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Cuperus, J.H.; Kalkhoran, H.A.; Codrington, H.; Visser, L.E.

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Research Paper

Real-world incidence of pneumonitis in different treatment modalities of advanced non-small cell lung carcinoma

Justine H. Cuperus [a,*], Hanieh Abedian Kalkhoran [a,b], Henk Codrington [c], Loes E. Visser [a,d,e]

[a] Department of Pharmacy, Haga Teaching Hospital, The Hague, the Netherlands
[b] Department of Clinical Pharmacy and Toxicology, Leiden University Medical Centre, Leiden, the Netherlands
[c] Department of Pulmonary Diseases – Pulmonic Oncology, Haga Teaching Hospital, The Hague, the Netherlands
[d] Department of Hospital Pharmacy, Erasmus Medical Centre, Rotterdam, the Netherlands
[e] Department of Epidemiology, Erasmus Medical Centre, Rotterdam, the Netherlands

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ABSTRACT

Background: The treatment landscape for non-small cell lung cancer (NSCLC) has evolved with the introduction of immunotherapy, targeted therapy, and combinations with chemotherapy. However, therapy-related pneumonitis (TRP) poses a significant challenge, often leading to treatment discontinuation and respiratory failure. The incidence of TRP is frequently underestimated in clinical trials, and its associated risk factors remain underexplored. This study aimed to investigate the real-world incidence and risk factors for TRP across various NSCLC treatment regimens.

Methods: This retrospective cohort study included patients diagnosed with stage III or IV NSCLC and who started at least one of the 11 predefined systemic anti-cancer treatment regimens (comprising chemotherapy, immunotherapy, or targeted therapy) at Haga Teaching Hospital between January 2016 and January 2024. Clinical data were extracted from Electronic Health Records using text-mining based software. The objective was to determine the incidence rate (IR) per 100 person-years (PY) of grade $\geq$2 TRP requiring systemic corticosteroids across the treatment regimens. Risk factors for TRP were analyzed using Cox proportional hazards models.

Results: A total of 801 treatment regimens were followed on TRP in our cohort of 636 patients. The IRs varied across regimens, with the highest IR observed in patients receiving durvalumab following chemoradiotherapy (CRT) (27.7 per 100 PY). Among CRT regimens, the IR was higher in patients treated with etoposide compared to those receiving pemetrexed (20.5 vs. 8.5 per 100 PY). Pembrolizumab monotherapy exhibited a lower IR compared to its combination with platinum/paclitaxel or platinum/pemetrexed (6.6 vs. 16.6 and 8.9 per 100 PY, respectively). Certain chemotherapy and targeted therapy regimens reported no cases of TRP during the study period. Furthermore, the real-world incidence of TRP was higher than reported in pivotal clinical trials. Identified risk factors for TRP included higher body mass index and radiation fractions.

Conclusion: As NSCLC treatment evolves, addressing TRP risks becomes pivotal for ensuring the best possible patient outcomes. This large-scale real-world study provides valuable insights into the association between NSCLC treatment regimens and TRP, as well as the risk factors of TRP.

1. Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide, accounting for 1.8 million deaths annually [1,2]. Non-small cell lung carcinoma (NSCLC) is the most prevalent subtype (85%) [3]. Treatment options for NSCLC have improved significantly in recent years with the introduction of immunotherapy and targeted therapy alone, or in combination with chemotherapy [4,5]. As a result, the five-year survival rate for NSCLC in the Netherlands has nearly doubled from 18% in 2005–2014 to 27% in 2015–2022 [6]. Despite these advances, therapy-related pneumonitis (TRP) poses a challenge to treatment continuation and patient outcomes.

TRP is a potentially life-threatening inflammatory condition of the lung parenchyma, triggered by treatment-induced lung injury and immune system over-activation. It presents with nonspecific respiratory symptoms such as cough and dyspnoea, along with pulmonary infiltrates

* Corresponding author.
E-mail address: j.cuperus@hagaziekenhuis.nl (J.H. Cuperus).

