

Evaluation of smoking status as a prognostic factor under immune checkpoint inhibitor treatment: A single center analysis

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Abstract. Smoking may influence cancer treatment outcomes; however, there is conflicting evidence on the efficacy of immune checkpoint inhibitors (ICIs) in active smokers. It has been suggested that smokers receiving ICIs may achieve improved outcomes compared with non-smokers. The present study aimed to challenge this assumption by investigating the prognostic impact of smoking status and other characteristics in patients with metastatic or advanced cancer undergoing ICI therapy. In the present study, patients with predetermined solid tumors who received ICIs either as a monotherapy or in combination regimens in a palliative treatment setting were retrospectively evaluated. Patients were included if they had received >1 dose of an ICI and had an available smoking status. Kaplan-Meier estimates were used to analyze the associations between smoking status and overall survival (OS) and progression-free survival (PFS). The patient baseline characteristics were assessed as potential prognostic markers using univariate and multivariate analyses. Of the 464 patients evaluated, 180 met the inclusion criteria. The cohort included patients with lung cancer (n=94), renal cell carcinoma (n=18), urothelial cancer (n=21), melanoma (n=3), and head and neck cancer (n=44). The median OS and PFS times for the whole cohort were 39.1 and 5.5 months, respectively. Patients were categorized as never-smokers (n=45, 25%), former smokers (n=81, 45%) and active smokers (n=54, 30%). The median OS times for the never, former and active smokers were 66.4, 31.6 and 13.9 months, respectively. When comparing the active smokers with the former and never smokers, the median OS

times were 13.9 vs. 41.1 months (P=0.069, trend). Multivariate analyses identified Eastern Cooperative Oncology Group (ECOG) performance status ≥ 3 [hazard ratio (HR), 5.85; P=0.002], neutrophil-to-lymphocyte ratio (NLR; HR, 1.11; P=0.017), lactate dehydrogenase (LDH; HR, 1.00; P<0.001) and C-reactive protein (CRP) levels as continuous variables (HR, 1.01; P=0.002) as significant predictors of a poorer OS. For PFS, multivariate analysis identified sex (HR, 0.69; P=0.049), age (HR, 0.98; P=0.014) and ECOG performance status ≥ 3 (HR, 5.83; P<0.001) as independent predictors of a shorter PFS. In conclusion, contrary to prior hypotheses suggesting improved outcomes for smokers undergoing ICI therapy, the results of the present study demonstrated a trend towards impaired survival outcomes in active smokers compared with never and former smokers. The independent prognostic factors for a poorer OS included a poor ECOG performance status, CRP level, LDH level and NLR.

Introduction

Cigarette smoking is a leading contributor to cancer development and mortality, accounting for an estimated 28.5% of all cancer-related deaths worldwide (1). Although the established link between smoking and cancer incidence is well-recognized, the impact of continued smoking during cancer treatment remains an active area of investigation. Tobacco smoke contains a number of carcinogens, including polycyclic aromatic hydrocarbons and nitrosamines, which not only initiate malignant transformation but also actively promote tumor progression (2). Moreover, smoking-induced mutagenesis can lead to the emergence of more aggressive tumor phenotypes that are characterized by accelerated growth, metastatic spread and resistance to therapy (3,4). Recent findings have also indicated that smoking can exacerbate genomic instability and epigenetic alterations, further driving tumor aggressiveness (5). Additionally, smoking-induced chronic inflammation and immune dysregulation create a tumor microenvironment that promotes progression, immune evasion and therapy resistance (6).

A concerning aspect of the impact of smoking is the associated increased risks of recurrence, metastasis and secondary malignancies (7,8). Smoking has also been shown to

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compromise the effectiveness of established cancer therapies including conventional chemotherapy and radiotherapy (3). Despite these well-documented risks, a significant number of patients continue to smoke post-cancer diagnosis, often due to psychological factors such as emotional regulation, habitual dependence and cognitive distortions including fatalistic thinking or self-blame. A number of patients use smoking as a coping mechanism for stress, anxiety and depressive symptoms, which often intensify after a cancer diagnosis (9). Additionally, nicotine dependence and depressive symptoms have been identified as significant predictors of relapse after cancer treatment, highlighting the challenge of quitting smoking (10). These barriers emphasize the urgent need for targeted interventions that address both the physical and psychological aspects of smoking addiction in this vulnerable population. By integrating psychological support, such as cognitive behavioral strategies and tailored counseling, smoking cessation programs can more effectively assist patients with cancer to overcome these challenges and improve their prognosis.

