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Impact of Thyroid Hormone Receptor alpha Expression and PD-L1 on Progression-Free Survival of NSCLC Patients Treated with Pembrolizumab Immunotherapy

Abdulameer Kareem. Leelo Al-Obaidy[*1], Hawraa A. Kareem[2], Yusra Jabbar Hasan[3]

[*1]Al-Qadisiyah University, Nursing College, Iraq.

[2]Iraqi Board of Medical Oncology, Senior of Oncology in Al-Jawad oncology center, Baghdad Iraq.

[3]Egyptian Board of Medical Oncology, Senior of oncology in Al-Jawad oncology center Baghdad Iraq.

***Corresponding Author:**

Email ID: Abdulameer.leelo@qu.edu.iq

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ABSTRACT

Lung cancer is categorized into small cell lung cancer and non-small cell lung cancer (NSCLC) based on histological distinctions. Pembrolizumab, an anti-programmed death-1 (PD-1) monoclonal antibody, is utilized for patients with NSCLC who exhibit modulation of the programmed death ligand (PD-L1) molecule. This study prospectively examined different patterns of Thyroid Hormone Receptor (THR) and PD-L1 immunohistochemical expression and their impact on the effectiveness of immunotherapy in improving progression-free survival (PFS) in 93 NSCLC patients. Variations were assessed according to histopathological subtype, TNM staging, tumor grade, Eastern Cooperative Oncology Group (ECOG) performance status, and other factors that may influence disease progression or treatment outcomes.

The mean age of patients was 59.97 years, comprising 26 females and 67 males. Among the 93 patients, 55 exhibited low PD-L1 expression (≤10%), while 38 patients exhibited high PD-L1 expression (>10%). THRα expression was observed at variable ratios, and the mean PFS was 48.9 weeks. A significant correlation was found between PD-L1 and THRα regarding PFS, with the highest PFS observed in patients exhibiting THRα expression levels between 26% and 50%, and the lowest PFS duration seen in patients with 76% to 100% THRα expression. The impact of PD-L1 expression on PFS duration increased with elevated levels of PD-L1 expression.

These findings demonstrate that THRα and PD-L1 expression are more prevalent in NSCLC patients, correlating with higher tumor grades, increased metastasis, and reduced ECOG performance status. The study found that the PFS of PD-L1-positive NSCLC patients treated with pembrolizumab was significantly better in those with 26% to 50% THR expression.

Keywords: *Immunohistochemistry, PD-L1, THRα, NSCLC, Immunotherapy*

1. INTRODUCTION

Lung cancer is a highly heterogeneous disease in terms of histopathology, response to treatment, and prognosis. Lung cancer is classified into small cell lung cancer and non-small cell lung cancer based on histological differences. Non-small cell lung cancer accounts for approximately 85% of all lung carcinomas and includes three major histopathological types. Adenocarcinoma, squamous cell carcinoma, and other types include large cell cancer shows large cells (1, 2 and 3). The development of immune checkpoint inhibitors has become the most successful strategy in the treatment of advanced NSCLC patients. Pembrolizumab and other anti-programmed death-1 (PD-1) monoclonal antibody, is widely used for patients who modulate the PD-L1 molecule. Although promising with remarkable therapeutic effects, some patients might experience nonresponse after PD-1 blockade. (4, 5 and 6)

Tri-iodothyronine (T3) and its inactive pro-hormone thyroxine (T4) govern the biological effects of thyroid hormones in normal lung cells. These hormones interact with their corresponding nuclear receptor proteins, known as thyroid hormone receptors (THRs). THR occurrence and function are significant factors in cancer biology. Thus, the expression and function

of THR, especially the expression of THRs, may serve as potential indicators of clinical outcomes in lung cancer patients (7). Different THR expression patterns in relapse-free lung cancer patients vary according to histopathological subtype, TNM staging, tumor grade, ECOG performance status, and other factors that may influence disease progression or treatment models. We analyzed the progression-free survival of patients who received adjuvant immunotherapy for NSCLC (8 and 9).