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on radiographic imaging [7]. Management strategies vary depending on severity, as outlined in the ESMO guidelines. Mild cases are managed with temporary treatment withholding and corticosteroids (e.g., oral prednisolone), whereas severe cases necessitate permanent discontinuation of therapy and administration of high-dose intravenous methylprednisolone or other immunosuppressive agents [8]. However, the efficacy of anti-cancer therapy is reduced by discontinuation of treatment and use of immunosuppressive therapy, probably already with prednisolone at daily doses of 10 mg [9,10].

Unlike other immune-related adverse events, which are often associated with improved responses to immune checkpoint inhibitors (ICIs), the onset of TRP correlates with increased morbidity, reduced survival, and, in some cases, mortality [11–13]. Safety data from randomized controlled trials (RCTs) indicate that TRP leads to treatment discontinuation in 3.1–6.3% of cases and mortality in 0.4–0.8% [14–17]. Notably, the risk of TRP is further elevated with combination therapies, where treatment discontinuation rates due to TRP reach 7.6% [18]. Furthermore, real-world evidence suggests that TRP incidence may be significantly higher than reported in clinical trials [19]. These discrepancies highlight the critical need to study TRP within the context of real-world clinical practice to gain a more comprehensive understanding of its true clinical impact.

Despite previous research, there is limited knowledge about the incidence of TRP for the commonly used different NSCLC treatment regimens. Furthermore, the influence of patient- and disease-specific factors on TRP risk remains inadequately explored. Addressing these gaps is crucial, especially as combination therapies and immunotherapies gain prominence, potentially increasing the incidence of TRP. This study aimed to provide an overview of the real-world incidence and risk factors of TRP in patients with advanced NSCLC receiving systemic anti-cancer treatment. By enhancing our understanding of TRP, we can optimize treatment strategies and reduce its impact on patient outcomes.

2. Methods

2.1. Study population

This retrospective observational cohort study included patients diagnosed with advanced NSCLC (stage III or IV, TNM classification), who received systemic cancer therapy at Haga Teaching Hospital in The Hague, the Netherlands [20]. Patients were eligible if they were aged 18 years or older, had a first Diagnosis Treatment Combination (DTC) code[1] for NSCLC registered between January 1, 2016, and January 1, 2024, and had received at least one of the specified treatments listed in Table 1.

2.2. Data collection

Patient, disease, and therapy variables, and clinical outcomes were extracted in a pseudonymised manner from Electronic Health Records (EHR; HiX v6.3, Chipsoft B.V., Amsterdam, The Netherlands) using natural language processing and text-mining based software CTcue (v4.8.1, IQVIA B.V., Amsterdam, The Netherlands). Additional information on carboplatin was collected from the hospital's Chemotherapy Management System (CareFlow Medicines Management, Basildon, United Kingdom) (Table S2). Data were collected from the first DTC code for NSCLC until the last follow-up date, which was determined by the date of the last clinic visit, death, or January 1, 2024, whichever occurred first.

[1] This code is used for hospital reimbursement in the Netherlands.

2.3. Outcomes

The primary outcome was the incidence of TRP, defined as symptomatic pneumonitis, occurring after the start of NSCLC systemic treatment and requiring systemic immunosuppressive therapy, defined as Grade $\geq$2 (according to the Common Terminology Criteria for Adverse Events (CTCAE) scale, Table S4). Diagnosis was based primarily on the clinical assessments of the treating physicians, incorporating reported symptoms, radiological findings, laboratory results, and the exclusion of alternative causes such as infection or disease progression. In cases of diagnostic uncertainty, the findings were reassessed by a thoracic oncologist (H.C.). The data collected and workflow for the diagnosis of TRP are summarized in Table S3 and Fig. S1. The secondary outcome was determinants of TRP. The potential determinants analyzed are listed in Table S2. Additionally, the incidence of TRP observed in this real-world cohort was compared with incidences reported in pivotal RCTs per treatment regimen.