While the detrimental effects of smoking on traditional cancer treatments are well documented, its influence on immune checkpoint inhibitor (ICI) therapy is more nuanced and paradoxical. Certain studies have suggested that smokers have an improved response to ICIs, potentially owing to a higher tumor mutational burden (TMB), which could enhance immune recognition and response (11,12). Supporting this notion, a meta-analysis by Mo *et al* (13) of phase II/III randomized controlled trials demonstrated that smokers experienced a significant overall survival (OS) benefit from programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors compared with chemotherapy, while non-smokers did not exhibit statistically significant improvements from ICI monotherapy. Similarly, Kim *et al* (14) reported that ICIs significantly prolonged the OS of ever-smokers but not of never-smokers among patients with non-small cell lung cancer (NSCLC). By contrast, Luo and Stent (4) found that immunotherapy benefited both smokers and non-smokers with lung cancer; however, the relationship between smoking status and ICI efficacy remains complex and multifaceted. These findings suggest that a smoking history may be associated with improved responses to ICI therapy, potentially due to the higher TMB in smokers, which enhances immune recognition. The complexity of these interactions highlights the need for further investigation to clarify the mechanisms underlying these observations and to refine the treatment strategies for patients with cancer who smoke. Therefore, the present study aimed to investigate the prognostic impact of smoking status and other characteristics in patients with metastatic or advanced cancer undergoing ICI therapy.

Patients and methods

Study population. Patients with predetermined solid tumors who received ICI (pembrolizumab or nivolumab) therapy, either as a monotherapy or in combination regimens in a palliative treatment setting, were retrospectively evaluated at a single-center institution (University Medical Center Hamburg-Eppendorf, Hamburg, Germany). Tumor types

were chosen for the present study based on frequent ICI use. Therefore, the solid tumor types included in the analysis were lung cancer, including NSCLC and small cell lung cancer (SCLC), renal cell carcinoma (RCC), melanoma, urothelial carcinoma (UC) and head and neck cancer, including head and neck squamous cell carcinoma (HNSCC) and head and neck adenosquamous carcinoma.

Inclusion criteria. Eligible patients included those diagnosed with the specified tumor types, those who had received >1 dose of ICI therapy at our center and those for whom data on the smoking status were available. Smoking status was categorized into three groups: Never, former and active smokers. Former smokers were defined as those who had quit smoking prior to ICI initiation. Informed consent and ethics approval were waived due to the retrospective design of the study. This approach was approved by the local ethics committee of the Hamburg Chamber of Physicians (2025-300686-WF) and was in accordance with the Hamburg Hospital Act (HmbKHG) §12.

Exclusion criteria. Patients were excluded from the analysis if they met any of the following criteria: i) Unclear smoking status; ii) the disease did not correspond to the predefined tumor types; or iii) insufficient data, such as missing follow-up information, incomplete medical records or an absence of key baseline characteristics.

Objectives and endpoints. The primary outcomes, OS and progression-free survival (PFS), were analyzed using Kaplan-Meier estimates to assess the impact of smoking status on treatment outcomes. Differences between survival curves were evaluated using the log-rank test. If no deaths were recorded, the survival time was censored at the date of the last follow-up. PFS was defined as the time from the initiation of ICI therapy to disease progression, whereas OS was defined as the time from the initiation of ICI therapy to death from any cause.

In addition to the primary outcomes, baseline patient characteristics, including age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, C-reactive protein (CRP) and lactate dehydrogenase (LDH) levels and neutrophil-to-lymphocyte ratio (NLR), were examined for their prognostic significance. Age, CRP, LDH and NLR were analyzed as continuous variables, to examine whether the increasing levels correlated with an impact on the outcomes; a hazard ratio (HR) of 1.00 reflects the per-unit increase.

Furthermore, the objective response rate (ORR) and disease control rate (DCR) were analyzed as secondary endpoints. ORR was defined as partial remission (PR) or complete remission (CR) and DCR was defined as stable disease, PR or CR.

To compare baseline characteristics between smoking groups, the Kruskal-Wallis rank sum test was applied for continuous variables, Pearson's χ^2 test was used for categorical variables with sufficient sample sizes, and Fisher's exact test was performed for categorical variables with small counts or sparse categories. Univariate and multivariate Cox regression models were used to identify independent predictors of OS and PFS. Variables with $P < 0.05$ in the univariate analysis were included in the multivariate Cox model. All statistical analyses were performed using R (v4.4.2) (15) with the 'gtsummary' (v2.0.4) (16), 'survival' (v3.8-3) (17), 'finalfit' (v1.0.8) (18) and

'survminer' (v0.5.0) (19) packages. Plots were generated using 'ggplot2' (v3.5.1) (20).

