TURKISH JOURNAL of ONCOLOGY

Turk J Oncol 2026;41(1):28–35
doi: 10.5505/tjo.2026.4731

ORIGINAL ARTICLE

Can TPS Expression Reliably Predict Treatment Outcomes and Survival in Nasopharyngeal Cancer?

Tuğba YILMAZ,[1,2] Gül KANYILMAZ,[1] Sıdıka FINDIK,[3] Seda TAS AYÇİÇEK[4]

[1]Department of Radiation Oncology, Necmettin Erbakan University, Konya-*Türkiye*
[2]Department of Radiation Oncology, Recep Tayyip Erdoğan University Rize Training and Research Hospital, Rize-*Türkiye*
[3]Department of Pathology, Necmettin Erbakan University Faculty of Medicine, Konya-*Türkiye*
[4]Department of Pathology, Meram Public Hospital, Konya-*Türkiye*

OBJECTIVE

Nasopharyngeal cancer (NPC) is highly treatment-sensitive, yet distant metastasis remains a challenge. Data on adjuvan therapy needs in non-metastatic (NM) cases from non-endemic regions (NERs) are limited. This retrospective cohort analysis aimed to evaluate the prognostic impact of PD-L1 and Tumor Proportion Score (TPS) in NM NPC patients from a NER.

METHODS

We retrospectively analyzed PD-L1 expression in tumor samples of patients with locoregionally confined NPC. TPS, derived from PD-L1 expression, was correlated with clinical outcomes. Data were analyzed using SPSS 26 with t-tests and chi-square tests for group comparisons, Kaplan–Meier, and Cox regression analyses for survival assessment.

RESULTS

The study included 60 patients with a mean follow-up of 114.5 months. The TPS expression stratified into two groups as <43 (n=24), and ≥43 (n=36). Statistically significant differences were observed in treatment response across the TPS subgroups ($p<0.05$). TPS≥43 was associated with significantly longer overall survival compared to lower TPS expression ($p<0.05$).

CONCLUSION

TPS expression ≥43 was significantly associated with longer survival and better treatment response in NM NPC. These findings support the use of TPS as a prognostic biomarker, which could guide clinical adjuvant treatment studies that improve survival rates and treatment effectiveness. These results underscore the significance of ongoing research and the development of personalized treatment plans for NM NPC patients.

Keywords: Immunotherapy; nasopharyngeal neoplasms; radiotherapy.

The manuscript was presented as an oral presentation at the 16th National Radiation Oncology Congress which held in Cyprus from April 9-13, 2025.

Received: October 22, 2025
Revised: November 26, 2025
Accepted: December 16, 2025
Online: March 02, 2026

Accessible online at:
www.onkder.org

Dr. Tuğba YILMAZ
Necmettin Erbakan Üniversitesi, Radyasyon Onkolojisi Bölümü,
Konya-Türkiye
Recep Tayyip Erdoğan Üniversitesi Rize Eğitim ve Araştırma Hastanesi,
Radyasyon Onkolojisi Bölümü,
Rize-Türkiye
E-mail: tugba.yilmaz1802@gmail.com

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is distinct from other head and neck cancers (HNC) given a number of factors, including Ebstein-Barr Virus (EBV) association, geographical endemic incidence patterns (in particular East and Southeast Asia), environmental and genetic factors, pathology and early hematogenous spread.[1–4] Despite the paucity of data on incidence and survival rates of NPC in non-endemic regions (NERs), it has been established that negative EBV status, WHO type I, higher stage, and older age at diagnosis are significantly associated with increased mortality.[5] Given the radiosensitivity of NPCs and the advances in radiation therapy (RT), local control has significantly improved over time, resulting in improved survival. However, distant metastasis continues to occur even when disease is locally controlled, necessitating the development of new therapeutic strategies.[1]

Immune checkpoint inhibitors (ICIs) are key in treating many cancers and may offer a promising option for NPC. Their exclusion from cornerstone HNC studies may be due to underlying biological and clinical differences between NPC and the other type of HNC malignancies.[6–9] However, the potential for NPC and EBV coincidence to create a beneficial microimmune environment for ICIs remains a subject of interest.[3] Current research focuses on how EBV contributes to NPC by driving cellular changes and immune evasion, as well as investigating EBV-associated molecules as potential early detection biomarkers. Understanding the interplay between EBV and PD-L1 (Programmed cell death ligand 1)/PD-1(Programmed cell death 1) is crucial for developing effective prevention and treatment strategies for NPC and other EBV-related conditions.[2,10]