2.4. Treatment regimens

The treatment regimens of interest are listed in Table 1, based on the regional treatment guidelines for NSCLC [21]. Stage III patients typically receive chemoradiotherapy (CRT) followed by adjuvant durvalumab. Stage IV patients receive immune checkpoint inhibitors (ICIs), as monotherapy or in combination with chemotherapy, or epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), with chemotherapy monotherapy reserved for second line.

Follow-up for each treatment regimen was defined as the period from the index date (i.e., initiation of the NSCLC treatment regimen) until the first occurrence of TRP, last follow-up date, one year after the last administration of treatment, or initiation of a subsequent NSCLC treatment regimen. Patients who started a subsequent treatment regimen during the follow-up, without developing TRP during the initial regimen, were followed separately for each regimen, as detailed in Fig. S2.

2.5. Validation

Data collection was performed using a semi-automated approach, with validation procedures implemented to assess the accuracy, completeness, and reliability of the extracted data. For structured data, validation in CTcue was automated using predefined search queries. Unstructured data was manually validated through contextual verification by reviewing 10% of records from selected EHR sections within the CTcue results interface. However, for all TRP results, which consisted entirely of unstructured data, all records underwent full manual validation to ensure accuracy. Additionally, CTcue generated a confidence score for each unstructured data query, indicating the system's level of confidence regarding text processing. Comprehensive details on CTcue's architecture and validation process are described by Van Laar et al. [22].

2.6. Statistical analyses

Demographic, disease-related, and therapy-related characteristics were summarized. Categorical variables were presented as counts and percentages, and continuous variables were reported as median with interquartile range (IQR). For each treatment regimen, the incidence rate (IR) of TRP was calculated as the number of TRP cases per 100 person-years (PY), and the median time to TRP onset was calculated in months [23,24].

Risk factors for TRP during NSCLC treatment, were identified using univariable and multivariable Cox proportional hazards regression models, the effect sizes were reported as hazard ratios (HR) [25,26]. The total person-time at risk for the calculation of IRs and HRs was the defined follow-up period in section 2.4. Results were reported with 95%

Table 1
NSCLC treatment regimens.

	Group	Regimens	Therapeutic Agents
Stage III	CRT	Etop/RT Peme/RT	Platinum, etoposide and radiotherapy Platinum, pemetrexed and radiotherapy
	ICI adjuvant	Durv	Durvalumab adjuvant chemoradiotherapy
Stage IV	ICI monotherapy	Atez Nivo Pemb	Atezolizumab Nivolumab, or combined with ipilimumab Pembrolizumab
	ICI combination	Pemb/Peme Pemb/Pacl	Platinum, pemetrexed and pembrolizumab Platinum, paclitaxel and pembrolizumab
	CT monotherapy	Doce Gemc	Docetaxel Gemcitabine
	EGFR-TKI	TKI	Afatinib, erlotinib, or osimertinib

Abbreviations: *CRT* chemoradiotherapy, *platinum* cisplatin or carboplatin, *radiotherapy* sequential or concurrent, *ICI* immune checkpoint inhibitors (immunotherapy), *CT* chemotherapy, *EGFR-TKI* epidermal growth factor receptor tyrosine kinase inhibitor (targeted therapy).

confidence intervals (CI), and a P-value of < 0.05 was considered statistically significant. Variables included in the multivariable Cox model comprised baseline characteristics (age and sex), therapy regimens associated with the highest IRs, and variables and interaction terms that reached statistical significance in univariable analyses. The number of radiation fractions was counted from one year prior to the initiation of the therapy regimen until the development of TRP, or the end of therapy regimen.

Descriptive comparisons were conducted between the proportion of TRP (as percentages) observed in the real-world cohort and that reported in RCTs.

Data management and statistical analysis were performed using R Statistical Software (v4.3.1, R Core Team, Vienna, Austria).

3. Results

3.1. Patient and disease characteristics

A cohort of 636 patients diagnosed with advanced NSCLC and who started one of the systemic treatment regimens was identified (Fig. 1).