Results

Patient characteristics. Among the 464 patients who received ICI treatment at our tertiary center, University Medical Center Hamburg-Eppendorf, and were initially evaluated in the present study, 170 did not meet the predefined tumor types criteria or were treated in a clinical trial. Of the 294 patients with the intended tumor types, 92 patients were lost to follow-up as most of these patients continued treatment externally. Additionally, the smoking status could not be clearly evaluated in 22 patients. Therefore, 180 patients met the eligibility criteria for analysis (Fig. 1). The cohort included patients with NSCLC or SCLC (n=94), RCC (n=18), UC (n=21), head and neck cancer (n=44) and melanoma (n=3). The majority (93%) of patients presented with metastatic disease at the initiation of ICI therapy. Patients without metastatic disease had locally advanced stage disease and were treated for palliative reasons. Of these patients, 143 (79%) received ICI treatment without chemotherapy. The median age of the cohort was 68 years (Q1-Q3, 59-74 years). Male patients constituted the predominant demographic group (71%), while female patients comprised 29% of the study population. Most patients demonstrated a favorable baseline performance status, with 76% having an ECOG score of 0 or 1. Notably, 83% of patients received ICI treatment in either the first- or second-line setting. Based on a detailed smoking history, the cohort was further stratified into never-smokers (n=45), former smokers (n=81) and active smokers (n=54). The median follow-up time for the entire cohort was 13 months (range, 5-34 months). The baseline characteristics of the study population are summarized in Table I.

When comparing patients with lung cancer (n=94) to those with other solid tumors (n=86) treated with ICIs, significant differences in the baseline characteristics and treatment outcomes were observed. Notably, the distribution of the smoking status differed significantly between the groups (P=0.022), with a higher prevalence of former (47 vs. 43%) and active (36 vs. 23%) smokers and a lower proportion of never-smokers (17 vs. 34%) in the lung cancer cohort compared with other malignancies. While the overall ORR, defined as PR or CR, did not significantly differ between the lung cancer group and the other cancer types group (26 vs. 20%; P=0.3), the DCR was significantly higher among patients with lung cancer (59 vs. 43%; P=0.029). These findings underscore the distinct patient characteristics, particularly the smoking history, and differential treatment responses to ICIs in lung cancer vs. other solid tumors.

Univariate and multivariate analyses of OS. The median OS and PFS times for the entire cohort from the initiation of ICI treatment were 39.1 and 5.5 months, respectively. Among the smoking subgroups, the median OS time was 66.4 months for never-smokers, 31.6 months for former smokers and 13.9 months for active smokers (P=0.15). When comparing active smokers to the combined former and never-smokers cohort, the median OS times were 13.9 vs. 41.1 months, respectively (P=0.069) (Fig. 2).

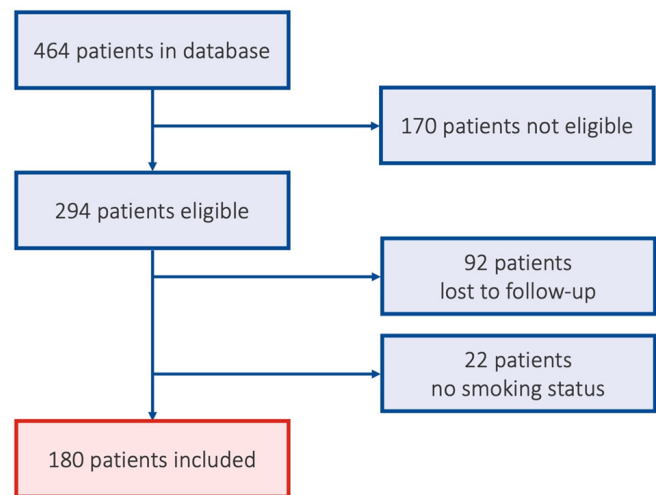


Figure 1. Study flow chart.

Further exploratory univariate analysis identified several factors associated with a poorer OS including ECOG performance status ≥ 3 [HR, 7.78; 95% confidence interval (CI), 3.22-18.80; P<0.001], baseline CRP levels (HR, 1.01; 95% CI, 1.00-1.01; P<0.001), NLR (HR, 1.12; 95% CI, 1.04-1.21; P=0.002) and LDH levels (HR, 1.00; 95% CI, 1.00-1.00; P<0.001). Multivariate analysis confirmed the significant negative prognostic impact of ECOG performance status ≥ 3 (HR, 5.85; 95% CI, 1.90-18.04; P=0.002), NLR (HR, 1.11; 95% CI, 1.02-1.21; P=0.017), LDH \geq mean (HR, 1.00; 95% CI, 1.00-1.00; P<0.001) and CRP levels (HR, 1.01; 95% CI, 1.00-1.01; P=0.002). All parameters from the univariate and multivariate analyses are summarized in Table II. As CRP, NLR and LDH were analyzed as continuous variables, hazard ratios represent the relative risk per unit increase of the respective parameter.

