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ORIGINAL RESEARCH

Incidence and Risk Factors of Pneumonitis in Patients with Non-Small Cell Lung Cancer: An Observational Analysis of Real-World Data

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ABSTRACT

Introduction: The incidence of pneumonitis, a treatment-related adverse event (AE) in non-small cell lung cancer (NSCLC) patients, has been studied in the United States mostly through clinical trials and retrospective chart reviews. Few analyses of real-world data have been published. This study of a large nationally representative health records database estimated the incidence and predictors of pneumonitis among treated NSCLC patients between 2008 and 2018.

Methods: The Optum® electronic health records (EHR) database includes data on over 80 million patients from more than 50 healthcare plans. The cohort of primary NSCLC patients was identified using ICD-9/10 codes. Natural language processing of unstructured data from physicians' notes facilitated extraction of biomarker (epidermal growth factor receptor [EGFR] and programmed death ligand-1 [PD-L1]) status. Cumulative incidence was estimated as the proportion with pneumonitis overall, by clinical characteristics, and line of therapy (LOT) after diagnosis and treatment. Univariate analysis of incidence rates (cases/1000 person-years) enabled the identification of significant predictors of risk. Competing risk regression identified predictors of pneumonitis.

Results: The cohort included 81,628 patients. Overall, 19.0% developed pneumonitis during any LOT, with a cumulative incidence of 33.7% and 17.0% for patients with a prior history of pneumonitis and those without, respectively. Univariate analyses revealed several factors associated with pneumonitis ($p < 0.05$). While factors varied between LOTs, common factors included male gender, squamous histology, history of diabetes or pneumonitis, EGFR-negative status, monotherapy immunomodulatory drugs, or history of radiation therapy. Multivariable competing risk regression showed that male gender, history of pneumonitis, EGFR-negative status, use of other targeted therapies, use of immunomodulatory drugs, and history of radiation therapy predicted pneumonitis.

Conclusion: Pneumonitis is significantly associated with NSCLC treatment. Knowledge of its predictors identified in this study may help devise strategies to mitigate its impact, enhancing treatment adherence and improving outcomes.

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PLAIN LANGUAGE SUMMARY

Pneumonitis is a side effect of non-small cell lung cancer (NSCLC) treatment. Real-world data on its incidence in the United States is not extensive. In this study, the Optum® electronic health records database with data on over 80 million patients from more than 50 healthcare plans across the United States was used to estimate the incidence and predictors of pneumonitis in NSCLC patients treated between 2008 and 2018. A total of 81,628 NSCLC patients were identified using disease-specific codes. Physicians' notes in their health records were subjected to natural language processing to identify presence of epidermal growth factor receptor (EGFR) and programmed death ligand-1 (PD-L1) receptors in tumors. Proportions of patients with pneumonitis overall, by clinical characteristics, and line of therapy (LOT) were calculated. Univariate analysis of incidence (cases per 1000 person-years) a multivariable competing risk regression helped identify risk predictors. Overall, 19.0% of patients developed pneumonitis during any LOT. Incidence was 33.7% and 17.0% in patients with and without prior pneumonitis, respectively. Univariate analysis revealed factors associated with pneumonitis, including male gender, squamous histology, history of diabetes or pneumonitis, EGFR-negative status, monotherapy immunomodulatory drugs, or history of radiation therapy. Multivariable competing risks regression analysis showed that male gender, history of pneumonitis, EGFR-negative status, use of other targeted therapies, use of immunomodulatory drugs, and history of radiation therapy were significantly associated with pneumonitis. Pneumonitis is significantly associated with NSCLC treatment. Knowledge of its predictors may help design interventions to lessen its impact, promoting compliance with treatment and improving outcomes.

Keywords: Incidence; Non-small cell lung cancer; NSCLC; Pneumonitis; Predictors; Real-world data

Key Summary Points
Why carry out this study?
Lung cancer ranks highest in mortality of all cancers in the United States.
Pneumonitis is a potentially serious side effect of non-small–cell lung cancer (NSCLC) treatment that may lead to treatment discontinuation.
The objective was to estimate the cumulative incidence and incidence rates, and identify predictors of treatment-related pneumonitis in NSCLC patients.
What was learned from the study?
Nineteen percent of patients developed pneumonitis over the course of their NSCLC treatment, with male gender, history of pneumonitis, use of other targeted therapies, use of immunomodulatory drugs, and history of radiation therapy all predicting pneumonitis.
Awareness of the pneumonitis predictors identified in this study may help clinicians devise strategies to mitigate the impact of pneumonitis, enhance treatment adherence, and improve outcomes.

DIGITAL FEATURES

This article is published with digital features, including a summary slide and plain language summary, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.14333708.

INTRODUCTION

Cancer of the lung ranks second among all cancer types in the United States in terms of incidence and first in terms of attributable deaths, with estimates indicating that this cancer type will account for 235,760 new cases and 131,880 deaths in 2021 [1]. An estimated 57% of patients with lung cancer have metastases at diagnosis, with a 5-year relative survival rate in such patients of only 5% [2]. A majority (85%) of all lung cancer cases are of the non-small cell lung cancer (NSCLC) histologic group, with squamous cell carcinoma and adenocarcinoma being the predominant histologic subtypes of NSCLC [3].

Treatment of NSCLC has evolved significantly in recent years. The approval of targeted therapies including third-generation tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs) has led to improved long-term survival, relegating conventional chemotherapy to a secondary role [4, 5]. However, these targeted therapies are associated with a potentially fatal treatment-induced adverse event (AE), pneumonitis, which has been documented in patients treated with programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) ICIs [6–9], epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) [10–12], and anaplastic lymphoma kinase (ALK) inhibitors [13]. Symptoms typically associated with pneumonitis resulting from the use of targeted NSCLC therapies include cough, dyspnea, fever, chest pain, and hypoxia, accompanied by pulmonary infiltrates that are evident in chest computer tomography (CT) images [14, 15]. Although patients usually respond to oral corticosteroids, some may develop significant dyspnea requiring the use of supplemental oxygen, discontinuation of NSCLC therapy, or intravenous corticosteroids and additional immunosuppressive agents (e.g., infliximab, cyclophosphamide, or mycophenolate mofetil) [14–16]. While rare, high-grade (grade 3/4) pneumonitis is associated with significant morbidity and mortality in a small proportion (1%) of those affected [14, 15, 17]. Guidelines issued by the American Society of Clinical Oncology (ASCO) recommend permanent discontinuation of NSCLC therapy in patients with severe pneumonitis (grades 3 and 4) [18], leading to cessation of potentially beneficial treatment.

