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RESEARCH

Clinical characteristics, outcomes, and predictive modeling of patients diagnosed with immune checkpoint inhibitor therapy-related pneumonitis

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Abstract

Purpose The aim of this study is to better characterize the clinical characteristics and outcomes of patients diagnosed with Immune checkpoint Inhibitor (ICI) pneumonitis and propose predictive models.

Patients and methods Patients diagnosed with ICI pneumonitis at Mayo Clinic from 2014 to 2022 were studied. All cases were independently reviewed by our pulmonology specialist (A.E.) to confirm the appropriate diagnosis. The grading of pneumonitis was defined in accordance with ASCO guidelines (Schneider et al. in J Clin Oncol 39(36):4073–4126, 2021. https://doi.org/10.1200/JCO.21.01440). Predictive modeling was performed using gradient boosting machine learning technology, XGBoost (Chen in 1(4):1, 2015), to conduct binary classification and model reverse engineering using Shapley statistics (Lundberg and Lee in Adv Neural Inf Process Syst 30, 2017).

Results One hundred and seventy patients with ICI pneumonitis were included (median age 67; IQR 59, 75). Median overall survival was 2.3 years (95% CI: 1.8, NR). A higher grade of ICI pneumonitis was associated with inferior survival (HR 5.85, 95% CI: 2.27, 15.09; $p < 0.001$). Patients who were rechallenged with immunotherapy had significantly improved hazard of survival compared to patients not rechallenged (HR 0.37, 95% CI: 0.21, 0.68; $p = 0.001$). Risk of death from ICI pneumonitis prior to starting immunotherapy was modeled with an area under the curve of the receiver operator characteristic (AUC-ROC) of 0.79 with the most contributory features including peripheral blood lymphocyte count, oxygen dependence, pulmonary function testing, and PD-L1 expression.

Conclusion The presentation of ICI pneumonitis is highly variable, and outcomes are dependent on severity, but favor grade 2 disease when patients are rechallenged with immunotherapy. However, using commonly available clinical data, we can accurately identify patients at high risk of death from ICI pneumonitis. Further effort is needed to produce clinical models able to provide clinician decision support when evaluating patients with ICI toxicities and considering ICI rechallenge.

Keywords Immunotherapy · Immune checkpoint inhibitor · Pneumonitis · PD-L1 · PD-1

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Introduction

Immune checkpoint inhibitor (ICI) therapy has revolutionized the field of oncology by markedly improving the prognosis of patients with cancer. To date, there have been multiple agents approved by the United States (US) Food and Drug Administration (FDA) for over 17 cancer types [1, 2]. Since the first FDA approval of an ICI in 2011, the use of ICI therapy has significantly increased. In 2018, the estimated percentage of US patients with cancer who are eligible for ICIs was 43.64%; this contrasts with 1.54% in 2011. This equates to more than 233,000 patients with cancer in the US eligible for these treatments yearly [1]. It is reported that up to 40% of patients will develop an immune-related adverse events (irAE) irAE during their course of treatment. The incidence of a fatal ICI-associated adverse event is estimated to be approximately 0.3–1.3% [3].

IrAEs are possible in any organ with variable incidence. ICI toxicity resulting in pneumonitis is a significant concern in patients receiving ICIs with a recently reported incidence of 2.5% [2]. Symptoms range from mild dyspnea and cough to respiratory failure [4, 5]. Often, it is difficult to determine whether symptoms and radiographic findings are due to ICI pneumonitis or infection, the latter often prevalent in immunocompromised populations. [5]

ICI pneumonitis is graded from 1 to 4 per the American Society of Clinical Oncology (ASCO) guidelines [6]. Grade 1 is defined as patients who are asymptomatic with confirmed radiographic findings. Grade 2 results in the development of symptoms with limitations in activities of daily living (ADLs). Grade 3 results in severe symptoms that may require hospitalization. Grade 4 is defined as life-threatening respiratory compromise requiring urgent medical intervention.

Unfortunately, due to the wide variability of symptoms, radiographic findings, and broad differential diagnoses, the diagnosis of ICI pneumonitis is challenging. Often, a wide diagnostic workup is implemented ranging from advanced imaging, empiric antibiotics, and bronchoscopy with bronchoalveolar lavage (BAL) and biopsy. [2, 7]

Once symptoms and radiographic findings are attributed to ICI pneumonitis, immediate medical intervention is indicated (excluding grade 1). Though ICI is held, patients generally also require immunosuppression for treatment. Not only does the development of ICI pneumonitis halt cancer-directed treatment, but the treatment of pneumonitis- depending on the degree of immunosuppression used- can lead to overwhelming and sometimes life-threatening opportunistic infections and clinical decline. Thus, it is critical for clinicians to recognize ICI pneumonitis and initiate treatment promptly with close monitoring.