The clinical characteristics of the study cohort are summarized in Table 2. Patient- and disease-related characteristics were assessed at the index date. The median age of patients was 67 years [IQR 60–72], and the majority were male (53.5%). Most patients had a body mass index (BMI) classified as normal (40.3%) or overweight (39.9%), and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1 (77.3%). The median smoking exposure was 32 pack-years [IQR 20–45], with 86.6% identified as current or former smokers. Common comorbidities included chronic obstructive pulmonary disease (COPD, 39.2%) and asthma (14.3%). Regarding disease characteristics, adenocarcinoma was the predominant histological subtype (70.0%), and the majority of patients presented with stage IV disease (70.9%).

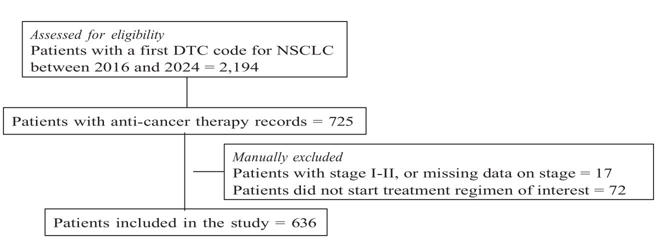


Fig. 1. Cohort selection process.

3.2. Pneumonitis incidence

A total of 801 treatments were followed, and 66 cases of TRP were identified. The IRs per 100 PY and the median time to TRP onset for the different treatment regimens are presented in Table 3. The IRs varied across regimens. Among ICI regimens, the highest rate was observed in patients receiving adjuvant durvalumab (27.7/100 PY; CI 16.7–43.3), followed by pembrolizumab in combination with paclitaxel (16.6/100 PY; CI 5.4–38.8) and with pemetrexed (8.9/100 PY, CI 4.6–15.6). Pembrolizumab monotherapy was associated with a lower IR (6.6/100 PY; CI 3.0–12.5). No TRP cases were observed during the study period for chemotherapy (e.g., docetaxel, gemcitabine) and targeted therapy regimens (e.g., afatinib, erlotinib, osimertinib). The median time to TRP onset ranged from 3 to 5 months across the different treatment regimens. Among the CRT regimens, the IR was higher in the regimen with etoposide (20.5/100 PY; CI 10.9–35.0) compared to the regimen with pemetrexed (8.5/100 PY; CI 1.8–24.8). Further analysis showed that, among patients receiving etoposide, 87 (91.6%) underwent concurrent CRT (cCRT), whereas 8 (8.4%) received sequential CRT (sCRT). Among patients treated with pemetrexed, 56 (73.7%) received cCRT, and 20 (26.3%) received sCRT. The IR of TRP in the cCRT regimen was 20.6/100 PY (CI 11.8–33.5), while no cases of TRP were observed among patients receiving sCRT. In the cCRT regimen, the median time to TRP onset was 4.5 months.

3.3. Risk factors

The results of the univariable and multivariable Cox proportional hazards regression analyses for variables associated with TRP are shown in Table 4. In univariable analysis, a higher BMI was modestly but significantly associated with increased risk of TRP (HR 1.05; CI 1.00–1.10; p = 0.038). The number of radiation fractions during the regimens was also associated with TRP risk: 1–24 fractions (HR 2.18; CI 1.04–4.59; p = 0.040) and ≥24 fractions (HR 2.74; CI 1.61–4.67; p = < 0.001) compared with no radiation exposure. To account for regimen-specific differences, ICI regimens and radiation fractions were included in the multivariable models. In multivariable analysis, higher BMI remained significantly associated with an increased TRP risk (HR 1.06; CI 1.01–1.11; p = 0.023). The number of radiation fractions remained associated with TRP risk, with HRs of 2.46 (CI 1.14–5.27; p = 0.021) for 1–24 fractions and 2.78 (CI 1.31–5.87; p = 0.008) for ≥24 fractions. The adjuvant ICI regimen therapy was associated with a higher risk of TRP compared to other regimens (HR 2.62; CI 1.27–5.42; p = 0.009). In addition, ICI combination regimens were associated with an increased TRP risk (HR 2.24; CI 1.04–4.82; p = 0.040).

Table 2
Clinical characteristics of cohort.