To date, studies using real-world data on NSCLC patients have focused on subgroups of interest such as those receiving a PD-L1 inhibitor [19–21], patients with stage III NSCLC [22], or, more recently, efforts evaluating the reliability of real-world endpoints [23–25]. We designed a study to examine an important safety concern among individuals diagnosed with NSCLC, which may compromise a patient's ability to complete the prescribed treatment. Here, we estimate the cumulative incidence and incidence rates, and identify predictors of treatment-related pneumonitis in NSCLC patients across all disease stages who had received currently approved therapies from a large and representative real-world data set in the United States.

METHODS

Data Source

The data analyzed were obtained from the Optum® electronic health records (EHR) database [26]. This database contains records from approximately 140,000 physicians at over 700 hospitals, and 7000 clinics across more than 80 integrated delivery networks (IDNs) in the United States [27]. De-identified information on demographic and socioeconomic categories, coded diagnoses and procedures, prescribed medications, laboratory results, and clinical administrative data is available for > 80 million patients from diverse settings (inpatient, outpatient, and ambulatory) across all census regions in the United States [27]. The information does not include any identifiable information as defined by the Health Insurance Portability and Accountability Act (HIPAA) of 1996 [28], eliminating the need for institutional review board (IRB) approval or waiver [29].

Optum's® proprietary natural language processing (NLP)-based data are used to identify concepts that may not be captured by

International Classification of Diseases (ICD) or procedure codes, and complements conventional data elements captured in EHR data relating to diagnosis, drugs, procedures, laboratory test results, and patient characteristics. The NLP concepts are identified and created based on broad topics such as Medications, Signs, Disease and Symptoms (SDS), Measurements, and Observations, and are harvested from the notes fields within the electronic medical records. The data used for development of each NLP concept is de-identified and accuracy is verified through a series of quality assurance steps prior to release for use. Each NLP concept included in the data is associated with a unique subject record and a date of observation, allowing longitudinal tracking of concepts such as "non-small cell lung cancer" or "pneumonitis" over time.

Cohort Assembly

The study cohort was identified using ≥ 1 primary lung cancer diagnosis code (ICD-9-CM: 162, ICD-10-CM: C33, C34), and no mention of small cell lung cancer (SCLC) in SDS data, ≥ 1 mention of NSCLC in SDS data or core NSCLC drug use, first active date ≥ 12 months prior to index lung cancer diagnosis date ("index date"), index date after January 1, 2008, no lung surgery or other cancer diagnosis during the 12-month period prior to the index date, and age ≥ 18 years on the index date. Core NSCLC drugs considered for the inclusion criteria were platinum- and non-platinum–based chemotherapies, ICIs (alone or in combination), EGFR-TKIs, and other targeted therapies (Table 1).

Lines of Treatment

Lines of therapy (LOT) for each patient were established using business rules centered on (1) identifying continuous periods of drug use, (2) establishing concurrent use of individual drugs and concatenating such drugs into a treatment regimen, and (3) earmarking periods of use of distinct regimens as LOTs. The drugs considered for this analysis are listed in Table 1 and

Table 1 Components of the lines of treatment and definitions of treatment categories for the competing risks regression analyses

Treatment categories for construction of LOTs	
Drug class	Therapeutic agents
Platinum-based chemotherapy	Carboplatin and cisplatin
Non-platinum–based chemotherapy	Docetaxel, gemcitabine, nab-paclitaxel, paclitaxel, pemetrexed, or vinorelbine
ICI (alone or in combination)	Nivolumab, pembrolizumab, atezolizumab, or durvalumab
TKI	Afatinib, erlotinib, gefitinib, osimertinib, alectinib, brigatinib, cabozantinib, ceritinib, crizotinib, nintedanib, or vandetanib
Other targeted therapies	Bevacizumab, dabrafenib, necitumumab, ramucirumab, trametinib, or ado-trastuzumab
Treatment categories for the competing risks regression analyses	
Category	Definition of category
Any ICI monotherapy	Regimen contains only one drug from among nivolumab, pembrolizumab, atezolizumab, or durvalumab
Any ICI combination therapy	Regimen contains at least two drugs, with nivolumab, pembrolizumab, atezolizumab, or durvalumab being one of the drugs in the regimen
EGFR-TKI therapy	Regimen contains at least one EGFR-TKI, and afatinib, erlotinib, gefitinib, osimertinib, alectinib, brigatinib, cabozantinib, ceritinib, crizotinib, nintedanib, or vandetanib is one of the drugs in the regimen

Table 1 continued

Treatment categories for construction of LOTs	
Other targeted therapy	Regimen contains at least one drug, and bevacizumab, dabrafenib, necitumumab, ramucirumab, trametinib, or ado-trastuzumab is one of the drugs in the regimen
Platinum-based chemotherapy	Regimen contains at least one drug, and carboplatin or cisplatin is one of the drugs in the regimen
Non-platinum–based chemotherapy	Regimen contains at least one drug, and docetaxel, gemcitabine, nab-paclitaxel, paclitaxel, pemetrexed, or vinorelbine is one of the drugs in the regimen

EGFR epidermal growth factor receptor; *ICI* immune checkpoint inhibitor; *LOT* line of therapy; *NSCLC* non-small cell lung cancer; *SCLC* small cell lung cancer; *SDS* signs, diseases, and symptoms; *TKI* tyrosine kinase inhibitor

comprise both chemotherapies and targeted agents (including EGFR-TKIs and ICIs).