Per the ASCO guidelines, patients with grade 1 pneumonitis are recommended to be closely monitored or have ICI held. All patients with grade 2 or higher should have ICI held or permanently discontinued. Grade 2 disease is often treated with prednisone at a dose range of 1–2 mg/kg/day. Grades 3 and 4 are treated with methylprednisolone 1–2 mg/kg/day. If no improvement is seen within 48 h, additional immunosuppressive agents may be added [4]. Unfortunately, despite best efforts, ICI pneumonitis can be fatal in greater than 10% of cases. [8, 9]

In recent years, the use of predictive modeling has been implemented to aid clinicians in cancer treatment [10]. By utilizing statistical prediction tools and machine learning, models can provide a probability of a specific event occurring. For instance, modeling can be used to predict radiation pneumonitis after definitive radiotherapy for locally advanced non-small cell lung cancer (NSCLC) using multi-region radiomics analysis [11]. However, to date, the role of predictive modeling for developing irAEs is limited.

The aim of this study is to better characterize the clinical attributes and outcomes of ICI pneumonitis and propose predictive models for ICI pneumonitis severity.

Methods

This is a retrospective study of all adult patients diagnosed with ICI pneumonitis at the Mayo Clinic from January 2014 to December 2022. This study was approved by the Mayo Clinic Institutional Review Board. A list of patients was compiled using Mayo Clinic's informatics tool, Advanced Text Explorer, with keywords "pneumonitis" and "immunotherapy" identified in provider documentation resulting in 848 patients in which ICI pneumonitis was suspected or confirmed by the treating clinician(s). Keywords were utilized given the absence of a specific ICD code for ICI pneumonitis to identify patients. All cases were independently reviewed by our pulmonology specialist (A.E.) to confirm the appropriate diagnosis, yielding 170 patients. Excluded patients were those with alternative diagnoses (e.g. bacterial pneumonia, radiation pneumonitis, interstitial lung disease) and not a confirmed diagnosis of ICI pneumonitis. The grading and diagnosis of pneumonitis was defined in accordance with ASCO guidelines [6]. ICI resolution was defined as a composite of clinical improvement ("yes") and radiographic improvement (complete or partial). Pulmonary function testing (PFT) parameters included forced expiratory volume (FEV1), forced vital capacity (FVC), total lung capacity (TLC), and uncorrected diffusing capacity for carbon monoxide (DLCO). Corrected diffusion capacity was not consistently available for all patients and thus was not collected. Due to variations in staining patterns, inclusion of PD-L1 expression was limited to only patients with NSCLC.

Retrospective analysis

The demographic, cancer, and pneumonitis characteristics of patients were summarized using median (interquartile range [IQR]) for continuous variables and counts and percentages for categorical variables. Similar summary statistics were provided for outcomes of interest. The outcome of ICI grade was analyzed using ordinal logistic regression, adjusted for non-small cell lung cancer (yes/no) and small cell lung cancer (y/n). ICI resolution was analyzed with logistic regression, adjusted for non-small cell lung cancer and small cell lung cancer. Overall survival (OS) and ICI pneumonitis event free survival were analyzed with Cox proportional hazards regression, adjusted for non-small cell lung cancer and small cell lung cancer. Explanatory variables included age, sex, PD-L1 expression, smoking history, PFT results, radiographic findings, and BAL measurements. Due to the ranges of distributions, age, PD-L1 expression, BAL total nucleated cells (TNC), BAL alveolar macrophages, BAL neutrophils, and BAL lymphocytes were assessed per five units. Kaplan–Meier curves were generated to illustrate the relationship between the time from ICI pneumonitis diagnosis to overall survival and pneumonitis-specific mortality stratified by stage and cancer type. Two-tailed *p*-values of 0.05 or less were considered statistically significant. Complete case analysis methods were used for missing data. Data management and statistical analysis were performed in SAS version 9.4 (SAS Institute Inc, Cary, North Carolina).

Predictive modeling

Modeling was used to determine if three clinical outcomes could be predicted, namely risk of death from: pneumonitis prior to starting ICI, pneumonitis at the time of diagnosis of ICI pneumonitis, and any cause at the time of ICI pneumonitis diagnosis. Clinical variables were isolated from before ICI pneumonitis diagnoses to model the propensity for developing low grade (1–2) versus high-grade (3–4) pneumonitis at the time of ICI initiation. The data used in the modeling consisted of 170 patients with annotation from the 71 clinical features that are presented in this study. The collected clinical features were included based on those commonly reported in studies as well as factors deemed clinically relevant by the authors. Only patients with prior lung radiation were included in the cohort, and pneumonitis had to involved areas outside the radiation field to be attributed to ICI pneumonitis. Data were divided into features available at the time of cancer diagnosis and at the time of ICI pneumonitis diagnosis. Exploratory modeling was performed using the gradient boosting technique XGBoost and conducted using k-fold balanced cross validation best practices as well as a train/test/validate schema with 70%/20%/10% data proportions, respectively. [12] Model reverse engineering was done with Shapley statistics to determine which features had the largest contribution per model [13]. Once identified, only those highly weighted features were used for logistic regression analysis providing more reproducible predictions by decreasing model variance.