Characteristic	Total (n = 636)
Patient characteristics	
Age, years, median [IQR]	67 [60, 72]
Sex, n (%)	
Female	296 (46.5)
BMI, kg/m^2, median [IQR]	24.60 [22.0, 27.8]
BMI, n (%)	
Overweight	254 (39.9)
Normal	256 (40.3)
Underweight	33 (5.2)
Missing	93 (14.6)
ECOG PS, n (%)	
0/1	492 (77.3)
≥2	25 (3.9)
Missing	119 (18.7)
Comorbidity, n (%)	
COPD	249 (39.2)
Asthma	91 (14.3)
Pack-years, median [IQR]	32 [20, 46]
Disease-related characteristics	
Histology, n (%)	
Adenocarcinoma	445 (70.0)
Squamous cell carcinoma	122 (19.2)
Large cell carcinoma	20 (3.1)
Missing	49 (7.7)
Stage, n (%)	
III	185 (29.1)
IV	451 (70.9)
Therapy-related characteristics	
CRT, n (%)	
Platinum/etoposide	95 (14.9)
Platinum/pemetrexed	76 (11.9)
ICI adjuvant, n (%)	
Durvalumab	79 (12.4)
ICI monotherapy, n (%)	
Atezolizumab	34 (5.3)
Nivolumab	46 (7.2)
Pembrolizumab	133 (20.9)
ICI combination, n (%)	
Platinum/paclitaxel/pembrolizumab	48 (7.5)
Platinum/pemetrexed/pembrolizumab	153 (24.1)
CT, n (%)	
Docetaxel	34 (5.3)
Gemcitabine	54 (8.5)
EGFR-TKI, n (%)	
Afatinib	11 (1.7)
Erlotinib	7 (1.1)
Osimertinib	31 (4.9)
Radiotherapy, n (%)	
Concurrent CRT	143 (22.5)
Sequential CRT	28 (4.4)
RF count, median [IQR]	24 [10,30]

The patient- and disease-related characteristics are at index date.
Abbreviations: *n* number of patients, *IQR* interquartile range, *BMI* body mass index; *Overweight* ≥25 kg/m^2, *Normal* 18.5–25 kg/m^2, *Underweight* < 18.5 kg/m^2, *COPD* chronic obstructive pulmonary disease, *ECOG PS* Eastern Cooperative Oncology Group performance status, *CRT* chemoradiotherapy, *Platinum* cisplatin or carboplatin, *ICI* immune checkpoint inhibitors, *Nivolumab* monotherapy or in combination with ipilimumab, *CT* chemotherapy, *EGFR-TKI* epidermal growth factor receptor tyrosine kinase inhibitor, *RF* radiotherapy fractions.

Other variables, including age, sex, pack-years, ECOG PS, comorbidities, histology, and ICI monotherapy were not significantly associated with risk of TRP in either univariable or multivariable analyses. No significant interactions between variables were identified.

3.4. Clinical trials

The incidence of TRP observed in our cohort exceeded that reported in pivotal RCTs, as summarized in Table 5. For instance, in the PACIFIC trial, 10.7% of patients developed TRP during durvalumab treatment post-CRT, compared with 24.1% in our study [14]. Similarly, the KEYNOTE-189 trial reported an all-grade pneumonitis incidence of 4.4%, whereas 7.8% of patients receiving platinum, pemetrexed, and pembrolizumab in our cohort developed TRP (grade ≥2) [16]. This trend of higher observed incidence was consistent across most regimens, with the exception of certain CRT and TKI-regimens, where RCT-reported rates exceeded those in our study [27–31].

4. Discussion

In this retrospective observational cohort study, we investigated the real-world incidence and risk factors for TRP in patients with advanced NSCLC receiving systemic therapies in the Netherlands. Our findings reinforce that TRP remains a clinically significant complication, particularly in the context of ICIs and CRT-based regimens. The highest IR of TRP was observed in patients receiving adjuvant durvalumab following CRT. This may partly reflect delayed onset of radiation-induced pneumonitis, consistent with patterns observed in PACIFIC trial [14]. Additionally, the heightened IR with durvalumab may reflect the cumulative risk of multiple treatment modalities administered in rapid succession [32]. Patients receiving etoposide-based CRT had higher TRP rates than those on pemetrexed-based CRT, likely due to a higher proportion receiving cCRT, which is known to carry greater pneumonitis risk compared to sCRT [33].