Analyses Performed

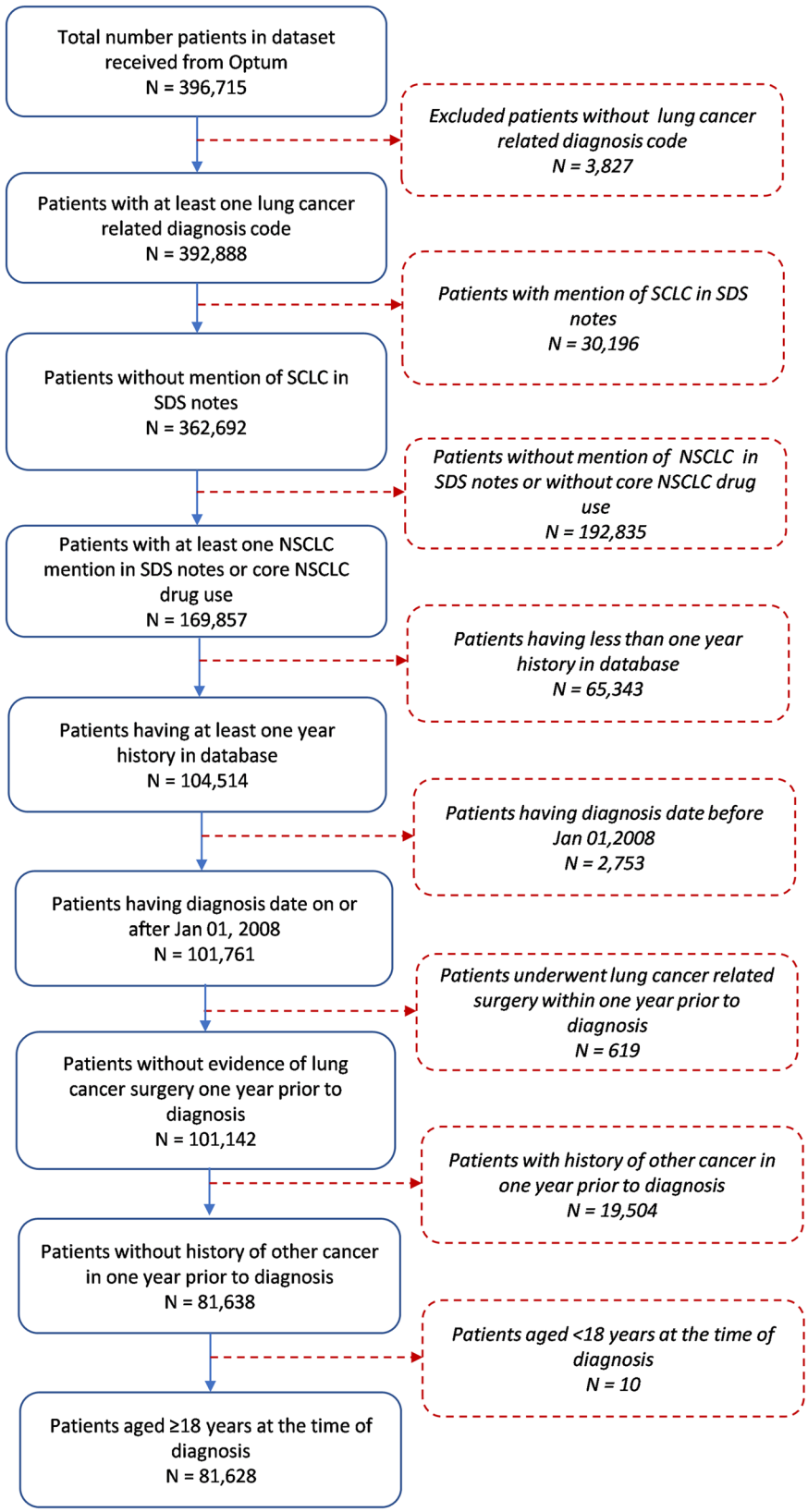
Pneumonitis occurrences were identified using ICD-9 codes (495.0–495.9, 506.0, 507.0, 507.1, 507.8, 508.0, 508.8, 516.32, 516.33, 516.35, 518.3, and 997.39), ICD-10 codes (J67.0–J68.0, J69.0, J69.1, J69.8, J70.0, J70.2, J82, J84.113, J84.114, J84.2, J95.4), and SDS terms ("allergic interstitial pneumonitis," "chemical pneumonitis," "cryptogenic organizing pneumonitis," "desquamative interstitial pneumonitis," "interstitial pneumonitis," "organizing pneumonitis," "pneumonitis," "radiation pneumonitis"). These data were then used to perform the analyses described below.

Cumulative Incidence

The cumulative incidence of pneumonitis was defined as the percentage of patients with a diagnosis of pneumonitis during (1) the entire follow-up period and (2) in each respective LOT period. Cumulative incidence estimates were stratified by the presence/absence of a history of pneumonitis prior to the start of the evaluation period, LOT, and biomarker subgroup (EGFR-positive/negative and PD-L1-positive/negative). A patient was deemed to be an EGFR mutant if identified as EGFR-positive from the SDS data set or had received osimertinib, erlotinib, afatinib, gefitinib, or dacomitinib (monotherapy or in combination with chemotherapy drugs) in LOT1.

Incidence Rates and Relative Risk

Incidence rates, expressed as cases per 1000 person-days, were calculated as the number of patients diagnosed with at least one occurrence of pneumonitis between the start and end of follow-up for each of the two respective evaluation periods, divided by the sum of the duration from the start of the evaluation period to the first occurrence of pneumonitis for those patients with at least one diagnosis of pneumonitis in the evaluation period and the sum of the duration from the start to the end of the evaluation period (or end of follow-up) for patients without a pneumonitis event in the evaluation period. The entire follow-up period was defined as the time from index date to the end of follow-up. Each LOT evaluation period was defined as the start of a LOT to 30 days after the end of that LOT or one day prior to the start of the next LOT, whichever was earlier, or (where there was no next LOT) up to the end of follow-up for or the end of the last LOT plus 30 days, whichever was earlier. These incidence rates were used to carry out a univariate analysis of 16 covariates (Table 4) to determine the relative risk (RR) of each covariate. The RR was calculated as IR1/IR2, where IR1 is the incidence rate for patients having the condition reported in terms of incidents/1000 person-days and IR2 is the incidence rate for patients who do not