Results

Patient characteristics

In total, 170 patients were diagnosed with ICI pneumonitis. The median age was 67 (IQR 59, 75) and 48% were male. Current smokers made up 9% of patients with 58% of patients having a prior smoking history and a median pack year of 35 (IQR 15, 50). 45% of patients had an underlying lung condition. NSCLC was the most common malignancy observed in 82 (48%), followed by melanoma in 30 (18%). Nineteen (11%) patients had prior lung surgery and 60 (35%) had a history of radiation to the lung (median dose range of 60 Gy and 19 fractions). The most prescribed ICIs were pembrolizumab (61%) followed by nivolumab (12%). Combination nivolumab and ipilimumab was used in 5% of patients. At the time of ICI pneumonitis diagnosis, 112 (67%) patients were receiving concurrent chemotherapy. Complete patient characteristics are shown in Table 1.

ICI pneumonitis diagnosis

The severity of ICI pneumonitis was as follows: grade 1 $n=17$ (10%), grade 2 $n=85$ (50%), grade 3 $n=53$ (31%), and grade 4 $n=15$ (9%). The most common presenting symptoms were dyspnea (80%) followed by cough (45%) and hypoxia (31%). Fifty-one (30%) patients required oxygen at the time of diagnosis. Forty-seven (28%) had an additional ICI toxicity. The median time from initiation of ICI to development of ICI pneumonitis was 4 months (IQR 2—9.5) (Table 2).

Receiving ICI and a prior history of lung radiation (regardless of chemotherapy) was associated with an increase in ICI pneumonitis grade (OR 2.06, 95% CI: 0.96, 4.40; $p=0.06$). The median time from radiation to ICI pneumonitis was 334 days (IQR 119, 538 days). In contrast, those receiving ICI with chemotherapy alone or receiving dual checkpoint blockade (nivolumab in combination with ipilimumab) were not associated with an increased pneumonitis grade (OR 1.87, 95% CI: 0.87, 4.04; $p=0.11$; and OR 1.22, 95% CI: 0.33, 4.59; $p=0.77$, respectively). Patients who had intrathoracic tumors were associated with higher-grade pneumonitis (OR 2.22, 95% CI: 1.13, 4.37; $p=0.021$), (Supplemental Table 1).

Table 1 Baseline characteristics of patients diagnosed with immune checkpoint inhibitor therapy-related pneumonitis

	Overall ($n=170$)
Age at diagnosis, median (IQR)	67.0 (59.0, 75.0)
Sex, *n* (%)	
Female	89 (52)
Male	81 (48)
Race, *n* (%)	
White	162 (95)
Black or African American	2 (1)
American Indian/Alaska Native	1 (1)
Asian	1 (1)
Unknown/Not Reported	4 (2)
Smoking status, *n* (%), $N=168$	
Former	98 (58)
Current	15 (9)
Never	55 (33)
Pack year smoking history, median (IQR), $N=108$	35.0 (15.0, 50.0)
Underlying lung Condition, *n* (%)	77 (45)
COPD	52 (31)
Asthma	18 (11)
ILD	4 (2)
Other lung disease	3 (2)
Oxygen dependent at baseline, *n* (%), $N=163$	12 (7)
Underlying autoimmune disease, *n* (%), $N=169$	34 (20)
Underlying immunodeficiency, *n* (%), $N=169$	16 (10)
On immunosuppressive medication, *n* (%)	22 (13)
Primary cancer type, *n* (%)	
Non-small cell lung cancer	82 (48)
Melanoma	30 (18)
Head and neck cancer	9 (5)
Renal cell carcinoma	8 (5)
Breast cancer	7 (4)
Mesothelioma	6 (4)
Small cell lung cancer	6 (4)
Other*	22 (13)
Prior lung surgery, *n* (%)	19 (11)
Prior lung radiation, *n* (%)	60 (35)
Radiation dose (Gy), median (IQR)	60.0 (45.0, 60.0)
Radiation fraction, median (IQR)	19.0 (10.0, 30.0)
PD-L1 Expression in NSCLC (%), median (IQR)	15.0 (1.0, 75.0)
Drug Name, *n* (%)	
Pembrolizumab	103 (61)
Nivolumab	20 (12)
Durvalumab	19 (11)
Atezolizumab	12 (7)
Nivolumab and Ipilimumab	9 (5)
Cemiplimab	5 (3)
Dostarlimab	1 (1)
Received concurrent chemotherapy, *n* (%)	112 (67)

