhanced immunotherapy efficacy. Further prospective research is needed to clarify the underlying mechanisms and confirm the potential prognostic value of this endocrine irAE.

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TABLES AND FIGURES WITH LEGENDS

Table 1. Baseline characteristics of patients

Characteristic	Total (n = 50)	With Thyroid Dysfunction (n = 24)	Without Thyroid Dysfunction (n = 26)	p-value
Age (years), median (range)	68 (59–82)	70 (59–76)	64.5 (60–82)	0.06
Gender, n (%)				0.98
Male	27 (54%)	13 (54.2%)	14 (53.8%)	—
Female	23 (46%)	11 (45.8%)	12 (46.2%)	—
ECOG Performance Status, n (%)				0.74
0	32 (64%)	16 (66.7%)	16 (61.5%)	—
1	14 (28%)	7 (29.2%)	7 (26.9%)	—
2	4 (8%)	1 (4.2%)	3 (11.5%)	—
TNM Stage, n (%)*				—
IIIB/IIIC	7 (14%)	4 (16.7%)	3 (11.5%)	—
IV	43 (86%)	20 (83.3%)	23 (88.5%)	—
Tumor Grade (subset n = 22)**				—

G2	14 (64%)^	9 (75.0%)†	5 (50.0%)‡	—
G3	8 (36%)^	3 (25.0%)†	5 (50.0%)‡	—
PD-L1 Expression, n (%)				0.19
< 1%	11 (22%)	4 (16.7%)	7 (26.9%)	—
1–49%	16 (32%)	7 (29.2%)	9 (34.6%)	—
≥ 50%	23 (46%)	13 (54.2%)	10 (38.5%)	—
***Most patients presented with advanced disease (stage IV).**				
****Tumor grade data were available for 22 patients only.*				
^ Percentage of the 22 total patients with known grade (G2 = 14/22, G3 = 8/22).				
† Percentage of the 12 patients (within the 24 "With Dysfunction") who had known grade.				
‡ Percentage of the 10 patients (within the 26 "Without Dysfunction") who had known grade.				

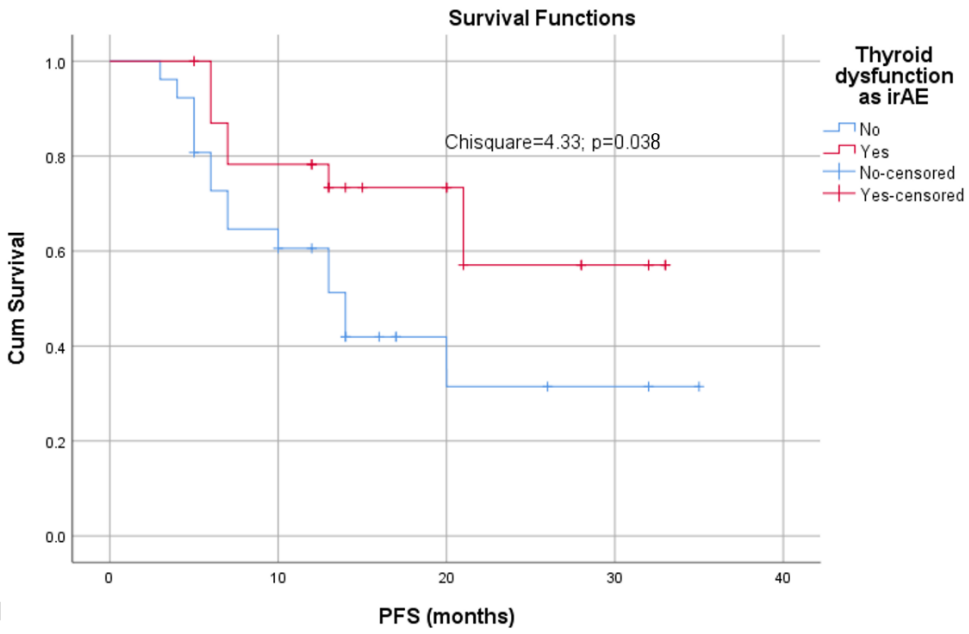

Figure 1. Kaplan-Meier curve for progression-free survival. The red line represents patients with thyroid dysfunction; the blue line represents those without thyroid dysfunction. A statistically significant difference in PFS is observed ($p = 0.038$, log-rank test), with patients who develop thyroid dysfunction showing improved outcomes.