The thyroid hormone receptors (THRs) were known to regulate a plethora of physiological functions by acting as ligand-dependent transcription factors. Through the recruitment of multiple coregulatory, THRs can modulate gene expression, impacting different cellular processes such as proliferation, differentiation, and apoptosis in a tissue-specific manner (10, 11, and 12). THR protein has two isoforms, TRα and TRβ, that are encoded by two distinct genes and share similar functions but also exert specific actions when expressed in tissues that do not co-express the alternative isoform. Ligand-bound TRα/β activates gene transcription after dimerization with the retinoid X receptor, binds to response elements in the promoter of target genes, and, depending on the recruited coregulators, can either directly repress or activate their expression. (13 and 14)

2. PATIENTS AND METHODS

2.1. Study Design

A prospective cohort research was performed at Al-Emamain Al-Kadimain Medical City, Al-Jawad Oncology Centre in Baghdad. Independent Variables: Expression of thyroid hormone receptors (THRα1) and PD-L1 (evaluated using immunohistochemistry). Dependent Variable: Progression-Free Survival (duration from the commencement of therapy to disease progression or mortality). The research was organized as an observational cohort with a cross-sectional study design. This prospective clinicopathological study examined patients with advanced non-small cell lung cancer, aiming to assess the impact of PD-L1 and THR expression on the effectiveness of immunotherapy in improving progression-free survival (PFS). Fundamental patient demographics and clinical attributes (age, sex, smoking history, cancer TNM stage, histological tumors type, Eastern Cooperative Oncology Group (ECOG) performance status of patients and tumor grade also detected. Randomized sampling was methodically performed on patients who sought consultation at the Al-Jawad Oncology Centre from June 2022 to September 1, 2024.

2.2. Ethical considerations

were rigorously followed in all research protocols to ensure compliance and integrity. The treatment schedule proceeded unaffected by the study's influence on the physicians' decisions only; this study primarily relied on tissue samples obtained for lung cancer diagnosis by the oncologist and/or surgeon. Paraffin-embedded tissue samples were sourced from the histopathological laboratory archives to assess PD-L1 and THRα expression after patient diagnosis and staging. The treatment course determined by the oncology committee was established without consideration of the studies pertaining to the treatment course. Patients received adjuvant treatment for NSCLC as determined by the oncologists at the Al-Jawad Oncology Centre, and any necessary assessment of PD-L1 expression was conducted independently of this research. The cost of the PD-L1 and THRα immunohistochemistry test was determined by the study and was derived from the study expenses, with no relation to the patients. Ethical approval was obtained from the Al-Jawad Oncology Centre and other private hospitals where the histopathological diagnosis was conducted. The study was carried out according to the Helsinki Declaration and good clinical practice principles, having been approved by the Institutional Review Board and Ethical Committee of Al-Jawad Oncology Center. All patients signed an informed consent before the treatment enrollment.

2.3. Patient Selection Criteria

We prospectively included data of 93 patients diagnosed with advanced or metastatic NSCLC who were eligible for treatment with immunotherapy in the first, second, or third line and who underwent NSCLC specified histology biopsy and informed consent for immunohistochemical analysis (15, 16). They diagnosed and reviewed histological NSCLC the viable tumor had to be available for molecular analysis. Histological confirmation of NSCLC was mandatory. All patients were staged according to the eighth edition of the American Joint Committee (AJCC). The cancer staging approach utilizes the TNM classification, whereby oncology specialists choose patients in Stage III and IV only for immunological treatment with Pembrolizumab. The tissue slides were categorized based on tumor differentiation. Grading system G1: Well-differentiated (low-grade), G2: Moderately differentiated (intermediate-grade), G3: Poorly differentiated (high-grade) (17 and 18). The ECOG performance status comprises a Six-point scale that evaluates a patient's functional capacity and daily activity performance, thereby assessing their health and prognosis, especially in the context of cancer treatment. Patients with scores ranging from 0 to 2 were included, whilst those with higher scores were eliminated at the discretion of the Oncology team. The individuals were diagnosed with advanced NSCLC and received treatment from certified oncology experts with PD-1 inhibitors, followed by assessment by CT scans (19).

Patients were ineligible for the study if they had other malignancies, had undergone an organ transplant, or were enrolled in another clinical study. Patients who had been treated with radiotherapy, chemotherapy, immunotherapy, or anti-angiogenic therapy in the previous three months were not included in this research. Patients with mixed histological tumors, with any

type of alterations activating mutations were excluded from the study to avoid dilution of survival results based on the inclusion of potential responses already known to approved first and second-line regimens. We also excluded patients with another composite malignancy within the last 5 years, untreated brain metastasis, symptomatic or not, active autoimmune disease. Lung cancer is a highly heterogeneous disease in terms of histopathology so classified into small cell lung cancer and non-small cell lung cancer based on histological differences. Non-small cell lung cancer accounts clustered into three major histopathological types, Adenocarcinoma, squamous cell carcinoma and others types which included (keratinization and/or intercellular bridges, large cell cancer) (20 , 21). The effects on disease outcome and therapy depend on the cellular origin and molecular alterations of each histopathological subgroup. Therefore, it is important to identify the characteristics of each histopathological type (22).