IQR Interquartile range

*4 patients each: adenocarcinoma of the colon, squamous cell carcinoma of the skin; 3 patients each: sarcoma; 2 patients each: pancreatic adenocarcinoma; 1 patient each: adrenal cancer, cancer of unknown primary, endometrial, Hodgkin lymphoma, hepatocellular carcinoma, neuroendocrine, non-Hodgkin lymphoma, adenocarcinoma of the rectum, urothelial cancer

Distinct radiographic patterns emerged among the 170 patients who underwent computed tomography (CT) chest scans for pulmonary complaints or cancer follow-up (Fig. 1). Diffuse inflammatory patterns were seen in 64% of chest CTs. The most common inflammation patterns noted on imaging were ground-glass (82%) and nodules (38%). Notably, thickened interlobular septa, as observed in radiographic findings (OR 2.33, 95% CI: 1.17, 4.65; $p=0.016$), was associated with a higher grade of ICI pneumonitis (Supplemental Table 1).

Forty-four (26%) patients underwent pre- and post-diagnosis spirometry. As expected, all PFT values (FEV1, FVC, TLC, and uncorrected DLCO) were significantly lower after ICI pneumonitis diagnosis compared to baseline values ($p<0.01$ for all comparisons).

Peripheral lymphocyte count was collected for all patients at the time of ICI pneumonitis diagnosis prior to corticosteroid administration. At the time of ICI diagnosis, 66% of patients were receiving concurrent chemotherapy. The median lymphocyte count for patients not receiving chemotherapy was 1.35 (range 0.32, 108.0; IQR 0.71, 1.80). The median lymphocyte count for those receiving chemotherapy was 0.86 (range 0.06, 9.0; IQR 0.54, 1.10).

BAL was performed in 24% of patients at diagnosis, within 5 days of starting corticosteroids. Macrophages (66%) were the most predominant cell type regardless of pneumonitis grade followed by neutrophils (18%) and lymphocytes (9%). A higher neutrophil count was associated with a more severe grade of ICI pneumonitis (OR 1.19, 95% CI: 1.04, 1.37; $p=0.014$). A higher uncorrected DLCO was associated with a less grade of ICI pneumonitis (OR 0.90, 95% CI: 0.83, 0.98; $p=0.019$). Other characteristics, including additional PFT variables, PD-L1 expression, choice of ICI drug, cancer stage, or combination ICI therapy, demonstrated an association with the grade of ICI pneumonitis (Supplemental Table 1).

Management of ICI pneumonitis

Most patients (89%) diagnosed with ICI pneumonitis received corticosteroids. Those that did not receive corticosteroids were diagnosed with grade 1 or grade 2. Most patients were predominantly managed with oral corticosteroids (72%). Higher doses (> 1 mg/kg) of corticosteroids were given intravenously in 16% of patients, mostly in grade 3 (28%) and grade 4 pneumonitis (47%). Corticosteroid-sparing agents such as mycophenolate or infliximab were administered in 7% of patients,

Table 2 Clinical features of immune checkpoint inhibitor therapy-related pneumonitis

	Overall ($n=170$)
Presenting symptoms, *n* (%)	
Dyspnea	136 (80)
Cough	77 (45)
Hypoxia	52 (31)
Fatigue	46 (27)
Chest pain	9 (5)
None	12 (7)
Time since first administration of ICI (months), median (IQR)	4.0 (2.0, 11.0)
Time since last ICI dose (weeks), median (IQR)	3.0 (2.0, 4.0)
Grade of pneumonitis, *n* (%)	
1	17 (10)
2	85 (50)
3	53 (31)
4	15 (9)
Need for supplemental oxygen at initial presentation, *n* (%)	51 (30)
Form, $N=49$	
Nasal cannula	41 (84)
Noninvasive intermittent positive pressure ventilation	5 (10)
High-flow nasal cannula	3 (6)
Form at 12 h (if hospitalized), $N=42$	
Nasal cannula	30 (71)
Noninvasive intermittent positive pressure ventilation	5 (12)
High-flow nasal cannula	5 (12)
Intubated	2 (5)
Radiographic findings, *n* (%)	
Ground-glass	139 (82)
Nodular pattern	64 (38)
Consolidation	52 (31)
Reticular pattern	48 (28)
Thickened interlobular septa	43 (25)
Cystic air spaces	4 (2)
Extent of radiographic findings, *n* (%)	
Diffuse	109 (64)
Localized	23 (14)
Upper lobe predominant	39 (23)
Lower lobe predominant	48 (28)
Central predominant	25 (15)
Peripheral predominant	47 (28)
Additional ICI toxicities, *n* (%), $N=47$	
Hepatitis	11 (23)
Colitis	10 (11)
Adrenal insufficiency	8 (17)
Hypothyroidism	7 (15)
Myocarditis	7 (15)
Arthritis	6 (13)
Dermatitis	4 (9)
Myositis	3 (6)
Other*	6 (13)