A retrospective review of anti PD-1 treatment revealed that all HNC subgroups, including NPC, exhibited comparable survival outcomes.[11] A meta-analysis revealed significant advantages in overall survival (OS) with ICIs use in recurrent and metastatic NPC with anti PD-1 treatment.[3] In the context of non-metastatic (NM) settings, the administration of anti-PD-1 ICI has been demonstrated to yield encouraging results.[12,13] However less is known about ICIs use in EBV negativite disease and in the setting of adjuvant RT.[3] These controversies underscore the existing knowledge gap concerning the utilization of ICI in NPC, thereby underscoring the necessity for further research in this domain.[14–16]

PD-L1 has emerged as a critical biomarker in cancer prognosis and treatment response, particularly in malignancies such as melanoma, non-small cell lung cancer, and prostate cancer. High levels of PD-L1 expression are linked to a more aggressive disease course and poorer OS. This over expression enables cancer cells to evade immune detection, complicating treatment strategies. Research indicates that patients with tumors exhibiting elevated PD-L1 levels often respond better to ICIs targeting the PD-1/PD-L1 pathway.[17] A controversial issue in the field relates to the correlation between PD-L1 positivity and survival benefits, raising questions about the efficacy of PD-L1 as a reliable biomarker for the prognostication of NPC.[18,19] There has been a high degree of consensus among pathologists regarding the use of Tumor Proportion Score (TPS) and Combined Positive Score (CPS) to calculate PD-L1 expression.[20] Still, the relationship between TPS and CPS scores and survival outcomes in patients with NPC remains unclear. Therefore, this study aims to elucidate the prognostic significance of PD-L1 expression and its derived scoring systems, including TPS and CPS, on survival outcomes in patients with NM NPC treated with definitive RT or chemoradiotherapy. Unlike ICI trials, this biomarker-focused study evaluates standardly treated patients, providing real-world insight into PD-L1 expression within conventional therapy. These findings may serve as a foundation for future studies integrating ICI, supporting PD-L1's evolving role as both a prognostic marker and a potential guide for personalized treatment strategies.

MATERIALS AND METHODS

Study Population and Data Collection

This retrospective cohort study included patients with histologically confirmed NPC, treated at a single tertiary care hospital between January 2010 and March 2022. This study was approved by the Clinical Research Ethics Committee of Necmettin Erbakan University Faculty of Medicine (Decision number: 2022/3684, Date: 4 March 2022). Eligible patients were adults (≥18 years) who received RT, with or without chemotherapy, in accordance with clinical staging and treatment guidelines at the time of diagnosis.

Patients were excluded if they were younger than 18 years, had a second primary malignancy at the time of diagnosis (excluding non-melanoma skin cancer), lacked follow-up data, or did not have available formalin-fixed paraffin-embedded (FFPE) tumor tissue for immunohistochemical (IHC) staining. A total of 60 patients were included in the final analysis.

Clinical, pathological, and follow-up data were extracted from physical and electronic medical records.

Turk J Oncol 2026;41(1):28–35
doi: 10.5505/tjo.2026.4731

Table 1 Pre- and post-radiotherapy laboratory values and t-test results

	Pre-RT	Post-RT	t	p
Hg (g/dL)	13.74±1.72	12.24±1.41	5.717	0.000
RDW (%)	14.09±2.63	15.08±2.42	-3.594	0.001
Hg/RDW(HRR)	1.02±0.25	0.83±0.17	6.518	0.000
WBC (10^3/μL)	7.53±2.22	4.81±2.66	6.814	0.000
Lymp (10^3/μL)	1.90±0.75	0.43±0.29	15.111	0.000
Neu (10^3/μL)	4.79±1.91	3.84±2.51	2.536	0.014
Neu/plt (NLR)	0.02±0.01	0.02±0.02	-0.588	0.559
Plt (10^3/μL)	277.37±83.13	217.00±75.33	4.807	0.000
Plt/lymp (PLR)	167.91±89.30	669.69±410.07	-10.721	0.000

t:Dependent samples t-test; Mean±SD (min-max) is used for continuous variable, including all pre-RT and post-RT values. Hg: Hemoglobin, RDW: Red cell distribution width; HRR: Hemoglobin/RDW ratio; WBC: White blood cell count; Lymp: Lymphocyte; Neu: Neutrophil; NLR: Neutrophil/lymphocyte ratio; Plt: Platelet count; PLR: Platelet/lymphocyte ratio