2.4. Data Collection

Tumor tissue was acquired in paraffin-embedded tissue blocks utilized for this study were sourced from teaching laboratories in Al-Emamain Al-Kadimain Medical City or private laboratories, previously obtained from the patients for histological diagnosis, and are unrelated to the treatment methods or decisions made by oncologists at Al-Jawad Oncology Centre, which is anticipated to serve as predictors of therapeutic response in patients suffering from advanced stage NSCLC undergoing immune checkpoint inhibitors (ICIs) therapy. The whole tissue specimens, which could be either biopsy samples or surgical resection of cuboid measure tissues, were considered to the histopathology laboratory for processing, where IHC staining was performed to assess PD-L1 levels (22). The PD-L1 (E1L3N) antibody kit (IHC), primary antibody clone E1L3N from MEDx Translation Medicine, kit No. EU008A01, is utilized for the detection of Programmed Death-Ligand 1 (PD-L1) in tissue samples. Also THRA (thyroid hormone receptor alpha) ready-to-use reagent kit, catalogue number: KHC1523, for immunohistochemistry from Chromo Tek GmbH and Proteintech Germany. Immunohistochemical staining for the diagnosis of thyroid hormone receptor expression and PD-L1 expression was performed according to the manufacturers' instructions. Preparation was employed for the identification of thyroid hormone receptors alpha in tissue slices (4-5 µm thick) derived from paraffin-embedded blocks, affix the sections to positively charged glass slides, perform deparaffinization and rehydration, conduct antigen retrieval, incubate sections with a blocking buffer, apply primary antibody PD-L1 diluted per the manufacturer's instructions, and incubate for 1-2 hours at room temperature or overnight at 4°C. Rinse sections in PBS for three intervals of five minutes to eliminate unbound primary antibody, apply a biotinylated secondary antibody detection system, proceed according to the manufacturer's instructions, counterstain sections with haematoxylin for one to two minutes, and mount. Observable staining in the cell membranes signified PD-L1 expression. Assessed the PD-L1 expression levels in tumor cells utilizing a digital imaging microscope for each tumor section, and calculated the mean of all data (23, 24 and 25). PD-L1 expression was assessed utilizing scoring methodologies, namely the Combined Positive Score (CPS), which measures PD-L1 expression on tumor cells as well as inflammatory cells, including lymphocytes and macrophages, inside the tumor microenvironment. The CPS is determined by dividing the quantity of PD-L1-positive cells, encompassing both tumor and immune cells, by the total number of viable tumor cells, and subsequently multiplying by 100. A CPS of 1-10 % (Group 1) often suggests a possible therapeutic benefit, whereas a CPS of 10% or greater (Group 2) is occasionally regarded as a benchmark for more conclusive therapy results (26). The initial assessment involved examining haematoxylin and eosin stained slides to determine staining quality and tissue preservation. The control tissue was subsequently analyzed. Tonsil of human PD-L1 membrane staining in the crypt epithelium and macrophages within the lymphoid follicles, served as positive control tissue. Negative control slides without addition of primary PD-L1 antibody. Slides were evaluated for PD-L1 expression, excluding necrotic or degraded tumor cells. Each slide included a minimum of 100 live tumor cells appropriate for assessment. PD-L1 expression was evaluated (27 and 28).

To describe the effect of PD-L1 expression on the potential response to immunotherapy, we collected clinical data on therapeutic outcomes, including progression free survival (PFS). Patients who accepted immunotherapy with definite treatment responses were included in this study. Patient baseline characteristics were obtained by chart review or by communicating with their primary oncology physicians. We collected relevant medical records at least every 3 to 6 months (29, 30). The effects of immunotherapy on progression-free survival (PFS) were analyzed as the dependent variable, with independent variables comprising elevated PD-L1 and THR expression, alongside other covariates, using several survival tests. Ratio of Positive Staining the proportion of tumor cells displaying positive staining for TRH alpha expression was assessed, categories include: 0%: Absence of positive cells, 1% to 10%, 11% to 25% (group 1), 26% to 50% (Group 2), 51% to 75% (Group 3), and 76% to 100% (Group 4). We employed the Kaplan-Meier technique , Cox Regression and the log-rank test for progression-free survival analysis (31, 32, 33).