Univariate and multivariate analyses of PFS. Univariate analysis of PFS showed that female sex (HR, 0.69; 95% CI, 0.48-1.00; P=0.049), age (HR, 0.98; 95% CI, 0.97-1.00; P=0.026) and ECOG performance status ≥ 3 (HR, 5.83; 95% CI, 2.60-13.09; P<0.001) were significantly associated with PFS. Multivariate analysis confirmed that age (HR, 0.98; 95% CI, 0.96-1.00; P=0.014) and ECOG performance status ≥ 3 (HR, 5.55; 95% CI, 2.37-12.99; P<0.001) were independent predictors of a shorter PFS time. Regarding the smoking status, no statistical differences were detected in terms of PFS. Table III provides a complete overview of all parameters from both analyses.

Overall outcome and response rate. Among the evaluable patients, the ORR was 23% and the DCR was 51%, which were comparable to the reported rates for NSCLC [19% (21)] and HNSCC [30% (22)]. However, subgroup analysis stratified by the smoking status demonstrated no statistically significant differences in either the ORR or DCR (Table I).

Subgroup analysis on lung cancer. Subgroup analysis based on the smoking status was conducted for the 94 patients with lung cancer treated with ICIs. In this subgroup analysis,

Table I. Patient characteristics.

Characteristic	Never (n=45)	Former (n=81)	Active (n=54)	P-value ^a
Sex, n (%)				0.008
Male	24 (53%)	64 (79%)	40 (74%)	
Female	21 (47%)	17 (21%)	14 (26%)	
Median age, years (SD) [IQR]	73.0 (11.7) [13]	68.0 (9.4) [14]	64.0 (10.9) [13]	0.002
ECOG, n (%)				0.406
0	11 (26%)	18 (25%)	12 (24%)	
1	24 (57%)	40 (55%)	21 (42%)	
2	5 (12%)	12 (16%)	10 (20%)	
3	2 (4.8%)	3 (4.1%)	7 (14%)	
N/A	3	8	4	
BMI category, n (%)				0.032
Healthy weight	29 (64%)	37 (49%)	28 (56%)	
Obesity	3 (6.7%)	10 (13%)	5 (10%)	
Overweight	13 (29%)	25 (33%)	9 (18%)	
Underweight	0 (0%)	4 (5.3%)	8 (16%)	
N/A	0	5	4	
Tumor, n (%)				<0.001
NSCLC	16 (36%)	43 (53%)	31 (57%)	
SCLC	0 (0%)	1 (1.2%)	3 (5.6%)	
RCC	12 (27%)	5 (6.2%)	1 (1.9%)	
Melanoma	2 (4.4%)	1 (1.2%)	0 (0%)	
Urothelial	5 (11%)	13 (16%)	3 (5.6%)	
HNSCC	9 (20%)	18 (22%)	16 (30%)	
HNAdSC	1 (2.2%)	0 (0%)	0 (0%)	
Metastasis, n (%)				0.049
No	4 (8.9%)	2 (2.5%)	7 (13%)	
Yes	41 (91%)	79 (98%)	47 (87%)	
Treatment, n (%)				0.034
ICI mono	30 (67%)	66 (81%)	41 (76%)	
ICI + chemotherapy	8 (18%)	14 (17%)	12 (22%)	
ICI + CTLA4	4 (8.9%)	1 (1.2%)	1 (1.9%)	
ICI + VEGFR	3 (6.7%)	0 (0%)	0 (0%)	
Line of treatment, n (%)				0.600
1	21 (47%)	33 (41%)	29 (54%)	
2	16 (36%)	34 (42%)	16 (30%)	
3+	8 (17.8%)	14 (17%)	9 (16.8%)	
Median LDH, U/l (SD) [IQR]	248.0 (187.8) [107.5]	224.5 (132.5) [97.0]	214.0 (118.8) [100.8]	0.309
N/A	2	1	2	
Median CRP, mg/l (SD) [IQR]	9.5 (51.2) [27.8]	18.5 (50.6) [58.3]	18.0 (54.5) [56.5]	0.011
N/A	1	1	3	
Median NLR (SD) [IQR]	3.4 (2.0) [2.2]	4.4 (2.6) [3.5]	4.0 (4.3) [3.3]	0.031
N/A	9	13	12	
Median doses, n (SD) [IQR]	7.0 (20.3) [15.0]	7.5 (17.0) [10.3]	6.0 (15.5) [7.8]	0.335
N/A	0	1	0	
Median follow-up, months (SD) [IQR]	17.0 (25.7) [43.0]	14.0 (25.3) [26.0]	7.5 (24.3) [22.3]	0.025
ORR, n (%)				>0.900
PD/stable disease	33 (77%)	63 (78%)	37 (76%)	

Table I. Continued.