Total number patients in dataset received from Optum
N = 396,715
Excluded patients without lung cancer related diagnosis code
N = 3,827
Patients with at least one lung cancer related diagnosis code
N = 392,888
Patients with mention of SCLC in SDS notes
N = 30,196
Patients without mention of SCLC in SDS notes
N = 362,692
Patients without mention of NSCLC in SDS notes or without core NSCLC drug use
N = 192,835
Patients with at least one NSCLC mention in SDS notes or core NSCLC drug use
N = 169,857
Patients having less than one year history in database
N = 65,343
Patients having at least one year history in database
N = 104,514
Patients having diagnosis date before Jan 01,2008
N = 2,753
Patients having diagnosis date on or after Jan 01, 2008
N = 101,761
Patients underwent lung cancer related surgery within one year prior to diagnosis
N = 619
Patients without evidence of lung cancer surgery one year prior to diagnosis
N = 101,142
Patients with history of other cancer in one year prior to diagnosis
N = 19,504
Patients without history of other cancer in one year prior to diagnosis
N = 81,638
Patients aged <18 years at the time of diagnosis
N = 10
Patients aged ≥18 years at the time of diagnosis
N = 81,628

◀**Fig. 1** Selection of the analysis cohort. NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; SDS, signs, diseases, and symptoms

have the condition reported as incidents/1000 person-days. *P* values to test the relative risk of developing pneumonitis were derived from a generalized linear model after accounting for differential patient follow-up times. Patients with unknown histology were excluded from this analysis. The covariates included demographic characteristics, histology, biomarker status, prior history of comorbidities/adverse events, and treatment groups. There were six treatment groups defined: any ICI monotherapy, any ICI combination therapy, EGFR-TKI therapy, other targeted therapy, platinum-based chemotherapy, any non-platinum-based chemotherapy (Table 1).

Competing Risk Regression

A multivariable competing risk regression (30) was used in order to account for the competing risk of death prior to the development of pneumonitis. We used 16 covariates (Table 5) used to identify significant predictors of pneumonitis. The significance level was 0.05.

RESULTS

Selection of the Study Cohort

The study cohort included a total of 81,628 patients identified as depicted in Fig. 1. Almost half (49%) of the cohort were male, 46.9% resided in the Midwest followed by 28.4% in the South, and 85% were Caucasian (Table 2). The mean age of patients at diagnosis was 69 years (SD = 10.1), and patients with Eastern Cooperative Oncology Group (ECOG) score ≥ 2 constituted 30% of patients with a valid score. Sixty percent of patients had localized disease, while 38.3% were EGFR-positive. The mean Charlson Comorbidity Index (CCI) was 1.8 (SD = 2.56).

Drug-Treated Patients

A total of 21.7% of patients were treated with medications for ≥ 1 LOT and had a median follow-up (MFU) of 401 days from their index diagnosis, with 8.8% having ≥ 2 LOTs (MFU: 566 days) and 3.8% having ≥ 3 LOTs (MFU: 742) (Table 3).

Pneumonitis Cumulative Incidence

Overall, 19.0% (95% confidence intervals [CI]: 18.5–19.6%) of treated patients developed pneumonitis during any LOT, while 26.2% (95% CI: 24.3–28.1%) of those with a prior history of pneumonitis in any time prior to LOT 1 and 17.0% (95% CI: 16.4–17.6%) of those without a previous history of pneumonitis developed the condition during any LOT. Regardless of biomarker subgroup, histologic category, or LOT, in general, a higher proportion of patients with a prior history of pneumonitis developed the condition than patients without a prior history (Fig. 2). Except for PD-L1+ non-squamous cell carcinoma patients, an increase in the cumulative incidence of pneumonitis in each subsequent LOT was observed across EGFR and PD-L1 status, by squamous/non-squamous histology. Overall, there was an increase in cases of pneumonitis of 2.7% from LOT 1 to LOT 3 (data not shown). Between the various subgroups, the largest increase between LOTs 1 and 3 was seen for PD-L1− patients with a non-squamous histology, with cumulative incidence going up from 13.6% to 22.7%. The smallest increase was seen in EGFR+/non-squamous patients (9.7–12.1%). PD-L1+/non-squamous patients was the only exception to this pattern going from 17.9% in LOT 1 to 13.8% in LOT3.

Of the 16 variables that were evaluated as risk factors for the development of pneumonitis in univariate analysis, several were shown to be significantly ($P < 0.05$) associated with a higher risk for developing the condition in at least two LOTs (Table 4). Some common factors included: male gender, squamous histology, EGFR-negative status, history of pneumonitis, history of diabetes, monotherapy treatment with an

Table 2 Demographic and clinical characteristics of the analytical cohort by histology

Baseline characteristics	Histology							
	Overall		Non-squamous[a]		Squamous		Not otherwise specified	
	n 81,628	%[b] 100%	*n* 46,670	%[b] 57%	*n* 21,540	%[b] 26%	*n* 13,418	%[b] 16%
Year of diagnosis								
2008	2535	3.1%	1125	2.4%	613	2.8%	797	5.9%
2009	3781	4.6%	1809	3.9%	998	4.6%	974	7.3%
2010	5186	6.4%	2566	5.5%	1362	6.3%	1258	9.4%
2011	6575	8.1%	3455	7.4%	1533	7.1%	1587	11.8%
2012	8037	9.8%	4334	9.3%	1966	9.1%	1737	12.9%
2013	9423	11.5%	5275	11.3%	2483	11.5%	1665	12.4%
2014	10254	12.6%	5909	12.7%	2674	12.4%	1671	12.5%
2015	10077	12.3%	6072	13.0%	2740	12.7%	1265	9.4%
2016	9870	12.1%	6097	13.1%	2696	12.5%	1077	8.0%
2017	8948	11.0%	5590	12.0%	2523	11.7%	835	6.2%
2018	6942	8.5%	4438	9.5%	1952	9.1%	552	4.1%
Gender								
Male	39987	49.0%	20762	44.5%	12722	59.1%	6503	48.5%
Female	41599	51.0%	25885	55.5%	8809	40.9%	6905	51.5%
Unknown	42	0.1%	23	0.0%	9	0.0%	10	0.1%
Region								
Midwest	38317	46.9%	21450	46.0%	10708	49.7%	6159	45.9%
South	23171	28.4%	13070	28.0%	6445	29.9%	3656	27.2%
West	7559	9.3%	4671	10.0%	1828	8.5%	1060	7.9%
Northeast	10380	12.7%	6263	13.4%	1974	9.2%	2143	16.0%
Other/Unknown	2201	2.7%	1216	2.6%	585	2.7%	400	3.0%
Race								
Caucasian	69138	84.7%	38996	83.6%	18659	86.6%	11483	85.6%
African American	7270	8.9%	4385	9.4%	1795	8.3%	1090	8.1%
Asian	1164	1.4%	869	1.9%	137	0.6%	158	1.2%
Other/unknown	4056	5.0%	2420	5.2%	949	4.4%	687	5.1%
Ethnicity								
Non-Hispanic	73931	90.6%	42329	90.7%	19718	91.5%	11884	88.6%
Hispanic	1507	1.8%	970	2.1%	320	1.5%	217	1.6%