2.5. Statistical Analysis

The clinical data of ninety-three suitable patients is continually analyzed to delineate statistical trends. The statistical method employed to assess the impact of PD-L1 and THR expression in lung cancer on progression-free survival (PFS) is the Kaplan-Meier survival analysis, supplemented by the log-rank test for the comparison of survival curves across distinct groups like patients exhibiting high PD-L1 expression versus those with low or absent PD-L1 expression. Cox proportional hazards regression models were employed to evaluate the influence of PD-L1 or THRα expression on progression-free survival in separate manner or both together, while adjusting for other variables. Continuous variable data are shown as means with

interquartile ranges. Hazard ratios and odds ratios are calculated using univariable and multivariate analyses. Cox and logistic regression analyses employed Omnibus Tests of Model Coefficients to evaluate the time-dependent effects of parameters associated with progression-free survival and immunotherapy response rate, as determined by Kaplan-Meier survival analysis, Cox Regression, Log Rank (Mantel-Cox), Breslow (Generalised Wilcoxon), and Tarone-Ware tests. The cutoff value for progression-free survival was identified through Receiver Operating Characteristic (ROC) curve analysis for analytical purposes (34, 35, 36, and 37).

3. RESULTS

A prospective research was conducted to assess the prognostic significance of thyroid hormone receptor expression in relation to checkpoint inhibitor therapy in non-small cell lung cancer (NSCLC) patients receiving immunotherapy with pembrolizumab, which targets programmed cell death protein 1. The overall response rate among the 93 patients diagnosed with advanced or metastatic NSCLC (Table 1), eligible for immunotherapy in the first, second, or third line of treatment, undergoing immune therapy. To evaluate the relationship between PD-L1 expression levels, progression-free survival (PFS), staging and other variables in patients with non-small cell lung cancer (NSCLC). The mean age of patients was $\bar{x} = 59.97$ years, with a minimum age of 36 years and a maximum age of 80 years. Seventy-eight patients (83.9%) have a history of smoking, whereas fifteen patients (16.1%) do not. Based on the sex distributions, there are 26 female patients (28%) and 67 male patients (72%).

The judgements about the patient's Eastern Cooperative Oncology Group (ECOG) Performance Status, histological tumor classification, progression-free survival durations, suitability for immunotherapy, staging, and grading were determined by the surgeons, histopathologists, and oncologists. All patients are classified as stage three: 51 patients (54.8%) and stage four: 42 patients (45.2%), based on TNM staging. In terms of histological tumour grading, 24 patients (25.8%) were classified as well-differentiated, 41 patients (44.1%) as moderately differentiated, and 28 patients (30.1%) as poorly differentiated. Histopathological analysis of tumour tissue revealed that 57 patients (61.3%) had adenocarcinoma, 27 patients (29%) had squamous cell carcinoma, and 9 patients (9.7%) had other kinds. As per the Eastern Cooperative Oncology Group (ECOG) Performance Status scale, 43 patients (46.2%) achieved a score of zero, 39 patients (41.9%) received a score of one, and 11 patients (11.8%) were assigned a score of two, while patients with higher scores (3-5) are excluded from immunotherapy based on the oncologist's assessment.

Regarding the Combined Positive Score (CPS) for PD-L1 expression, 55 patients (59.1%) (group 1) exhibited a CPS of 1-10%, while 38 patients (40.9%) (group 2) demonstrated a CPS over 10%. No patients had absent PD-L1 expression. The assessment of thyroid hormone receptor expression (Figure 1) involved evaluating the ratio of positive staining, specifically the fraction of tumour cells exhibiting positive staining for TRH alpha expression, categorized as follows: 0%: No positive cells; 1% to 10% No individuals were identified in this group. Among 19 patients, 11% to 25% (group 1) expression ratio was seen (20.4%). A total of 23 patients exhibited a 26% to 50% (group 2) expression ratio, representing 24.7%. Additionally, 32 patients (34.4%) had a 51% to 75% (group 3) expression ratio, while 19 patients (20.4%) had a 76% to 100% (group 4) expression ratio. The average progression-free survival duration for patients was $\bar{x} = 48.9$ weeks, with a standard deviation of 14.2 weeks. The shortest PFS was 23 weeks, while the highest was 86 weeks (Table 1).

Table 1: Depicted the frequency of several research factors in patients with NSCLC .

Variables		Number Of Patients	Percentage
Sex	Female	26	28 %
	Male	67	72 %
Smoking	Smoker	78	83.9 %
	Non Smoker	15	16.1 %
Grading	Well-differentiated	24	25.8 %
	Moderately differentiated	41	44.1 %
	Poorly differentiated	28	30.1 %
TNM Staging	Stage III	51	54.8 %
	Stage IV	42	45.2 %