Patients were monitored every 3 months for 2 years, then biannually for 3 years, and annually thereafter. Follow-up included nasopharynx, neck, thoracic and abdominal CT and/or MRI, along with routine blood tests. Staging was performed according to the AJCC 8th edition.[21] EBV status was determined solely from diagnostic pathology specimens using IHC; routine plasma EBV DNA testing was not performed in our institution and therefore was not included in the analysis. Laboratory parameters were recorded within 1 month before (pre-RT) and after (post-RT) RT. The specific hematologic markers evaluated including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and hemoglobin-to-red cell distribution width (HRR)—are detailed in Table 1.

None of the patients had received ICIs either prior to or following treatment. RT-related parameters, including irradiation volumes, total dose, and treatment technique, were extracted from the treatment planning system.

We analyzed PD-L1 expression, PD-1 expression, and EBV status. All three markers were assessed using IHC on primary tumor tissue. PD-L1 was additionally scored using the TPS and CPS, based on established criteria. TPS and CPS were calculated by trained pathologists. TPS was further stratified using a cut-off value of 43, determined through receiver operating characteristic (ROC) curve analysis.

Immunohistochemical Preparation and Interpretation

Haematoxylin-Eosin stained preparations obtained from parafin blocks fixed with 10% formaldehyde solution and prepared with routine tissue follow-up were evaluated under a light microscope (Olympus BX43) for histopathological examination. For immunohistochemical staining, the block containing the optimal size material that best represented the tumor, had high histological grade, and minimal necrosis was selected.

To apply PD-L1, PD-1 and EBV IHC stains, three-micron-thick sections were taken from each selected paraffin block onto positively charged slides. Sections from two different samples were mounted on a single slide. The tissue samples were placed onto lysin slides and then sent to the Dako Omnis automatic immunohistochemistry device for deparaffinization and IHC staining. Deparaffinization was achieved by washing with a cleaning agent at 25°C for one minuteand with deionized water for five seconds. PD-1 (IHC001 Clone, Genome) was used at a dilution of 1:150. The PD-L1 (22C3 Clone, Dako, Omnis) and EBV (CS 1-4 Clone, Dako, Omnis) were used undiluted. The PD-1 sample was subjected to 30 minutes of EDTA incubation, the PD-L1 sample underwent 30 minutes of citrate incubation, and the EBV sample was incubated in EDTA for 30 minutes. The staining process was conducted in accordance with standard protocol, following 30 minutes of antibody incubation for PD-1 and PD-L1 and 20 minutes for EBV. Subsequent to the drying of the slides, they were subjected to two cycles of xylene. Balsam (Entellan Mounting Medium) was utilized as a covering material.

The region exhibiting the minimum of 100 tumor cells was selected for the interpretation. The quantification of PD-L1 expression was calculated with two additional factors: The TPS and CPS, both of which are scored on a scale from 0 to 100. According to prior descriptions, the task of calculating TPS and CPS based on PD-L1 expressions was assigned to the same pathologist.[22]

Statistical Analyses

The data was analyzed with IBM SPSS Statistics 26, a program utilized by experienced statistician. The following descriptive statistics were calculated: Mean, stan-

Table 2 Patient characteristics

Characteristics	n	%	Characteristics	n	%
Gender			GTV-NF RT Dose (Gy)	69.93±0.37 (68–70)	
Female	12	20	GTV-NF volume (cm^3)	26.78±23.36 (0–103.8)	
Male	48	80			
Age (years)	49.30±12.39 (19–77)		Tumor differentiation		
			Keratinizing carcinoma	12	20.3
KPS			Non-keratinizing carcinoma	34	57.6
≥70	60	100	Undifferentiated/ Lymphoepithelioma-like type	13	22
General stage			Treatment response		
Stage I	3	5	Complete response	48	80
Stage II	11	18.3	Partial response	9	15
Stage III	25	41.7	No response	3	5
Stage IVa	21	35	PD-1		
T stage			Negative	60	100
T1	18	30	EBV		
T2	23	38.3	Negative	43	74.1
T3	6	10	Positive	15	25.9
T4	13	21.7	PD-L1, mean±SD (min-max)	11.47±20.21 (0–80)	
N stage					
N0	10	16.7	<1	31	51.7
N1	9	15	≥1	29	48.3
N2	30	50	CPS, mean±SD (min-max)	14.67±24.59 (0–90)	
N3	11	18.3			
M stage			<1	30	50
M0	60	100	≥1	30	50
CCT					
Used CCT	53	91.4	TPS, mean±SD (min-max)	65.68±45.97 (0–162)	
No CCT	5	8.6			
RT technique			<43	24	40
3D Conformal	8	14	≥43	36	60
IMRT	49	86			