Characteristic	Never (n=45)	Former (n=81)	Active (n=54)	P-value ^a
PR/CR	10 (23%)	18 (22%)	12 (24%)	
N/A	2	0	5	
DCR, n (%)	25 (58%)	43 (53%)	21 (43%)	0.316
N/A	2	0	5	

^aP-values were calculated using the Kruskal-Wallis rank sum test for continuous variables (age, LDH, CRP, NLR, doses and follow-up); P-values for tumor and treatment were calculated using Fisher's exact test; and Pearson's χ^2 test for all other categorical variables (sex, ECOG, BMI, metastasis, line, ORR and DCR). BMI, body mass index; CR, complete remission; CRP, C-reactive protein; CTLA4, cytotoxic T-lymphocyte-associated protein 4; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; HNSCC, head and neck squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; ICI, immune checkpoint inhibitor; IQR, interquartile Range; LDH, lactate dehydrogenase; N/A, not available; NLR, neutrophil-to-lymphocyte ratio; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PR, partial remission; RCC, renal cell carcinoma; SCLC, small cell lung cancer; SD, standard deviation; VEGFR, vascular endothelial growth factor receptor.

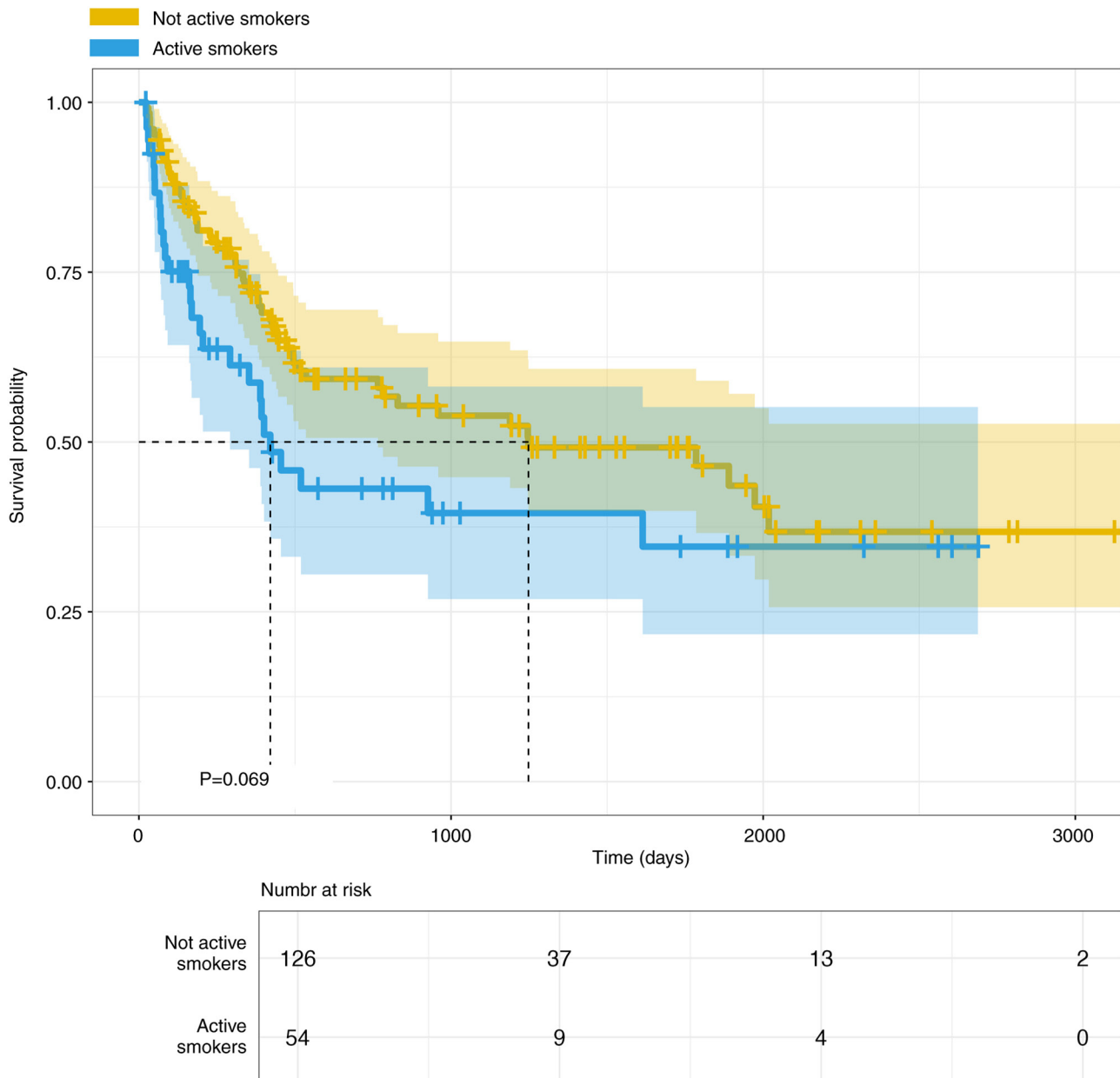


Figure 2. Active smoking reveals impaired overall survival compared to non-active-smokers under ICI treatment.

Table II. Results of univariate and multivariate analyses of overall survival.

Variable	Value	HR (univariate)	HR (multivariate)
Smoking status, n (%)			
Not active	126 (70.0)	-	-
Active	54 (30.0)	1.52 (95% CI 0.97-2.40, P=0.069)	-
Sex, n (%)			
Male	128 (71.1)	-	-
Female	52 (28.9)	0.95 (95% CI 0.59-1.51, P=0.818)	-
Mean age (SD), years	66.6 (10.7)	1.00 (95% CI 0.98-1.02, P=0.804)	-
ECOG status, n (%)			
0	41 (24.8)	-	-
1	85 (51.5)	0.86 (95% CI 0.50-1.51, P=0.609)	0.62 (95% CI 0.33-1.14, P=0.124)
2	27 (16.4)	1.88 (95% CI 0.92-3.85, P=0.082)	1.03 (95% CI 0.43-2.46, P=0.948)
≥3	12 (7.3)	7.78 (95% CI 3.22-18.80, P<0.001)	5.85 (95% CI 1.90-18.04, P=0.002)