Histopathological Types	Adenocarcinoma	57	61.3 %
	Squamous cell carcinoma	27	29.0 %
	Others types	9	9.7 %
ECOG performance status	Score 0	43	46.2
	Score 1	39	41.9
	Score 2	11	11.8
Thyroid Hormone Receptor alpha Expression	0 %-10 %	0	0%
	11% to 25% (group1)	19	20.4 %
	26% to 50% (group 2)	23	24.7 %
	51% to 75% (group 3)	32	34.4 %
	76% to 100% (group 4)	19	20.4 %
Programmed Death Ligand 1 Expression by CPS using method	1 to 10 %	55	59.1 %
	10 or above %	38	40.9 %
Patients Progression Free Survival in Weeks	Mean	$\bar{x}$ = 48.9032	
	Median	48.0000	
	Std. Deviation	14.20354	
	Minimum	23.00	
	Maximum	86.00	
Patients Age in Years	Mean	$\bar{x}$ = 59.9677	
	Median	63.0000	
	Std. Deviation	11.34676	
	Minimum	36.00	
	Maximum	80.00	

The Kaplan-Meier survival analysis, Cox regression, and log-rank test were employed for statistical analysis to compare survival curves among many groups. Receiver Operating Characteristic (ROC) curve analysis is utilized to statistically assess the 40-week progression-free survival (PFS) period, which is considered the cutoff value for assessment. The impact of PD-L1 and THRα expression on progression-free survival (PFS) in lung cancer patients, differentiating between high and low levels of PD-L1 or THRα expression. Cox proportional hazards regression models were employed to evaluate the influence of PD-L1 or THRα expression on progression-free survival and other variables, individually or in combination, while adjusting for other covariates.

Regarding the correlation between PD-L1 and THRα as independent variables (Figures 1, 2, and 3), with progression-free survival (PFS) as the dependent variable, a significant association is evident in THRα expression across all NSCLC patient cohorts, particularly in group 2, where an extended PFS duration is noted in comparison to the other THRα groups (1, 3, and 4). The shortest progression-free survival duration was seen in NSCLC patients from group four, followed by groups three and one. The influence of PD-L1 expression on the progression-free survival (PFS) duration escalated with higher levels of PD-L1 expression (Table 2).

Figure 1: The effect of PD-L1 expression levels in NSCLC patients categorized into low and high expression groups on progression-free survival (PFS) durations, measured in weeks, concerning the survival function at the mean of covariates, utilizing 40 weeks as the threshold value.

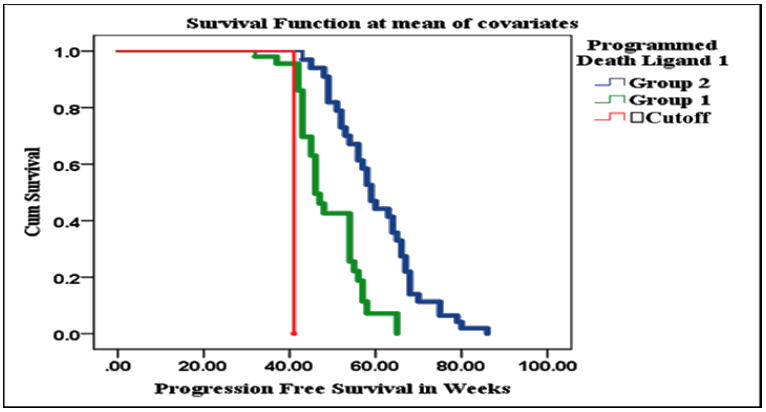


Figure 2: The influence of the four THRα group expressions on progression-free survival (PFS), measured in weeks, in NSCLC patients exhibiting low PD-L1 expression, with a threshold established at 40 weeks.

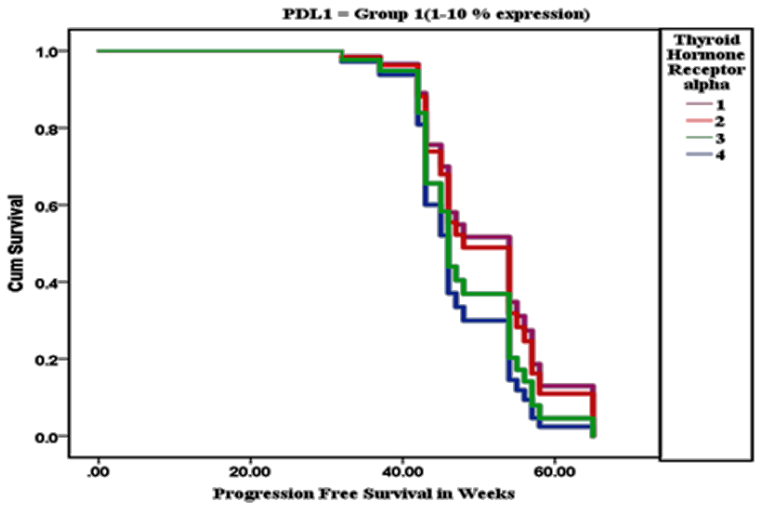


Figure 3: The impact of the four THRα group expressions on progression-free survival (PFS), quantified in weeks, in NSCLC patients with elevated PD-L1 expression, with a threshold set at 40 weeks.