Mean±SD (min-max) is used for continuous variable, including age, GTV-NF RT Dose, GTV-NF volume, PD-L1, CPS, TPS. Categories with 0% frequency, including M stage, KPS <70 and PD-1, are not shown. T: Tumor; N: Node; M: Metastasis; KPS: Karnofsky performance status; CCT: Concurrent chemotherapy; RT: Radiation therapy; IMRT: Intensity-modulated RT; GTV: Gross tumor volume; NF: Nasopharynx, Gy: Gray, SD: Standart deviation; EBV: Epstein-barr virus; PD-1: Programmed cell death-1; PD-L1: Programmed cell death ligand 1; CPS: Combined positive score; TPS: Tumor proportion score

dard deviation, minimum, and maximum for numerical variables; and numbers, percentages for categorical variables. The differences between the groups were analyzed using independent sample t-tests and chi-square tests. The repeated measurements were analyzed using dependent sample t-tests and repeated measures variance analysis. Finally, the cut-off value for the parameters was determined using receiver operating characteristics (ROC) analysis. Furthermore, Kaplan-Maier analysis and Cox regression analysis were employed to assess OS in addition to examining the factors that affect these outcomes. The primary outcomes of interest was OS. Time-to-event outcome was measured from the end of radiotherapy to death, or last follow-up. Kaplan–Meier methods and log-rank tests were used, with $p<0.05$ considered significant. Radiologic treatment response was assessed using post-treatment imaging according to RECIST 1.1 criteria and categorized as complete response, partial response, stable disease, or progressive disease.

Potential confounders considered in the survival analysis included age, sex, tumor stage, and treatment modality (RT alone vs. chemoradiotherapy). No formal effect modification analysis was performed due to sample size limitations. For the purposes of this study, a p-value of less than 0.05 was accepted as significant. This retrospective cohort study was conducted and reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

Turk J Oncol 2026;41(1):28–35
doi: 10.5505/tjo.2026.4731

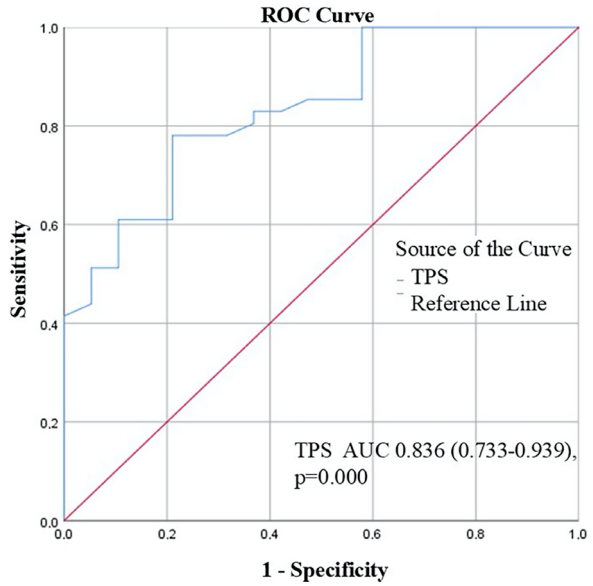

Fig. 1. The Receiver Operating Characteristic (ROC) curve to evaluate Tumor Proportion Score (TPS) expression cut-off in nasopharyngeal cancer.

RESULTS

A total of 60 patients with NPC were included in this study. For detailed overview of cancer staging, pathology, and other clinical factors are summarized in Table 2.