*nephritis (1), hypophysitis (1), pancreatitis (1)

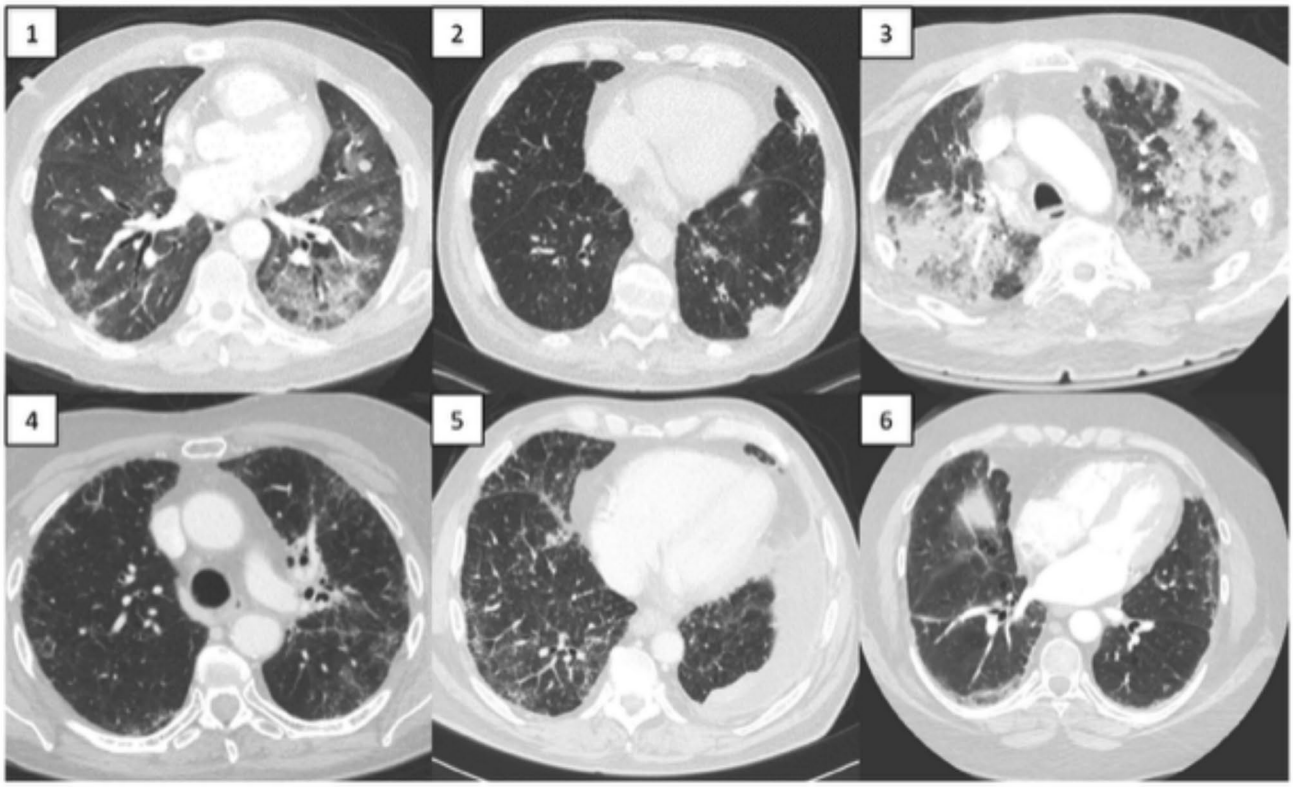

Fig. 1 Radiographic patterns seen in immune checkpoint inhibitor-related pneumonitis: 1) Diffuse bilateral predominantly ground-glass opacities, 2) Peripheral predominant regions of nodular consolidation, 3) Consolidation within the bilateral upper lobes, 4) Reticulation and some ground-glass opacities bilaterally with a peripheral predominance, 5) Extensive interlobular septal thickening with ground-glass and faintly nodular opacities, 6) Scattered pulmonary cystic changes in addition to bibasilar reticulations

predominantly in those diagnosed with grade 4 pneumonitis (Supplemental Table 2).

Clinical outcomes and resolution

Median OS for the entire cohort was 2.5 years (95% CI: 1.8, NR). Median OS was 2.3 years (95% CI: 1.1, NR) for stage 4 disease. Median OS was 2.1 years (95% CI: 1.1, NR) for non-small cell lung cancer and 4.3 years (95% CI: 1.8, NR) for melanoma. An ICI pneumonitis grade 3 or 4 was associated with inferior survival compared to grades 1 or 2 (HR 5.85, 95% CI: 2.27, 15.09; $p < 0.001$). The median OS based on grade of ICI pneumonitis was 2.3 years (95% CI: 1.8, NR) for grade 1; 5.6 years (95% CI: 4.3, NR) for grade 2; 1.1 years (95% CI: 0.7, NR) for grade 3; and 0.2 years (95% CI: 0.1, NR) for grade 4. The event free survival for ICI pneumonitis at 6 months were the following: 100% for grade 1, 94% for grade 2, 84% for grade 3, and 55% for grade 4 (Fig. 2).