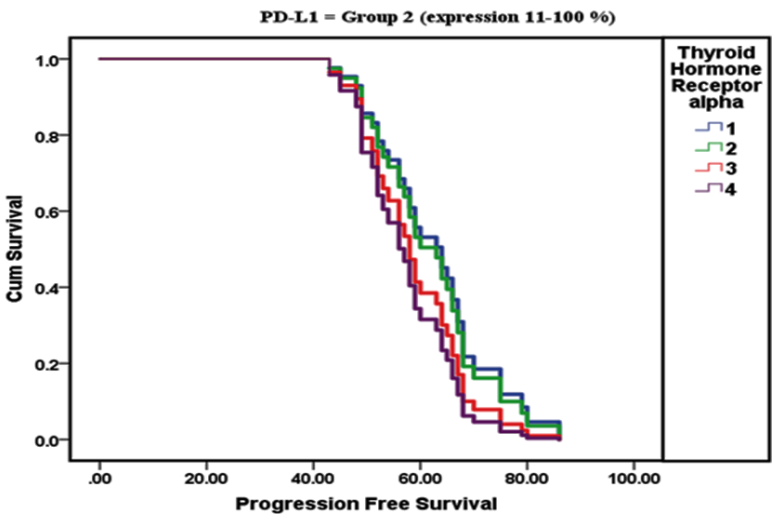
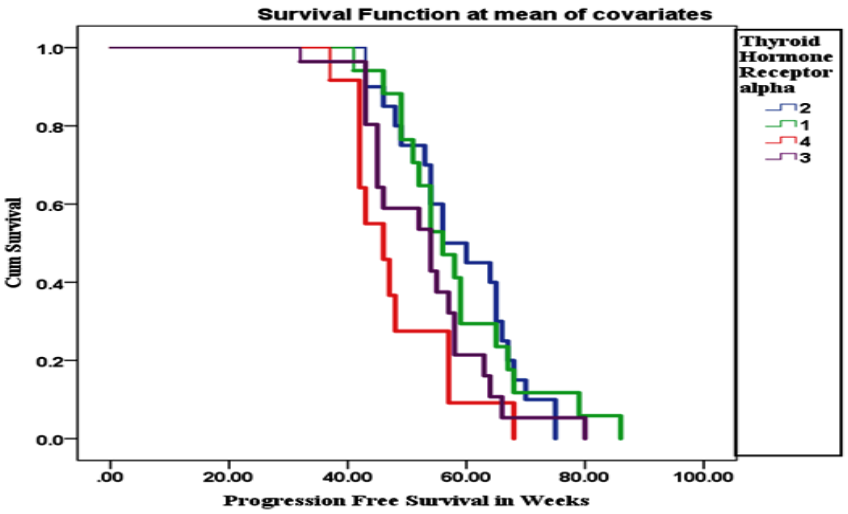


Figure 4: The influence of THRα on the duration of progression-free survival (PFS) in NSCLC patients, quantified in weeks, is assessed by the survival function at the mean of variables, and established by a threshold of 40 weeks.



A notable disparity was observed in NSCLC patient progression-free survival (PFS) durations relative to TNM staging, with a P value below 0.005. Stage III patients demonstrated superior PFS compared to those in stage IV. Additionally, well-differentiated cancer patients exhibited better PFS than those with moderate and poorly differentiated cancers, and moderate differentiated patients outperformed those with poor differentiation (Table 2).

The ECOG Performance Status significantly influences progression-free survival (PFS) in NSCLC patients, with higher PFS observed in those with lower scores, which diminishes as the ECOG Performance Status increases (table 2).

In patients with NSCLC, the longest progression-free survival (PFS) duration is observed in those with adenocarcinoma, followed by squamous cell carcinoma, whereas the shortest PFS period is noted in individuals with other NSCLC subtypes. Concerning the sex differences and smoking status of the patients, there is no significant variation in the progression-free survival (PFS) periods among NSCLC patients; nonetheless, PFS decreases with advancing age of the NSCLC patients. (Table 2)**.**

Variables concerning Progression Free Survivals Duration in Weeks	Kaplan –Meier Survival Test						Mean 95% Confidence Interval	
	Log Rank (Mantel-Cox) Test		Breslow (Generalized Wilcoxon) Test		Tarone-Ware Test			
	Sig.	Chi-Square	Sig.	Chi-Square	Sig.	Chi-Square	Lower Bound	Upper Bound
Programmed Death Ligand 1	.000	47.531	.000	40.319	.000	44.209	52.714	57.990
PD-L 1(Group 1)							46.362	51.673
PD-L 1(Group 2)							57.707	64.460
Thyroid Hormone Receptor alpha	.038	8.450	.009	11.689	.014	10.670	52.714	57.990
THRα(Group 1)							52.876	63.948
THRα (Group 2)							54.432	63.268
THRα (Group 3)							48.430	57.892
THRα (Group 4)							42.859	53.508