As shown in Table 2, IH staining results were stratified based on PD-1, EBVand PD-L1 expressions, and TPS and CPS. The expression of PD-1 was negative for tumor cells among the entire cohort of patients (n=60). However, the expression was positive for immune cells when utilized as an internal control provided in supplementary materials. EBV was negative 74.1% in the study population. The cut-off value for TPS stratification was determined using ROC curve analyses. In this analysis, the optimal cut off value for TPS was identified as 43 yielding a sensitivity of 0.789 and specificity of 0.780. The area under the ROC curve was 0.836 (95% CI: 0.733–0.939, p=0.000) (Fig. 1). The mean TPS was 65.68±45.97, with a range from 0 to 162. We stratified TPS into two groups as <43 (n=24), and ≥43 (n=36). For PD-L1 and CPS, ROC curve analysis did not yield reliable cut-off values. Therefore, a threshold value of 1 was selected for both markers, based on published literature.[6,7,23–25] The mean PD-L1 expression was 11.47 (±20.21), with a range from 0 to 80 and when stratified into two groups as <1 (n=31), and ≥1 (n=29). The mean CPS was 14.67±24.59, with a range from 0 to 90 and was stratified into two groups as <1 (n=30), and ≥1 (n=30).

Statistically significant differences in gross tumor volume of the primary nasopharyngeal carcinoma (GTV-NF, cm^3), age, and treatment response were observed across the PD-L1, CPS, and TPS subgroups ($p<0.05$), as shown in Table 2. Specifically, GTV-NF (cm^3) was significantly higher in the PD-L1≥1 group compared to PD-L1<1. Both GTV-NF (cm^3) and age were significantly higher in the CPS≥1 group compared to CPS<1. Additionally, the rate of complete response to treatment was significantly higher in the TPS≥43 subgroup compared to the TPS<43.

Patients demonstrated significant changes in several laboratory parameters prior to radiation(pre-RT) compared to after radiation (post-RT) (Table 1). Statistically significant reductions were observed in White Blood Cell Count (WBC) (from 7.53±2.22 to 4.81±2.66, p= 0.000), Lymphocyte count (Lymp) (from 1.90±0.75 to 0.43±0.29, p= 0.000), Hemoglobin (Hg) (p=0.000), HRR (p=0.000), Neutrophil count (Neu) (p=0.014) and Platelet Count (Plt) (p=0.000). Conversely, Red Cell Distribution Width (RDW) (p=0.001) and PLR (p=0.000) were significantly increased after radiation. Furthermore, a subgroup analysis was conducted to compare the change in laboratory parameters between pre-RT and post-RT values within the PD-L1 (<1, ≥1), CPS (<1, ≥1), and TPS (<43, ≥43) subgroups. There were no statistically significant differences in any of laboratory values comparing pre-RT and post-RT values within any of these subgroups (all p>0.05). An independent evaluation of pre-RT and post-RT laboratory values was performed across the TPS subgroups (<43 and ≥43). Significant differences were observed in pre-RT WBC, neutrophil (Neu), and neutrophil-to-lymphocyte ratio (NLR), as well as in post-RT lymphocyte (Lymp) values. Specifically, pre-RT WBC (p=0.012), Neu (p=0.003), and NLR (p=0.024) were higher in the TPS <43 group, whereas post-RT Lymp (p=0.022) was lower in the same subgroup.

In addition to subgroup analyses, EBV status, classified as positive or negative, was also evaluated in relation to changes in laboratory parameters pre-RT and post-RT. Unlike the other subgroups, EBV groups demonstrated a statistically significant difference in Lymp values comparing prre-RT and post-RT (p=0.017). Specifically, the post-RT Lymp value was higher in the EBV-negative group compared to the EBV-positive group.

The mean follow-up durations were 114.5 months for OS (range 97.2–131.7 months). In subgroup analyses, patients with TPS≥43 (n=36) had significantly longer estimated survival outcome, including OS (147.9 months; 95% CI: 135.2–160.6) compared to those with TPS <43 (n=24). Mean survival time was OS: 29.4 months (95%

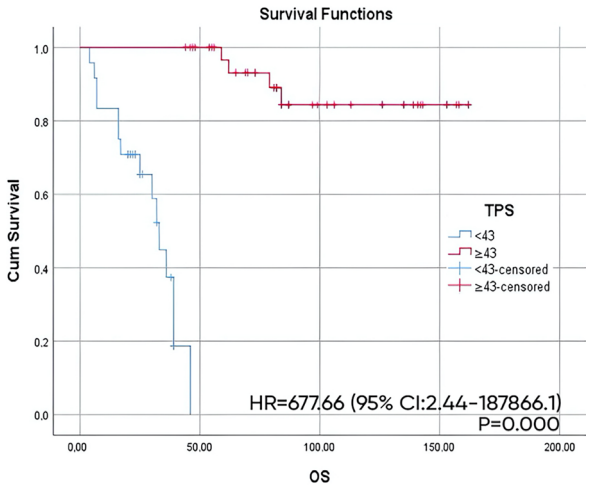

Fig. 2. Kaplan–Meier survival curves illustrate overall survival (a), progression-free survival (b), and metastasis-free survival (c) based on Tumor Proportion Score (TPS) expression levels.