Regardless of pneumonitis grade, most patients achieved complete (46%) or partial (39%) resolution of radiographic changes after treatment. No radiographic improvement was seen in 15% of patients. Clinical improvement was observed in 134 (89%) of patients following treatment (Table 3).

Overall mortality from pneumonitis was 15%. Mortality from ICI pneumonitis was higher in patients with decreased baseline PFTs, specifically in FEV1, FVC, and TLC. Age, sex, PD-L1 expression, and BAL testing were not found to be associated with increased risk of mortality from ICI pneumonitis. Further, no PFT parameter was associated with change in odds of resolution. Additionally, age, sex, PD-L1 expression, and smoking history were not associated with resolution (Supplemental Table 3).

Rechallenge with immunotherapy

In our cohort, 51 (30%) patients were rechallenged with ICI after an initial episode of ICI pneumonitis. Among those rechallenged, 23 (45%) developed recurrent pneumonitis (78% grade 1–2, 22% grade 3–4). Patients who were rechallenged with ICI had significantly improved OS compared to patients who were not rechallenged (HR 0.38, 95% Cl: 0.21, 0.68, $p = 0.001$). On subset analysis, most of the benefit was likely coming from patients with grade 2 severity (Fig. 3).

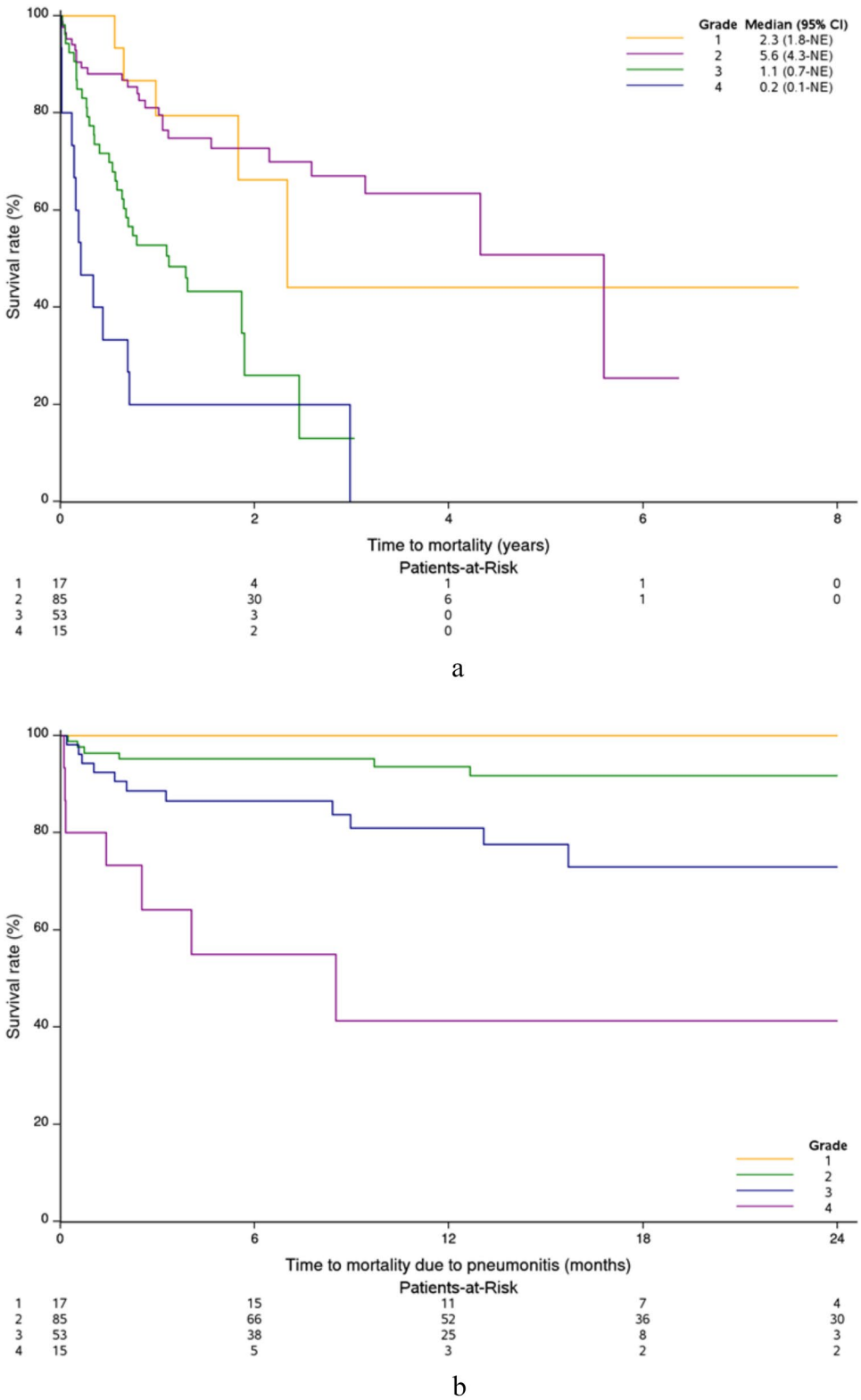

Fig. 2 Kaplan–Meier curves for grade 1–4 immune checkpoint inhibitor therapy-related pneumonitis Graph 1: Overall survival. Graph 2: Event free survival

Predictive modeling for risk of death from ICI pneumonitis

Risk of death from pneumonitis prior to starting ICI was modeled with an area under the curve of the receiver operator characteristic (AUC-ROC) of 0.79 with the most contributory features including peripheral blood lymphocyte count obtained at diagnosis of ICI pneumonitis (prior to

Table 3 Treatment outcomes immune checkpoint inhibitor-related pneumonitis

	Overall ($n=170$)
Immunosuppressive treatments, *n* (%)	
Corticosteroids	150 (89)
Mycophenolate	7 (4)
Infliximab	5 (3)
Other	1 (1)
Initial prednisone dose (mg), median (IQR)	60.0 (40.0, 80.0)
Mortality related to pneumonitis, *n* (%)	25 (15)
Resolution*, *n* (%), $N=133$	109 (82)
Clinical improvement, *n* (%), $N=151$	134 (89)
Radiographic improvement, *n* (%), $N=146$	
Complete	67 (46)
Partial	57 (39)
No	22 (15)
Oxygen dependent, *n* (%)	49 (29)
Nasal cannula	49 (100)
L/min at rest, median (IQR), $N=45$	3.0 (2.0, 3.0)