ECOG Performance Status Scale	.000	22.190	.000	21.659	.000	22.467	52.714	57.990
ECOG Scale(0)							55.283	62.242
ECOG Scale(1)							43.607	50.278
ECOG Scale(2)							50.565	60.324
TNM Staging	.000	57.553	.000	59.745	.000	60.395	52.714	57.990
Stage III							57.717	62.979
Stage IV							42.193	46.743
Grading	.000	32.012	.000	24.160	.000	28.327	52.714	57.990
Well-differentiated							58.957	68.932
Moderately differentiated							50.184	55.331
Poorly differentiated							42.965	50.296
Histopathological Type	.004	11.119	.013	8.678	.008	9.729	52.714	57.990
Adenocarcinoma							53.552	61.115
Squamous Cell Carcinoma							50.498	57.936
Other Types							40.790	51.210
Smoking	.025	5.036	.111	2.542	.055	3.67	52.714	57.990
Smoker							51.664	56.769
Non Smoker							52.545	72.566
Gender	.334	.933	.094	2.812	.143	2.15	52.714	57.990
Female							54.162	63.394
Male							50.950	57.229
Patients Age	Pearson Chi-Square Test			Asymptotic Significance (2-sided) = 0.001			Chi-Square = 1293.364[a]	

4. DISCUSSION

Thyroid hormone receptors (THRs) are implicated in carcinogenesis, and their expression has not been thoroughly examined across several histological subtypes of NSCLC. Our findings indicate that THRα and PD-L1 are expressed more often in NSCLC patients, correlating with higher tumor grades, increased metastasis, and diminished ECOG performance status, as demonstrated in other study (38, 3, and 17,). The research identified distinct variations in THRα expression patterns across the histopathological subtypes of NSCLC. Histopathological subtypes have been reported to exhibit high levels of THRα in squamous cell carcinoma and other types, whereas moderate expression is observed in adenocarcinoma. THRs regulate cell proliferation, apoptosis, and survival of carcinoma NSCLC cells in a manner dependent on histopathological context. THR-based biomarkers inform clinical applications and research regarding the advancement of radioligand therapy strategies (39 ,40 and 41).

The PD-1/PD-L1 pathway is important in the escape of the immune system by tumors. Monoclonal antibodies that block the PD-1/PD-L1 pathway neutralize the effect on T cells of PD-1 expressing Regulatory T cells. Such treatments have been approved as second- and third-line monotherapies in NSCLC and are advancing testing as first-line treatments, mostly in combination with chemotherapy. Although these treatments have long-lasting disease control and are well-tolerated with low systemic toxicity in a small number of NSCLC patients, the majority of NSCLC patients—approximately 70–80%—will suffer from disease progression within 12 months after immunotherapy administration and this go with the finding of this

study. (10, 30, 42, 43 and 44) The clinical value of using PD-L1 expression on tumor cells as a biomarker for such immunotherapy is justified because it has a good sensitivity to detect responders, but it has a low specificity compared with durable clinical benefit, which led some researchers to consider other predictive biomarkers. However, the present work establishes a novel insight into thyroid hormone receptor PD-L1 co-action in NSCLC, where the expression levels of both receptors were associated with progression-free survival (45, 46, 47 and 48). This study found that the percentage of patients deriving therapeutic benefit from Pembrolizumab rose with higher PD-L1 expression on tumor cells. An ongoing analysis examines a subgroup of patients based on TNM staging, grading, histopathological subtypes of NSCLC, and ECOG performance status, assessing their impact on progression-free survival periods in relation to THRα and PD-L1 expression among patients who received PD-1 immune therapy followed by conventional anti-cancer treatments within a valid intention-to-treat population (49, 50, and 51) Because the prevalence of resistance mutations and oncogenic driver mutations in the entire NSCLC patient cohort is representative of the high prevalence reported in NSCLC, we believe the results of our ongoing study will be applicable to and have relevance for the whole patient population with non-small cell lung cancer. Furthermore, analysis of response has been performed according to the most recent publication(52, 53, and 54). Our study examined the THRα expression profile in tumors of patients receiving immunotherapy and found that moderate THRα expression (26% to 50%) in resected tumor cells was significantly associated with favorable post-immunotherapy clinical outcomes in NSCLC patients, while both elevated and low expression correlated with reduced progression-free survival (PFS). To improve the prediction of THRα's influence on immunotherapy in NSCLC, it is essential to evaluate THRβ expression as well. Alternative studies indicate that the expression of the THR gene correlates with non-small cell lung cancer susceptibility to tyrosine kinase inhibitors via the KRAS-AMPK-TSC2 signaling axis and 3 beta-hydroxysteroid-Delta24 reductase. This discovery indicated that the expression of THR genes may serve functions beyond those associated with the endocrinological characteristics of thyroid hormones. (55 and 56). This result requires further examination of the relationship between PD-L1 expression on tumor cells, evaluated by TPS, and THRα expression in surgically excised tumor tissues, as well as the survival outcomes of patients receiving immunotherapy. Accumulating evidence has pointed to the immune suppressive role of PD-L1 in cancer progression. When PD-L1 binds to a PD-1 receptor, it causes inactivation of the immune system, leading to cancer growth. The use of monoclonal antibodies for PD-1 or PD-L1 is a breakthrough in the development of the immunotherapy strategy in cancer patients. However, variable percentage of cancer patients showed good responses to monoclonal antibodies, and the mechanism underlying the disparate clinical responses has yet to be addressed. In line with the multiple physiological roles of thyroid hormone in the immune system, researcher discovered that the synergistic effects of THRα and the expression of PD-L1 may be involved in the progression of cancer cells (57 , 58 , 59 and 60).