Table 2 continued

Baseline characteristics	Histology							
	Overall		Non-squamous[a]		Squamous		Not otherwise specified	
	n 81,628	%[b] 100%	*n* 46,670	%[b] 57%	*n* 21,540	%[b] 26%	*n* 13,418	%[b] 16%
Unknown	6190	7.6%	3371	7.2%	1502	7.0%	1317	9.8%
Age at diagnosis (in years)								
Mean (SD)	69.1 (10.12)		68.5 (10.44)		70.3 (9.32)		69.4 (10.02)	
Median (IQR)	70 (62–77)		69 (61–77)		71 (64–78)		70 (63–77)	
Min–Max	(18–89)		(18–89)		(23–89)		(21–89)	
≤ 34	117	0.1%	89	0.2%	11	0.1%	17	0.1%
35–44	835	1.0%	614	1.3%	92	0.4%	129	1.0%
45–54	6161	7.5%	4004	8.6%	1151	5.3%	1006	7.5%
55–64	18797	23.0%	11475	24.6%	4423	20.5%	2899	21.6%
65+	55718	68.3%	30488	65.3%	15863	73.6%	9367	69.8%
ECOG score								
Index ± 30 days								
0	3054	28.8%	2201	31.5%	701	23.5%	152	23.9%
1	4372	41.2%	2866	41.0%	1261	42.3%	245	38.5%
2	1909	18.0%	1143	16.3%	633	21.3%	133	20.9%
3	1010	9.5%	630	9.0%	301	10.1%	79	12.4%
4	262	2.5%	155	2.2%	80	2.7%	27	4.2%
5	4	0.0%	2	0.0%	2	0.1%	0	0.0%
Missing	71017		39673	–	18562	–	12782	-
Stage								
Index through follow-up (localized unknown) ± 30 days (locally advanced metastatic)								
Localized (stage ≤ 3a)	20425	59.4%	13103	54.0%	6807	70.6%	515	100.0%
Locally advanced/metastasis (≥ 3b)	13973	40.6%	11142	46.0%	2831	29.4%	0	0.0%
Unknown	24516	–	11395	–	6270	–	6851	–
Missing	22714	–	11030	–	5632	–	6052	–
Cytogenetics								
Any time								
EGFR-positive[c]	9267	38.3%	8208	44.6%	704	15.6%	355	27.2%
EGFR-negative	5575	23.0%	4303	23.4%	988	22.0%	284	21.7%
PD-L1–positive	1933	8.0%	1140	6.2%	730	16.2%	63	4.8%

Table 2 continued

Baseline characteristics	Histology							
	Overall		Non-squamous[a]		Squamous		Not otherwise specified	
	n 81,628	%[b] 100%	*n* 46,670	%[b] 57%	*n* 21,540	%[b] 26%	*n* 13,418	%[b] 16%
PD-L1–negative	487	2.0%	354	1.9%	122	2.7%	11	0.8%
Both	448	1.8%	399	2.2%	38	0.8%	11	0.8%
Other	6510	26.9%	4010	21.8%	1917	42.6%	583	44.6%
Missing	57408	–	28256	–	17041	–	12111	-
Charlson comorbidity[d]	*n* = 81778		*n* = 38455		*n* = 18004		*n* = 6715	
Mean (SD)	1.8 (2.56)		2 (2.74)		1.7 (2.34)		1.4 (2.22)	
Median	1 (0–3)		1 (0–3)		1 (0–2)		0 (0–2)	
Min–Max	(0–16)		(0–15)		(0–16)		(0–14)	

ECOG Eastern Cooperative Oncology Group; *EGFR* epidermal growth factor receptor; *PD-L1* programmed death-ligand 1; *IQR* interquartile range; *SD* standard deviation

[a] Patients with squamous cell carcinoma were compared against patients with non-squamous cell carcinoma only; non-squamous NSCLC includes adenocarcinoma and large cell lung cancer; patients with unknown histology were excluded from this analysis

[b] Percentages are based on non-missing values in respective cohort

[c] A patient was EGFR-mutant if identified as EGFR-positive from the SDS data set or had received osimertinib, erlotinib, afatinib, gefitinib or dacomitinib (monotherapy or in combination with chemotherapy drugs) in LOT1. Chemotherapy drugs: Carboplatin, cisplatin, docetaxel, gemcitabine, nab-paclitaxel, paclitaxel, pemetrexed, or vinorelbine

[d] Comorbidities identified during the 180-day pre-index period

Table 3 Distribution of eligible patients with LOT(s) with their average length of follow-up

	Eligible patients (*N* = 81,628)	% of eligible patients	% patients with subsequent LOT(s)	Median follow-up[a] (days)
Patients with no treatment	63,949	78.3	–	146
Patients with ≥ 1 LOT	17,679	21.7	40.5	401
Patients with ≥ 2 LOTs	7158	8.8	42.8	566
Patients with ≥ 3 LOTs	3062	3.8	43.0	742