Furthermore, pembrolizumab combined with chemotherapy was associated with a higher TRP IR than pembrolizumab monotherapy, with the highest rate observed in paclitaxel-based regimen. This aligns with prior evidence suggesting the synergistic immunostimulatory effect of taxanes with ICI, thereby increasing pneumonitis risk [34]. Notably, an increase in TRP incidence was observed after 2019, coinciding with the broader implementation of ICIs, underscoring their pivotal role in TRP development. Certain regimens, such as docetaxel, gemcitabine, and TKIs, had no reported TRP cases during the study period. While this may suggest a more favorable safety profile, these findings should be interpreted cautiously given the limited sample sizes and exposure durations. Moreover, prior trials have reported pneumonitis with TKIs, emphasizing the need for ongoing vigilance [18,27,28].

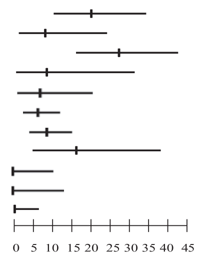
Compared to RCTs, our study found a higher overall incidence of TRP. This disparity is likely due to the broader, more heterogeneous patient population in real-world settings and less stringent eligibility criteria. Conversely, our incidence was slightly lower than reported in some prior real-world studies, possibly due to fewer patients receiving ICI combination regimens and the exclusion of grade 1 pneumonitis in our study [13,19]. The median time to TRP onset in our cohort was slightly delayed compared to RCTs, but consistent with real-world evidence suggesting later presentation and potentially delayed recognition in routine clinical practice [13,35,36]. In the nivolumab regimen, the median time to TRP onset appeared longer compared to other regimens. This was primarily driven by one patient with very late-onset pneumonitis after more than 50 cycles of treatment. Therefore, this finding should be interpreted with caution. These findings underscore the importance of long-term surveillance and improved diagnostic vigilance.

Univariable and multivariable analyses were performed on a combined dataset including all treatment regimens. Stratified analysis by treatment regimen was constrained by sample size. However, it is conceivable that the relevance of these factors varies for each specific treatment regimen. For instance, radiation fractions is especially relevant in CRT regimens, and for ICI regimens, prior study have indicated that females may be at a higher risk of TRP [19]. By including ICI regimens and radiation fractions in the multivariable model, we attempted to account for such variations. Nevertheless, treatment selection bias may exist, as clinicians may opt for less intensive therapies in patients with risk factors, potentially underestimating true TRP risk.

Our multivariable analysis identified higher BMI, radiation fractions,

Table 3
Incidence rates and time to onset of TRP.

Regimen	IR [CI]	Time to TRP (months) [IQR]
Etop/RT	20.5 [10.9–35.0]	4.4 [3.4–5.2]
Peme/RT	8.5 [1.8–24.8]	4.7 [2.4–6.3]
Durv	27.7 [16.7–43.3]	3.1 [1.1–4.6]
Atez	8.9 [1.1–32.0]	3.1 [1.7–4.4]
Nivo	7.2 [1.5–21.0]	13.3 [7.5–34.9]
Pemb	6.6 [3.0–12.5]	5.2 [0.6–9.5]
Pemb/Peme	8.9 [4.6–15.6]	4.5 [2.1–8.5]
Pemb/Pacl	16.6 [5.4–38.8]	3.1 [2.2–12.9]
Doce	0 [0–10.6]	-
Gemc	0 [0–13.4]	-
TKI	0 [0–6.5]	-



Incidence rates per 100 person-years and median time in months to onset of TRP for different treatment regimens.
Abbreviations: *TRP* therapy-related pneumonitis (grade ≥2), *IR* incidence rate, *CI* 95% confidence interval, *IQR* interquartile range.