Rechallenged, *n* (%)	51 (30)
Recurrent pneumonitis, *n* (%)	23 (45)
Recurrent pneumonitis grade, *n* (%)	
Grade 1–2	18 (78)
Grade 3–4	5 (22)

*Defined as composite of clinical improvement (yes) and radiographic improvement (complete or partial)

corticosteroid administration), oxygen dependence, adverse PFT values involving FEV1/FVC and TLC, and PD-L1 expression. These features represented both categorical and continuous data and were determined to be significant by model reverse engineering and isolated feature permutation. Logistic regression produced an AUC-ROC of 0.87 (95% CI: 0.72, 1.0; $p<0.0013$). Risk of death from pneumonitis at the time of ICI pneumonitis diagnosis was modeled with an AUC-ROC of 0.85 and the most contributory features were similar to the list described in the previous endpoint. Logistic regression produced an AUC-ROC of 0.89 (95% CI: 0.81, 0.96; $p<0.0001$). Risk of death from any cause at the time of ICI pneumonitis diagnosis until follow-up concluded by 12/2022 produced a model with an AUC-ROC of 0.75 with the most contributory features including need for supplemental oxygen, decreased baseline DLCO obtained from PFT, basic laboratory values contained within a complete blood count with differential and a complete metabolic profile (obtained at diagnosis of ICI pneumonitis), and PD-L1 expression. Logistic regression produced an AUC-ROC of 0.85 (95% CI: 0.76, 0.93; $p<0.001$) (Fig. 4).

Predictive modeling for the development of low versus high-grade ICI pneumonitis

The propensity to develop low versus high-grade pneumonitis was modeled using a binary classification model with an AUC-ROC of 0.74. The features most predictive of whether a patient would develop high-grade pneumonitis were decreased baseline DLCO obtained from PFTs, ICI choice, and laboratory values obtained at diagnosis of ICI pneumonitis including hemoglobin concentration, monocyte count and white blood cell count.

Discussion

In this study, we present the largest comprehensive analysis of patients diagnosed with confirmed ICI pneumonitis and, to the best of our knowledge, the first study to incorporate predictive modeling in this patient population. As shown in this analysis and others, ICI pneumonitis continues to remain a feared complication of ICI therapy necessitating the need of risk stratifying tools. We demonstrate that commonly available clinical data can be used to identify patients at