LOT line of therapy; *NSCLC* non-small cell lung cancer

[a] Time from index NSCLC diagnosis until the end of continuous follow-up

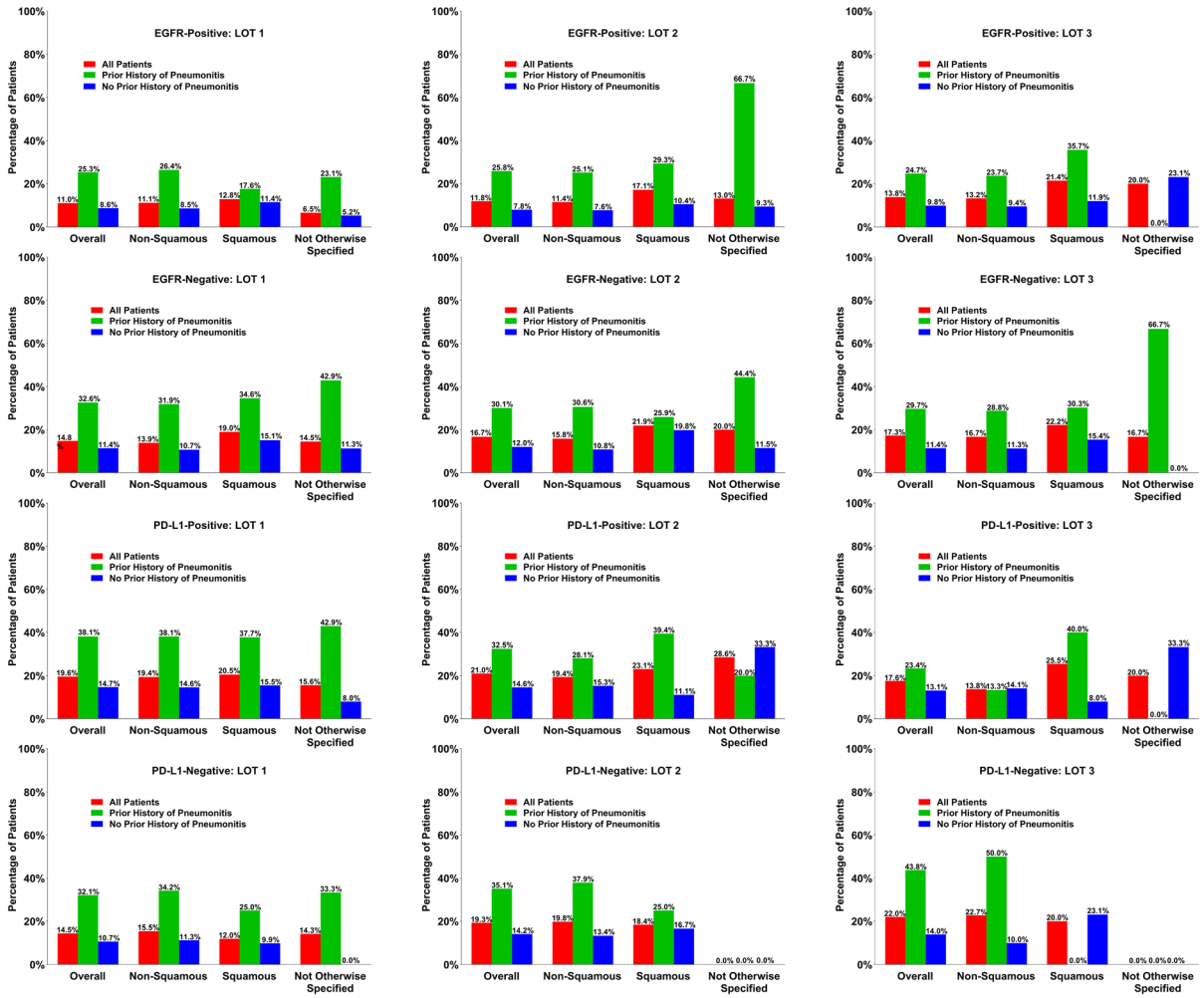


Fig. 2 Cumulative incidence of pneumonitis by biomarker subgroup, LOT, histology, and prior history of pneumonitis. *EGFR* epidermal growth factor receptor; *LOT* line of therapy; *PD-L1* programmed death-ligand 1

immunomodulatory drug, and history of radiation therapy. Patients treated with other targeted therapies and non-platinum-based chemotherapy showed a lower risk for developing pneumonitis in at least two LOTs.

The multivariable competing risk regression model to identify predictors of pneumonitis for each LOT showed history of pneumonitis to be significant across all three LOTs. Additionally, there were a number of significant predictors across at least two LOTs. Specifically, male gender (LOTs 1–2), EGFR-negative status (LOTs 1–2), and history of radiation therapy (LOTs 1 and 3) were positively associated ($P < 0.05$) with the development of pneumonitis (Table 5). Treatment with other targeted therapy (LOTs 1–2) was negatively associated with developing pneumonitis.

DISCUSSION

Pneumonitis is a significant and serious AE associated with drugs used to treat NSCLC. Our study estimated the risk of pneumonitis, among patients diagnosed with NSCLC who received drug interventions, across clinical and treatment characteristics of interest including prior history of pneumonitis, regimen, LOT, histology, and biomarker status. The incidence of pneumonitis in NSCLC has previously been studied mostly in primary and meta-analyses of

Table 4 Relative risk of developing pneumonitis reported in NSCLC while on treatment[a] by LOT