Table 4
Results of univariable and multivariable Cox proportional hazards regression analysis for factors associated with TRP.

Variables		Mean (SD) or n (%)	Univariable			Multivariable		
			HR	CI	p	HR	CI	p
Age		65.1 (9.3)	1.01	0.98–1.03	0.585	1.01	0.98–1.04	0.520
Sex	Female	364 (45.4)	1	Reference		1	Reference	
	Male	437 (54.6)	1.47	0.90–2.42	0.127	1.36	0.82–2.25	0.236
Body Mass Index		25.0 (4.6)	1.05	1.00–1.10	0.038	1.06	1.01–1.11	0.023
ECOG PS	0/1	624 (96.1)	1	Reference		–	–	
	≥2	25 (3.9)	0.51	0.07–3.73	0.511	–	–	
COPD	No	477 (59.6)	1	Reference		–	–	
	Yes	324 (40.4)	1.16	0.71–1.89	0.547	–	–	
Asthma	No	687 (85.8)	1	Reference		–	–	
	Yes	114 (14.2)	1.45	0.79–2.65	0.235	–	–	
Pack-years		32.5 (19.7)	0.99	0.97–1.01	0.268	–	–	
Histology	Adenocarcinoma	554 (74.8)	1	Reference		–	–	
	Squamous cell carcinoma	164 (22.1)	0.69	0.34–1.40	0.302	–	–	
	Large cell carcinoma	23 (3.1)	1.03	0.25–4.23	0.969	–	–	
Radiation fractions	0	456 (56.9)	1	Reference		1	Reference	
	1–24	100 (12.5)	2.18	1.04–4.59	0.040	2.46	1.14–5.27	0.021
	≥24	245 (30.6)	2.74	1.61–4.67	<.001	2.78	1.31–5.87	0.008
ICI adjuvant	No	722 (90.1)	–	–		1	Reference	
	Yes	79 (9.9)	–	–		2.62	1.27–5.42	0.009
ICI monotherapy	No	588 (73.4)	–	–		1	Reference	
	Yes	213 (26.6)	–	–		1.69	0.77–3.70	0.189
ICI combination	No	600 (74.9)	–	–		1	Reference	
	Yes	201 (25.1)	–	–		2.24	1.04–4.82	0.040

Abbreviations: *SD* standard deviation, *n* number of patients (patients are followed twice, if not developed TRP in the first treatment regimen and transition to a subsequent treatment regimen), *CI* 95 % confidence interval, *HR* hazard ratio, *ECOG PS* Eastern Cooperative Oncology Group performance status, *COPD* chronic obstructive pulmonary disorder, *Comorbidity* COPD or/and asthma, *p* p-value.

Table 5
TRP incidence in our study versus pivotal RCT.

Regimen	This study	Randomized controlled trial	
	TRP, % (n)	TRP, % (n)	Study
Etop/RT	13.7 (13)	18.9 (18)	NCT01494558
Peme/RT	3.9 (3)	17.0 (48)*	PROCLAIM
Durv	24.1 (19)	10.7 (51)	PACIFIC
Atez	5.9 (2)	1.5 (45)	NCT03191786
Nivo	6.5 (3)	2.8 (8)*	CheckMate-017, 057
Pemb	6.8 (9)	5.8 (9)*	KEYNOTE-024
Pemb/Peme	7.8 (12)	4.4 (18)*	KEYNOTE-189
Pemb/Pacl	10.4 (5)	8.3 (23)*	KEYNOTE-407
Doce	0	1.9 (6)	KEYNOTE-010
Gemc	0	0.7 (3)*	SQUIRE
TKI	0	1–6.7 (17)	FLAURA, LUX-Lung, DELTA

[*] Any grade pneumonitis.
Abbreviations: *TRP* therapy-related pneumonitis (grade ≥2), *n* number of patients.