CI: 23.5–35.4). A statistically significant discrepancy was observed among the TPS subgroups with respect to OS (p=0.000), as illustrated in Figure 2. In contrast, PD-L1 and CPS expression results did not show any statistically significant association with survival outcomes.

In the Cox proportional hazards regression analysis, higher TPS expression (≥43) was significantly associated with improved overall survival (p<0.001). The hazard ratio for patients with TPS ≥43 was 677.657 (95% CI: 2.444–187,867.110), indicating a strong protective effect. There is not any significant correlation between CPS and TPS values (r=-0.061, p=0.645).

DISCUSSION

In this retrospective, single-center, cohort study, we found that TPS <43 was associated with poorer outcomes in terms of OS and the complete response to treatment. These findings suggest that TPS <43 could serve as a predictive marker of worse survival and may indicate the potential need for adjuvant therapy in NM NPC, pending validation in further studies.

Novel treatment approaches should be explore as early hematogenous dissemination remains a major cause of treatment failure. Furthermore, as NPC is less commonly seen in NER, there remains a substantial gap in our understanding of its biological behavior and prognostic markers in these populations.[3] Unlike other tumor types, utilizing PD-L1 expression as a prognostic factor poses a significant challenge in the context of NPC literature.[18,19] Unlike previous studies of patients with metastatic NPC, the present study did not demonstrate a correlation between CPS and survival outcomes, though a correlation was found with TPS.[26] This could be because TPS is calculated based solely on tumor cells and is therefore more applicable to localized disease. In agreement with the other published date on IHC previously identifing a higher NLR count prior to treatment as a poor prognostic factor in NPC, a higher NLR count is present in our cohort was found in our TPS<43 subgroup which was found to have worse survival outcomes.[27]

There is emerging literature on the correlation between PD-L1 expression and tumor volume in other tumor types, which could provide helpful clinical information for treatment sequencing and decision-making regarding subsequent treatments.[28,29] In this study, we present the first NPC data showing a significant correlation between tumor volume (GTV-NF) and both CPS and PD-L1 expression in NM NPC.

Notably, EBV-negative NPC is more frequently observed in NER, where literature remains limited.[3,5] In our study, we found a statistically significant difference in Lymp count changes between EBV-positive and EBV-negative groups, with post-RT Lymp levels being higher in EBV-negative group. This may reflect differences in host immune response or tumor microenvironment characteristics related to EBV presence. Given the emerging role of ICIs in NPC, the observed lymphocyte elevation in the EBV-negative group post-RT may point toward a potentially more favorable immunologic landscape for ICI responsiveness.

While this study provides insights into the predictive significance of PD-L1, TPS, CPS, and EBV expressions in NPC, several limitations should be acknowledged. This was a retrospective, single-center study with a relatively small cohort, which may limit generalizability. Potential residual confounding remains, as peripheral blood cell counts can be influenced by infections or nutritional status, and PD-1 staining interpretation did not account for tumor-infiltrating lymphocyte density. EBV status was assessed solely by IHC on diagnostic specimens, and plasma EBV DNA levels were unavailable, preventing a reliable evaluation of EBV–TPS interactions, particularly given the small number of EBV-negative cases. Subgroup analyses are limited by multiple comparisons, small sample size, and potential confounding from factors such as tumor volume, age, and stage. Cox regression included only a restricted set of covariates (age, sex, tumor stage, treatment modality) to avoid overfitting, leav-

Turk J Oncol 2026;41(1):28–35
doi: 10.5505/tjo.2026.4731

ing residual confounding possible. Extremely wide hazard ratios and confidence intervals reflect statistical instability due to the limited number of events. Effect sizes and confidence intervals were reported where possible, but survival estimates should be interpreted with caution. Despite these limitations, the study provides a basis for future prospective studies with larger cohorts to evaluate whether TPS, together with clinical parameters such as GTV-NF, can guide personalized treatment strategies in NM-NPC, especially in non-endemic regions.