Assessment	LOT 1 (*N* = 17,679)		LOT 2 (*N* = 7,158)		LOT 3 (*N* = 3,062)	
	RR (95% CI)	*P* value	RR (95% CI)	*P* value	RR (95% CI)	*P* value
Demographic characteristics						
Age ≥ 65 (yes vs. no)	1.023 (0.935, 1.119)	0.6177	1.174 (1.032, 1.336)	0.0150*	0.882 (0.729, 1.067)	0.1975
Gender—male (yes vs. no)	1.254 (1.148, 1.370)	<0 .0001*	1.441 (1.269, 1.637)	<0 .0001*	1.178 (0.975, 1.424)	0.0902
Race (African American vs. Caucasian)	0.932 (0.799, 1.088)	0.3736	0.887 (0.715, 1.100)	0.2733	1.030 (0.756, 1.404)	0.8513
Race (Asian vs. Caucasian)	0.983 (0.700, 1.381)	0.9219	0.772 (0.477, 1.248)	0.2904	0.657 (0.339, 1.273)	0.2136
Histology						
Squamous vs. non-squamous [[2]]	1.443 (1.314, 1.585)	<0 .0001*	1.843 (1.607, 2.114)	<0 .0001*	1.623 (1.301, 2.025)	<0 .0001*
Biomarker status						
EGFR[c] (positive vs. negative)	0.853 (0.736, 0.988)	0.0339*	0.793 (0.653, 0.963)	0.0195*	0.836 (0.645, 1.083)	0.1745
PD-L1 (positive vs. negative)	1.302 (0.922, 1.839)	0.1335	0.986 (0.644, 1.508)	0.9470	0.754 (0.393, 1.446)	0.3953
History of adverse events						
CCI score (1–4 vs. 0)	1.129 (1.031, 1.236)	0.0086*	1.043 (0.917, 1.185)	0.5234	1.077 (0.890, 1.303)	0.4465
History of pneumonitis (yes vs. no)	1.178 (1.067, 1.302)	0.0012*	1.193 (1.035, 1.376)	0.0147*	1.228 (0.989, 1.526)	0.0630
History of diabetes (yes vs. no)	3.632 (3.296, 4.002)	<0 .0001*	3.768 (3.317, 4.281)	< 0.0001*	3.215 (2.659, 3.886)	<0 .0001*
Treatment category						
Any ICI monotherapy (yes vs. no)	1.397 (1.210, 1.613)	<0 .0001*	1.856 (1.629, 2.116)	<0 .0001*	1.322 (1.085, 1.610)	0.0056*
Any ICI combination therapy (yes vs. no)	1.495 (1.159, 1.930)	0.0020*	1.395 (0.970, 2.007)	0.0726	1.347 (0.696, 2.608)	0.3762
EGFR TKI therapy (yes vs. no)	0.936 (0.805, 1.087)	0.3841	0.909 (0.729, 1.133)	0.3943	1.671 (1.304, 2.142)	<0 .0001*
Other targeted therapy (yes vs. no)	0.416 (0.338, 0.512)	<0 .0001*	0.337 (0.258, 0.442)	< 0.0001*	0.440 (0.300, 0.646)	< .0001*
Any platinum-based chemotherapy (yes vs. no)	1.128 (1.023, 1.244)	0.0156*	1.141 (0.977, 1.333)	0.0954	1.069 (0.794, 1.439)	0.6614
Any non platinum-based chemotherapy (yes vs. no)	0.753 (0.638, 0.888)	0.0008*	0.648 (0.564, 0.743)	<0 .0001*	0.625 (0.510, 0.764)	<0 .0001*

Table 4 continued

Assessment	LOT 1 (*N* = 17,679)		LOT 2 (*N* = 7,158)		LOT 3 (*N* = 3,062)	
	RR (95% CI)	*P* value	RR (95% CI)	*P* value	RR (95% CI)	*P* value
Radiation therapy						
History of radiation therapy (yes vs. no)	1.532 (1.387, 1.692)	<0 .0001*	1.435 (1.216, 1.693)	<0 .0001*	1.837 (1.387, 2.433)	<0 .0001*

All categories within the "assessments" column represent the presence of the condition during the baseline period, which is defined as any time prior to index date or start of LOT. Shaded cells represent parameters that were significant at the 0.05 level

N = Number of patients eligible for analysis

[a] Evaluation period is from start of LOT to 30 days after end of current LOT or day prior to start of next LOT, whichever was earlier, or (where there was no next LOT) up to end of follow-up for patient or end of LOT + 30, whichever was earlier

RR: Relative risk of developing pneumonitis derived by calculating IR1/IR2. *P* values to test the relative risk of developing pneumonitis were derived from a generalized linear model after accounting for differential patient follow-up times

[b] Patients with squamous cell carcinoma were compared against patients with non-squamous cell carcinoma only. Non-squamous NSCLC includes adenocarcinoma and large cell lung cancer. Patients with unknown histology were excluded from this analysis

[c] A patient was deemed to be EGFR-mutant if identified as EGFR-positive from the SDS data set or had received osimertinib, erlotinib, afatinib, gefitinib or dacomitinib (monotherapy or in combination with chemotherapy drugs) in LOT1

Regimens whose start date were lying on or after January 1, 2008, were considered for the analysis

CCI Charlson Comorbidity Index; *EGFR* epidermal growth factor receptor; *ICI* immune checkpoint inhibitor; *LOT* line of therapy; *NSCLC* non-small cell lung cancer; *PD-L1* programmed death-ligand 1; *SDS* signs, diseases, and symptoms; *TKI* tyrosine kinase inhibitor

Table 5 Fine and Gray competing risk model for time to pneumonitis while on treatment by LOT[a]

Parameter	During LOT 1		During LOT 2		During LOT 3	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Demographic characteristics						
Age (≥ 65 vs. < 65)	0.95 (0.86–1.05)	0.3388	1.08 (0.93–1.25)	0.3079	0.98 (0.79–1.21)	0.8634
Gender (male vs. female)	1.15 (1.04–1.27)	0.0051*	1.2 (1.04–1.39)	0.0143*	1.02 (0.81–1.27)	0.8916
Race (African American vs. Caucasian)	0.94 (0.79–1.11)	0.4602	1.01 (0.79–1.28)	0.9534	1.12 (0.8–1.58)	0.5115
Race (Asian vs. Caucasian)	1.26 (0.88–1.81)	0.2114	0.85 (0.48–1.53)	0.5931	0.98 (0.49–1.96)	0.9498
Race (other/unknown vs. Caucasian)	1.11 (0.87–1.41)	0.4031	0.92 (0.61–1.38)	0.6853	1.09 (0.56–2.12)	0.8042
Histology						
Squamous vs. non-squamous[b]	1.32 (1.18–1.47)	<0 .0001*	1.16 (0.98–1.38)	0.0901	1.28 (0.98–1.67)	0.0694
Unknown vs. non-squamous	0.85 (0.66–1.09)	0.1951	1.33 (0.94–1.9)	0.1093	0.93 (0.42–2.03)	0.8538
Biomarker status						
EGFR[c] (positive vs. negative)	0.82 (0.69–0.98)	0.0273*	0.78 (0.62–0.99)	0.0370*	0.86 (0.63–1.16)	0.3085
EGFR (unknown vs. negative)	0.82 (0.71–0.95)	0.0072*	0.83 (0.68–1.01)	0.0645	0.84 (0.62–1.12)	0.2315
PD-L1 (positive vs. negative)	1.16 (0.8–1.69)	0.4410	0.89 (0.56–1.39)	0.5984	0.71 (0.34–1.47)	0.3538
PD-L1 (unknown vs. negative)	0.82 (0.58–1.16)	0.2643	0.69 (0.46–1.03)	0.0698	0.61 (0.32–1.17)	0.1383
History of adverse events						
CCI score (1–4 vs. 0)	0.98 (0.89–1.09)	0.7420	0.89 (0.77–1.03)	0.1046	1.02 (0.82–1.27)	0.8500
History of diabetes (yes vs. no)	1.02 (0.91–1.14)	0.7113	1.01 (0.86–1.19)	0.9171	0.98 (0.76–1.25)	0.8445
History of pneumonitis (yes vs. no)	2.91 (2.6–3.25)	<0 .0001*	2.9 (2.51–3.36)	< 0.0001*	2.91 (2.35–3.6)	<0 .0001*
Treatment category						
Any ICI monotherapy (yes vs. no)	1.64 (0.89–3.02)	0.1104	1.92 (1.04–3.56)	0.0375*	1.45 (0.68–3.09)	0.3302