Metastasis, n (%)			
No	13 (7.2)	-	-
Yes	167 (92.8)	1.03 (95% CI 0.45-2.35, P=0.953)	-
Mean NLR (SD)	4.6 (3.1)	1.12 (95% CI 1.04-1.21, P=0.002)	1.11 (95% CI 1.02-1.21, P=0.017)
Mean LDH, U/l (SD)	262.9 (144.9)	1.00 (95% CI 1.00-1.00, P<0.001)	1.00 (95% CI 1.00-1.00, P<0.001)
Mean CRP, mg/l (SD)	39.5 (52.2)	1.01 (95% CI 1.00-1.01, P<0.001)	1.01 (95% CI 1.00-1.01, P=0.002)

CI, confidence interval; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; SD, standard deviation.

16 patients were never-smokers, 44 were former smokers and 34 were active smokers. Regarding the baseline characteristics, a statistically significant difference was observed in terms of age, with never-smokers being the oldest (median, 72.5 years), followed by former smokers (median, 69.0 years) and active smokers being the youngest (median, 65.0 years) (P=0.034). The DCR also showed a significant difference (P=0.039), with the highest DCR observed in never-smokers (80%), followed by former smokers (64%) and then active smokers (44%). While a trend towards significance was noted in the sex distribution (P=0.052), with a higher proportion of female patients in the never-smokers group (56%) compared with the former (23%) and active (32%) smokers groups, other characteristics did not show statistically significant differences. These included the ORR (P=0.5), ECOG performance status (P=0.3), BMI category (P=0.6), tumor type (predominantly NSCLC across all groups), presence of metastasis (P=0.3), high-risk metastasis (P=0.12), type of ICI treatment (P=0.3), line of therapy (P=0.3), LDH levels (P=0.6), CRP levels (P=0.2), NLR (P=0.4), number of ICI doses (P=0.11), incidence of immune-related adverse events (irAEs; P=0.5), type of irAEs (P=0.7) and median follow-up time (P=0.3). Regarding the survival analysis, the OS time was 25.5 months for never-smokers, 63 months for former smokers and 14 months for active smokers (P=0.61).