CONCLUSION

This study investigates the prognostic relevance of PD-L1 and its derived TPS in patients with NM-NPC, focusing on its associations with tumor volume, treatment response, and survival outcomes. Although PD-L1 expression was not was not independently prognostic in our cohort, prior studies in other malignancies suggest its potential predictive role, particularly for response to ICIs. Despite limitations due to the retrospective design and small sample size, our findings provide a preliminary foundation for integrating TPS with clinical and biological parameters to support more personalized management strategies for NM-NPC, particularly in non-endemic regions. Larger prospective studies with comprehensive biomarker assessment are warranted to validate these observations and clarify their clinical applicability.

Ethics Committee Approval: The study was approved by the Necmettin Erbakan University Faculty of Medicine Clinical Research Ethics Committee (no: 2022/3684, date: 04/03/2022).

Informed Consent: The study was approved by the institutional ethics committee, and informed consent was waived due to the retrospective design.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Funding: The Scientific Research Projects Unit of the Necmettin Erbakan University funded this study under the Project number 221518037.

Use of AI for Writing Assistance: AI-based tools were used solely for language editing and grammar correction. No AI tools were used for the generation of scientific content.

Author Contributions: Concept – T.Y., G.K.; Design – T.Y., G.K., S.F.; Supervision – G.K. S.F.; Materials – T.Y., S.T.A.; Data collection and/or processing – T.Y., S.T.C.; Literature search – T.Y.; Writing – T.Y.; Critical review – G.K., S.F., S.T.A.

Peer-review: Externally peer-reviewed.

REFERENCES

1. Nakanishi Y, Wakisaka N, Kondo S, Endo K, Sugimoto H, Hatano M, et al. Progression of understanding for the role of Epstein-Barr virus and management of nasopharyngeal carcinoma. Cancer Metastasis Rev 2017;36(3):435–47.
2. Su ZY, Siak PY, Leong CO, Cheah SC. The role of Epstein-Barr virus in nasopharyngeal carcinoma. Front Microbiol 2023;14:1116143.
3. Guven DC, Stephen B, Sahin TK, Cakir IY, Aksoy S. Immunotherapy in the first-line treatment of advanced nasopharyngeal carcinoma: A systematic review and meta-analysis. Laryngoscope 2024;134(1):7–17.
4. Yu MC, Yuan JM. Epidemiology of nasopharyngeal carcinoma. Semin Cancer Biol 2002;12(6):421–9.
5. van Velsen JS, van der Vegt B, Plaat BEC, Langendijk JA, Epskamp-Kuijpers CCHJ, van Dijk BAC, et al. Nasopharyngeal carcinoma: Nationwide trends in subtype-specific incidence and survival over 3 decades in a non-endemic area. J Cancer Res Clin Oncol 2024;150(2):49.
6. Ferris RL, Blumenschein G, Jr., Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med 2016;375(19):1856–67.
7. Burtness B, Harrington KJ, Greil R, Soulieres D, Tahara M, de Castro G, Jr., et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): A randomised, open-label, phase 3 study. Lancet 2019;394(10212):1915–28.
8. Kong X, Zhang J, Chen S, Wang X, Xi Q, Shen H, et al. Immune checkpoint inhibitors: Breakthroughs in cancer treatment. Cancer Biol Med 2024;20240055.
9. Shiravand Y, Khodadadi F, Kashani SMA, Hosseini-Fard SR, Hosseini S, Sadeghirad H, et al. Immune checkpoint inhibitors in cancer therapy. Curr Oncol 2022;29(5):3044–60.
10. Tsao SW, Tsang CM, Lo KW. Epstein-Barr virus infection and nasopharyngeal carcinoma. Philos Trans R Soc Lond B Biol Sci 2017;372(1732):20160270.
11. Sato Y, Fukuda N, Wang X, Urasaki T, Ohmoto A, Nakano K, et al. Efficacy of nivolumab for head and neck cancer patients with primary sites and histological subtypes excluded from the CheckMate-141 trial. Cancer Manag Res 2020;12:4161–8.
12. Yu YF, Lu GZ, Wang RJ, Song YK, Wu SG. Additional PD-1 inhibitor improves complete response to induction chemotherapy in locally advanced nasopharyngeal carcinoma. Front Immunol 2024;15:1415246.
13. Shi S, Li B, Zhou P, Chen L, Li H, Wang Y, et al. Analysis of the clinical efficacy and safety of anti-PD-1 immune checkpoint inhibitors in locally advanced nasopharyngeal cancer. Cancer Med 2024;13(14):e7359.