Immunotherapy response rates in PD-L1 high expression vs. low expression patients included studies, there were varied response rates observed depending on the PD-L1 expression level. In patients treated with nivolumab, response rates ranged from 29% to 78% in patients who were PD-L1 positive, with a comparison of PD-L1 negative response rates of 5-43%(61, 62 and 63). Likewise, in patients treated with pembrolizumab, similar differences were seen in response rates between PD-L1 positive and negative patients, with PD-L1 negative response rates ranging from 11-17% and 23-25% in PD-L1 positive patients. In patients treated with atezolizumab prior to progression, response rates of PD-L1 negative patients were relatively consistent, albeit with less data available; there were response rates ranging from 5-31% and 6-29% in PD-L1 positive patients (64, 65 and 66).

However, some studies did not confirm that patients with higher expression of PD-L1 have better efficacy. Overall, these also suggest that PD-L1 is not only a predictive biomarker but also a potential prognostic biomarker in NSCLC (67 and 68) However, it might also be necessary to treat some patients with PD-1/PD-L1 inhibitors in the absence of molecular biomarkers in NSCLC who do not derive benefit from approved front-line chemotherapy. (69 , 70 , 71 and 72).

5. CONCLUSION

We found that PFS of PD-L1 positive expression NSCLC patients treated with pembrolizumab was significantly shorter in patients with the high expression of thyroid hormone receptor expression. Since little is known about the impact of either the expression of THRα and β or its regulation by thyroid hormone signaling on cancer biology or immunotherapy, our results might encourage the development of strategies that would prolong the PFS of PD-L1 positive NSCLC patients treated with pembrolizumab. We acknowledge a number of limitations of our study. Firstly, our conclusions are based on a relatively small sample, and we note the importance of a larger prospective trial to confirm our findings. Secondly, our study only demonstrates a correlative relationship, and further studies are essential to establish functional links between THR α and β expression and PD-1/PD-L1 signaling with clinical mediators. Thirdly, the hierarchical assignment criteria for the THRα and β IHC scores for nuclei and membrane have not been interpreted in previous literature, and we should acknowledge this controversy in the evaluation of THR expression. A number of important questions remain to be answered. The relationship between the localization of THR variants and metastasis of PD-L1 negative or positive NSCLC should be clarified in future research. Used in combination with IHC staining, additional approaches to determine the activities of T3, T3R, and the downstream signaling of the T3-THRB in PD-L1 positive NSCLC might provide useful diagnostic information that it will contribute to the optimization of cancer care in the era of immunotherapy. In conclusion, our results suggest that THR may be a promising indicator of the response of patients to treatment with PD-1/PD-L1 antibodies. Premature termination of T3-

THR signaling could shorten the progression-free survival of PD-L1 positive NSCLC patients treated with pembrolizumab.

In the future, it is likely that THRs, as a principal source of signal differentiation, could also be used as a target for the contents of liquid biopsy to track their potential tumoral transformation for the early diagnosis of NECs. (73)

6. RECOMMENDATION

We recommend conducting future multicenter studies to assess the expression of THRs in various types of lung cancer. This would provide a comprehensive evaluation of the potential implications of THR signaling in managing lung cancer patients. Additionally, research should focus on the mechanisms of THR regulation concerning different histopathological types of NSCLC. Practicing lung disease specialists must recognize the lesser-known management pathway for lung cancer associated with THR (73 and 74).

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