Immune-related adverse events. Based on the analysis of 180 patients receiving ICI therapy, 26% experienced irAEs overall. When stratified by smoking status, the frequency of any irAE did not differ significantly between never-smokers (31%;

n=14/45), former smokers (22%; n=18/81) and active smokers (28%; n=15/54), with P=0.5. Similarly, the distribution of the specific type of irAE did not show a statistically significant difference across the smoking groups (P=0.15).

Discussion

The present study analyzed the prognostic influence of smoking status in patients with metastatic or advanced solid tumors undergoing ICI therapy. Contrary to the initial hypothesis that smokers might exhibit improved outcomes due to a higher TMB, active smokers demonstrated a reduced OS time compared with both never-smokers and former smokers in the present study. These results align with existing evidence linking active smoking to more aggressive tumor biology, increased therapeutic resistance and poorer clinical outcomes (3).

In the present study, while the univariate analysis results suggested an association between smoking status and OS, this relationship narrowly missed statistical significance. The lack of significance likely reflects the impact of other prognostic factors, such as the baseline performance status and systemic inflammation markers, such as CRP and LDH, which have emerged as independent predictors of survival in previous studies. This suggests that the negative effects of active smoking may be mediated, at least in part, by its interactions with these factors. However, the patient selection in the present study was heavily weighted towards lung and head and neck cancer, which may limit generalizability.

Paradoxical reports of improved outcomes with ICI therapy in smokers (13,23-26) merit careful evaluation.

Table III. Results of univariate and multivariate analyses regarding PFS.

Variable	Value	HR (univariate)	HR (multivariate)
Smoking status, n (%)			
Not active	126 (70.0)	-	-
Active	54 (30.0)	1.26 (95% CI 0.88-1.80, P=0.216)	-
Sex, n (%)			
Male	128 (71.1)	-	-
Female	52 (28.9)	0.69 (95% CI 0.48-1.00, P=0.049)	0.68 (95% CI 0.45-1.03, P=0.071)
Mean age (SD), years	66.6 (10.7)	0.98 (95% CI 0.97-1.00, P=0.026)	0.98 (95% CI 0.96-1.00, P=0.014)
ECOG status, n (%)			
0	41 (24.8)	-	-
1	85 (51.5)	1.00 (95% CI 0.67-1.51, P=0.986)	1.00 (95% CI 0.66-1.52, P=0.983)
2	27 (16.4)	1.76 (95% CI 1.04-2.99, P=0.036)	1.42 (95% CI 0.81-2.49, P=0.217)
≥3	12 (7.3)	5.83 (95% CI 2.60-13.09, P<0.001)	5.55 (95% CI 2.37-12.99, P<0.001)
Metastasis			
No	13 (7.2)	-	-
Yes	167 (92.8)	0.95 (95% CI 0.50-1.80, P=0.867)	-
Mean NLR (SD)	4.6 (3.1)	1.01 (95% CI 0.94-1.08, P=0.797)	-
Mean LDH, U/l (SD)	262.9 (144.9)	1.00 (95% CI 1.00-1.00, P=0.006)	1.00 (95% CI 1.00-1.00, P<0.001)
Mean CRP, U/l (SD)	39.5 (52.2)	1.00 (95% CI 1.00-1.01, P=0.007)	1.00 (95% CI 1.00-1.01, P=0.281)

CI, confidence interval; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; HR, hazard Ratio; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PFS, progression-free survival; SD, standard deviation.

Several meta-analyses and cohort studies have shown that patients with a history of smoking often derive a greater clinical benefit from ICI therapy than never-smokers, particularly in NSCLC (14). This phenomenon is partly attributed to the higher TMB typically observed in smokers, which results in an increased neoantigen load and may enhance immune recognition and the responsiveness to ICIs. For instance, smokers with NSCLC treated with ICIs have demonstrated a longer PFS time and higher response rates than never-smokers, with the most notable effects observed in patients receiving anti-PD-1/PD-L1 monotherapy. Furthermore, the tumor immune microenvironment in smokers is often more inflamed and immunogenic, characterized by the increased infiltration of activated immune cells, further supporting improved responsiveness to ICI therapy (13,25,26). While the present study confirms the detrimental impact of active smoking, it does not entirely refute the hypothesis that a higher TMB in smokers enhances tumor immunogenicity, potentially improving ICI efficacy (26,27). However, the poorer outcomes observed in active smokers in the present study suggest that the negative effects of smoking, such as heightened systemic inflammation, impaired immune function and a greater burden of comorbidities, may outweigh any theoretical benefits of a higher mutational load or higher PD-L1 tumor proportion score (12,26-31). In the present study, biomarkers of systemic inflammation, including CRP, NLR and LDH, emerged as strong independent predictors of a reduced OS time, irrespective of smoking status. These findings imply that the inferior outcomes in active smokers are likely driven, at least in part, by the overriding negative impact of systemic inflammation.