Table 5 continued

Parameter	During LOT 1		During LOT 2		During LOT 3	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Any ICI combination therapy (yes vs. no)	1.06 (0.78–1.44)	0.6984	1.58 (1.04–2.4)	0.0305*	1.5 (0.77–2.95)	0.2370
EGFR TKI therapy (yes vs. no)	0.95 (0.52–1.76)	0.8729	0.94 (0.49–1.79)	0.8443	1.04 (0.49–2.22)	0.9149
Other targeted therapy (yes vs. no)	0.55 (0.43–0.71)	< .0001*	0.58 (0.41–0.83)	0.0027*	0.73 (0.45–1.21)	0.2247
Any platinum-based chemotherapy (yes vs. no)	0.92 (0.52–1.66)	0.7909	0.98 (0.53–1.79)	0.9395	0.76 (0.36–1.63)	0.4856
Any non-platinum-based chemotherapy (yes vs. no)	0.9 (0.49–1.65)	0.7342	1.12 (0.62–2.05)	0.7069	0.73 (0.36–1.51)	0.3957
Radiation therapy						
History of radiation therapy (yes vs. no)	1.33 (1.19–1.49)	<0 .0001*	1.14 (0.95–1.38)	0.1647	1.46 (1.07–2)	0.0181*

CCI Charlson Comorbidity Index; *EGFR* epidermal growth factor receptor; ICI immune checkpoint inhibitor; *LOT* line of therapy; *PD-L1* programmed death-ligand 1; TKI, tyrosine kinase inhibitor

[a] Regimens whose start dates were on or after January 1, 2008, were considered for the analysis. Assessment period is from start of LOT to 30 days after end of current LOT or day prior to start of next LOT, whichever is earlier, or (where no next LOT) up to end of follow-up for patient or end of LOT + 30, whichever is earlier. Shaded cells represent parameters that were significant at the 0.05 level

[b] Patients with squamous cell carcinoma were compared against patients with non-squamous cell carcinoma only. Non-squamous NSCLC includes adenocarcinoma and large cell lung cancer. Patients with unknown histology were excluded from this analysis

clinical trials [6, [7, 11], and in some retrospective chart reviews from select hospitals (8, 9). This has resulted in a wide range of estimates from 3–5% in the clinical trial setting [7, 31] to 19–21% from additional trials or hospital data [14, 32]. This discrepancy may be explained in part by the increased awareness of this AE in recent years and partly to enhanced pharmacovigilance following the administration of targeted agents [14].

In our analysis of EHR data from hospital clinics across the country, the cumulative incidence of pneumonitis among NSCLC patients was estimated to be 19.0% during any LOT, and 33.7% among those with a prior history of pneumonitis and 17.0% for those without a previous history of pneumonitis. Competing risk regression revealed various factors to be positively associated with the development of pneumonitis over multiple LOTs. Predictors of increased pneumonitis risk included a previous history of pneumonitis, male gender, history of radiation therapy, and EGFR-negative status.

To our knowledge, only two other studies have examined rates of pneumonitis in large real-world data sets. The first study used OptumLabs administrative claims data and examined frequencies of all immune-related

adverse events (irAEs) in NSCLC patients receiving PD-L1 inhibitors [19]. Pneumonitis was reported in 2.5% of 3164 patients within a month of receipt of a PD-L1 inhibitor, increasing to 14.3% after 9 months. The second study, a retrospective analysis of the Symphony Health administrative claims data, estimated incidence, and timing of radiation-induced pneumonitis following chemoradiotherapy in patients with stage III NSCLC [22]. The cumulative incidence of treatment-related pneumonitis was reported to be 12.4%, with the annual incidence ranging from 5.5% to 18.1%. The higher rates in our study are perhaps explained by the inclusion of more stage IV patients and the effect of more patients having been treated with PD-L1 inhibitors.

Limitations associated with using real-world data need to be recognized. The data for this study were not recorded for research purposes; as such there may be coding errors that could affect the treatment patterns and predictive factors associated with pneumonitis. While this is a large multi-source database, it may not be nationally representative of all NSCLC patients. A final limitation is with the use of NLP for identifying patients of non-small cell cancer histology and partly for diagnosis of pneumonitis. We rely on the data vendor's NLP algorithm for this and cannot know how well the NLP extracts the information from the physician notes.

Future research building on this study could include using another US-based EHR data source that is focused on community and academic based hematology-oncology clinics or using a non-US real-world data source.

Pneumonitis remains a significant risk in patients diagnosed with NSCLC. This study identified independent factors that may predispose individuals to pneumonitis risk such as previous history of pneumonitis, male gender, EGFR-negative status, ICI therapy, other targeted therapies, or history of radiation. Awareness and monitoring of these factors may help mitigate the risk of pneumonitis for these patients.

CONCLUSION

Pneumonitis is a significant side effect of medicines developed to treat NSCLC. Recognition of this fact and awareness of the different factors predisposing patients to its development will help physicians proactively tailor treatment regimens to reduce the likelihood of its onset. Patients may consequently be able to better adhere to treatment regimens, leading to positive clinical outcomes and improved quality of life.

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Compliance with Ethics Guidelines. The anonymized patient information used in this retrospective observational study does not include any identifiable information as defined by the Health Insurance Portability and Accountability Act (HIPAA) of 1996, and an institutional review board (IRB) approval or waiver is therefore not required. The authors licensed the data from Optum and had permission to use it for this research.

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Data Availability. The data sets generated and/or analyzed during the current study are not publicly available due to the proprietary nature of the database from which they were derived and used under license for the current study.

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