and specific ICI regimens as significant risk factors for TRP. While BMI was modelled as a continuous variable, it is plausible that both underweight and overweight patients carry distinct risks compared to those of normal weight. Prior research has also reported higher TRP risk in overweight individuals, potentially related to pharmacokinetic factors [37]. However, underweight patients constituted only 6% of our cohort, limiting our ability to analyze this subgroup separately. Chemotherapy and ICI dosages are typically standardized by body surface area but were not explored. Radiation fraction count was a strong predictor of TRP. Notably, the group receiving sCRT did not develop any cases of pneumonitis; however, they also received fewer radiation fractions and was smaller in size compared to the cCRT group. This suggests that the observed difference in pneumonitis incidence could potentially be attributed to the radiation fraction count rather than the timing of RT administration. Moreover, the radiation dose for CRT was not further explored, despite its known impact on pneumonitis risk [38]. Further investigation is needed to confirm this assumption conclusively.

Although our study focused on TRP incidence and risk factors, the potential impact of TRP on therapeutic outcomes was not evaluated. Prior studies have reported that TRP can lead to treatment interruptions, dose reductions, or premature discontinuation of ICI therapy, which may compromise overall treatment efficacy and patient survival [11,39]. Severe cases of pneumonitis may also require prolonged corticosteroid use, increasing the risk of infections and other complications. Some evidence suggests that the occurrence of immune-related adverse events may correlate with improved ICI efficacy. Future research should aim to clarify these associations and explore whether early recognition and optimized management of TRP can mitigate negative impacts on clinical outcomes.

While this study offers valuable insights, it is crucial to acknowledge its limitations. First, its retrospective nature and reliance on EHRs may have led to underreporting or incomplete documentation of patient and disease characteristics, and TRP. Thereby, the absence of a standardized diagnostic framework for TRP complicates case ascertainment. Although radiological and clinical criteria were used, exclusion of borderline or uncertain cases, and grade 1 cases, may have resulted in underreporting the true incidence of TRP. Second, dexamethasone use during CRT and chemo-immunotherapy was not excluded; while corticosteroids can mitigate pneumonitis symptoms, their brief use for anti-emetic prophylaxis likely had minimal influence on TRP incidence [40]. Finally, our heterogeneous population receiving various treatment regimens and single-center setting may limit generalizability.

Despite these limitations, this study provides valuable insights into TRP incidence and associated factors in real-world clinical settings. Further research is needed to develop predictive models and identify biomarkers that can support personalized treatment strategies. Additionally, expanding TRP research into early-stage NSCLC and tumor type – where TRP has also been reported during ICI, albeit at lower incidences – is warranted [39]. Ultimately, routine consideration of TRP risk, especially in ICI- and CRT-based regimens, is essential for informed treatment planning and improved patient outcomes.

5. Conclusion

Pneumonitis remains a clinically significant and potentially serious adverse event in patients with advanced NSCLC receiving systemic therapy. This retrospective observational cohort study provides real-world data on the incidence and risk factors of TRP across commonly used treatment regimens. The findings reveal considerable variability in TRP risk, with the highest rates observed in ICI- and radiation-based therapies. This highlights the need for individualized risk assessment, personalized treatment planning and vigilant clinical monitoring.

Further research is needed to refine risk stratification, identify predictive biomarkers, and elucidate the pathobiology of TRP. The development of predictive models and decision-support tools will be critical to advancing personalized treatment strategies. Improved detection and management of TRP are essential for improving treatment adherence, and enhancing both clinical outcomes and quality of life for patients with NSCLC.

Ethics statement

The local Medical Ethical Review Committee (METC Leiden Den Haag Delft) granted a waiver for obtaining informed consent. This research was approved by the Board of Directors of Haga Teaching Hospital. Patients who explicitly opted out of sharing their data for research purposes were excluded from the study.

Data availability

All data generated during this study are stored on the Haga Teaching Hospital network and are available upon request.

CRediT authorship contribution statement

Justine H. Cuperus: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Hanieh Abedian Kalkhoran:** Writing – review & editing, Validation, Supervision. **Henk Codrington:** Writing – review & editing, Validation, Data curation. **Loes E. Visser:** Writing – review & editing, Validation, Supervision.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2025.108744.

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