This complex interplay underscores the need for novel therapeutic strategies that can better navigate and modulate the tumor microenvironment. In this context, emerging research into advanced biomaterials offers potential avenues; for instance, nano-biomaterials are being explored for their ability to regulate the tumor microenvironment and enhance immunotherapy (32).

In the present study, the multivariate analysis identified baseline ECOG performance status ≥ 3 and elevated CRP, NLR and LDH levels as the strongest independent predictors of a diminished OS time, irrespective of smoking status. These biomarkers are crucial as they reflect both the functional status of the patient and the presence of systemic inflammation, which are known to drive tumor progression and resistance to therapy. In clinical practice, integrating these parameters into prognostic models could help stratify patients for tailored treatment approaches. Moreover, active smoking can increase the inflammatory environment in tumors and promote tumor progression and therapeutic resistance. A poor ECOG performance status is a well-established marker of overall patient fitness and the capacity to tolerate systemic therapies (33). Similarly, an elevated CRP level, a biomarker of systemic inflammation, correlates with unfavorable outcomes in various malignancies (34).

Although smoking status did not emerge as an independent predictor of survival in the present study, it remains a factor in prognosis and treatment planning. However, a number of patients with cancer struggle to quit due to inadequate psychological and behavioral support within

oncology care. Addressing the emotional and cognitive barriers associated with smoking in patients with cancer is crucial, as psychological distress, fatalistic thinking and nicotine dependence are key factors hindering smoking cessation (35). Additionally, incorporating smoking cessation support into routine oncology care, including regular follow-ups and tailored cessation programs, has been shown to improve cessation rates and significantly enhance overall patient outcomes (36). Providing structured psychological interventions, such as cognitive behavioral therapy and pharmacological treatments, allows for a more patient-centered approach that acknowledges the complex interplay between cancer-related stress and smoking behavior (37). Therefore, integrating comprehensive smoking cessation programs into routine oncology care is essential for improving treatment outcomes and overall patient well-being.

The present study has several limitations that should be acknowledged. Firstly, the heterogeneity of the solid tumor types included, with a notable predominance of lung and head and neck cancer, may limit the generalizability of the findings to other less represented malignancies. Different tumor entities exhibit distinct biological characteristics and immune microenvironments, which may interact variably with the smoking status and ICI efficacy. Secondly, although the outcomes related to ICI therapy were analyzed, the limited number of patients prevented a detailed analysis of the specific ICI regimens. This lack of granularity in treatment specifics could mask differential effects and contribute to the observed variability in outcomes. Thirdly, the categorization of smoking status, while standard, did not capture more nuanced details such as pack-years, duration of smoking or precise time since cessation for former smokers. Such granularity, if available, might reveal more complex dose-dependent or time-dependent effects of smoking on ICI outcomes and could explain some of the inconsistencies noted in the broader literature, especially considering the long-lasting immune alterations potentially induced by smoking. Regarding irAEs, this analysis faces potential limitations, primarily due to possible underreporting, given the retrospective setting. Finally, as a retrospective single-center analysis with a limited number of included patients, the present study is susceptible to inherent biases, including the potential for unmeasured confounding variables and selection bias, despite efforts to control for known prognostic factors. These limitations underscore the need for future prospective studies with more detailed data collection to further elucidate the complex interplay between tumor type, specific ICI regimens, detailed smoking history and clinical outcomes.

In conclusion, the findings of the present study underscore the need for a comprehensive approach to patient evaluation before initiating ICI therapy. Future efforts should focus on developing personalized treatment strategies that account for both tumor characteristics and host factors such as the inflammatory microenvironment. By adopting this comprehensive approach, the full therapeutic potential of ICIs can be fully realized, ultimately improving outcomes in patients with advanced cancer. Moreover, further studies are needed to elucidate mechanisms and optimize cessation strategies.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

CB, CSc, CSe and FB designed the study. CSc, CSe and FB wrote the manuscript. CSc, AP, AF and CSe collected data. CSc and CSe analyzed and interpreted data. All authors read and approved the final manuscript. CSc and CSe confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The study protocol was in line with the Hamburg Hospital Act (Hamburgisches Krankenhausgesetz, HmbKHG), and the Ethics Committee of the Hamburg Chamber of Physicians confirmed that consultation was not required (no. 2025-300686-WF).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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