14. Mai HQ, Chen QY, Chen D, Hu C, Yang K, Wen J, et al. Toripalimab plus chemotherapy for recurrent or metastatic nasopharyngeal carcinoma: The JUPITER-02 randomized clinical trial. JAMA 2023;330(20):1961–70.
15. Yang Y, Pan J, Wang H, Zhao Y, Qu S, Chen N, et al. Tislelizumab plus chemotherapy as first-line treatment for recurrent or metastatic nasopharyngeal cancer: A multicenter phase 3 trial (RATIONALE-309). Cancer Cell 2023;41(6):1061–72.e4.
16. Yang Y, Qu S, Li J, Hu C, Xu M, Li W, et al. Camrelizumab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (CAPTAIN-1st): A multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol 2021;22(8):1162–74.
17. Mino-Kenudson M. Programmed cell death ligand-1 (PD-L1) expression by immunohistochemistry: Could it be predictive and/or prognostic in non-small cell lung cancer? Cancer Biol Med 2016;13(2):157–70.
18. Huang ZL, Liu S, Wang GN, Zheng SH, Ding SR, Tao YL, et al. The prognostic significance of PD-L1 and PD-1 expression in patients with nasopharyngeal carcinoma: A systematic review and meta-analysis. Cancer Cell Int 2019;19(1):141.
19. Sahinli H, Akyürek N, Yılmaz M, Kandemir O, Duran AO, Kulaçoğlu S, et al. Good prognostic factor in patients with nonmetastatic nasopharyngeal carcinoma: Programmed death ligand-1 expression in tumor cells. J Cancer Res Ther 2020;16(Supplement):S43–7.
20. Mercier A, Conan-Charlet V, Quintin-Roué I, Doucet L, Marcorelles P, Uguen A. Reproducibility in PD-L1 immunohistochemistry quantification through the tumor proportion score and the combined positive score: Could dual immunostaining help pathologists? Cancers 2023;15(10):2768.
21. Lydiatt WM, Patel SG, O'Sullivan B, Brandwein MS, Ridge JA, Migliacci JC, et al. Head and neck cancers—Major changes in the American Joint Committee on cancer eighth edition cancer staging manual. CA Cancer J Clin 2017;67(2):122–37.
22. de Ruiter E, Mulder F, Koomen B, Speel EJ, van den Hout M, de Roest R, et al. Comparison of three PD-L1 immunohistochemical assays in head and neck squamous cell carcinoma (HNSCC). Mod Pathol 2020;34:1125–32.
23. Cogswell J, Goldberg SM, Gupta AK, Jure-Kunkel M, Wang XT, Wiggington JM. Cancer immunotherapy by disrupting PD-1/PD-L1 signaling. Nov 21, 2013. Available at: https://patents.google.com/patent/US10323093B2/en. Accessed Jan 23, 2025.
24. Freeman GJ, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med 2000;192(7):1027–34.
25. Latchman Y, Wood CR, Chernova T, Chaudhary D, Borde M, Chernova I, et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. Nat Immunol 2001;2(3):261–8.
26. Hsu CL, Kuo YC. Abstract 6404: Clinical scenario of immune checkpoint inhibitor treatment in metastatic nasopharyngeal carcinoma. Cancer Res 2023;83(7_Supplement):6404.
27. Song S, Chen H, Dou X, Wang K, Yan J, Yu C. The prognostic value of before treatment neutrophil-to-lymphocyte ratio in nasopharyngeal carcinoma. Eur Arch Otorhinolaryngol 2022;279(5):2485–92.
28. Zhang M, Dong Y, Liu H, Wang Y, Zhao S, Xuan Q, et al. The clinicopathological and prognostic significance of PD-L1 expression in gastric cancer: A meta-analysis of 10 studies with 1901 patients. Sci Rep 2016;6:37933.
29. Han Z, Wang N, Qiao Q, He X, Wang N. Association of PD-L1 expression with clinicopathologic characters in gastric cancer: A comprehensive meta-analysis. Curr Med Chem 2024;31(21):3198–216.