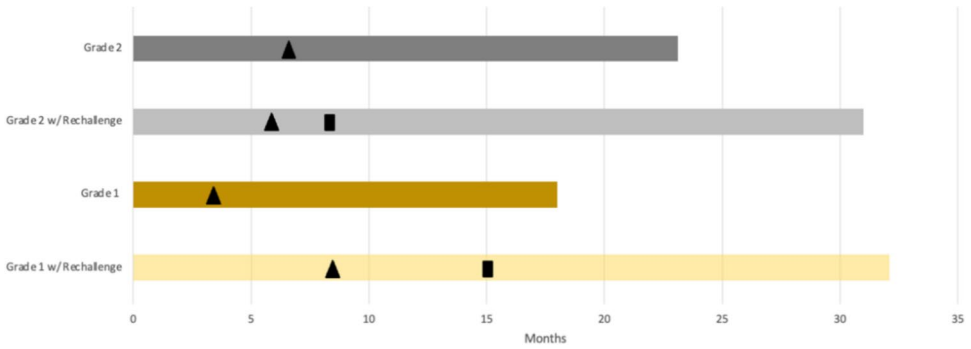

Fig. 3 Swimmers plot comparing overall survival of patients with grade 1–2 immune checkpoint inhibitor therapy-related pneumonitis with and without rechallenge of immunotherapy. Triangle Median Time from initiation of immunotherapy to pneumonitis (months). Square: Median Time from initiation of immunotherapy to rechallenge (months)

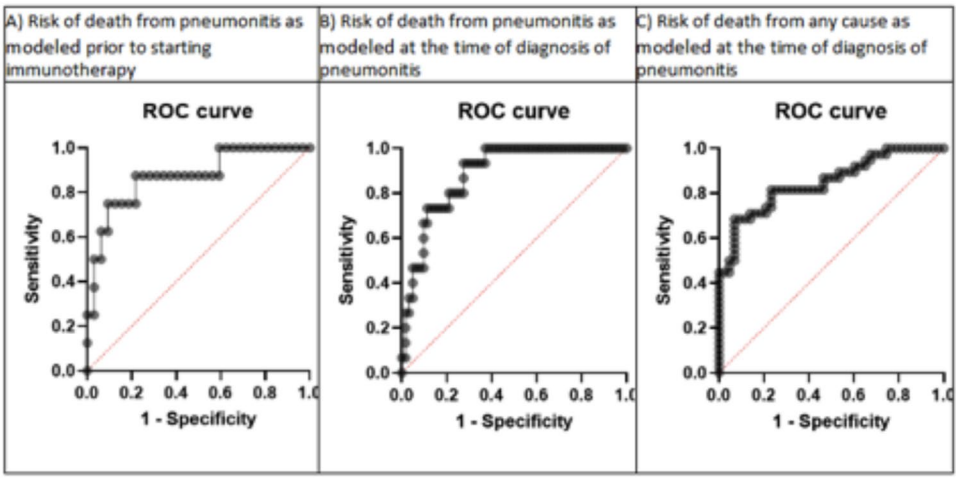

Fig. 4 Predicative modeling of the risk of death associated with Immune checkpoint inhibitor therapy-related pneumonitis

high risk of death from ICI pneumonitis and risk stratify from low/high-grade ICI pneumonitis at time of diagnosis with relative accuracy with at least an AUC-ROC of 0.74 or greater. Models such as these can aid clinicians in the management of ICI pneumonitis; however, further validation using large databases is required.

Since the first approval in 2011, ICI therapy has been a paradigm shift in oncological practice [14]. In the present study, we found that NSCLC and melanoma formed the largest percentage of patients diagnosed with ICI pneumonitis likely because until 2015, ICI was solely being used in NSCLC and melanoma [15, 16]. The higher incidence of pneumonitis in NSCLC has been presumed to be related to the underlying thoracic tumor burden and parenchymal destruction due to a concentrated inflammatory effect [17, 18]. Although our cohort did not show an increased severity of ICI pneumonitis in the setting of underlying pulmonary morbidities, it was seen more often in NSCLC [19]. Moreover, we found no correlation between cancer stage and ICI pneumonitis grade, in contrast to previous reports suggesting otherwise [20–24]. Further studies will be needed to understand which underlying cancers pose an inherent risk factor for developing ICI pneumonitis.

Risk factors traditionally associated with severity of ICI pneumonitis include interstitial lung disease, combination therapy, prior exposure to radiation, smoking status, age exceeding 70, and the specific histologic type of cancer [17, 21]. However, within our diverse cohort characterized by heterogeneity not only in tumor types but also in the selection of ICI, our findings present a departure from the established literature in predicting severe or negative outcomes. In our study, significant predictors of ICI pneumonitis severity included BAL neutrophils, baseline DLCO, and intrathoracic tumors. A history of lung radiation combined with ICI therapy showed a trend toward significance. This contrasts with the prevailing trend in existing literature, which often focuses on assessing risk factors within specific tumor types, such as NSCLC [22]. Pulmonary function parameters (FEV1, FVC, TLC) were significant predictors of both overall mortality and pneumonitis-related mortality, while other factors, such as PD-L1 expression and BAL lymphocyte count, did not short consistent associations across both conditions. To our knowledge, this is the first study to look at risk factors contributing to mortality from ICI pneumonitis.

Our study is one of the few detailing PFT changes before and after initiation of ICI. Unlike other reports, spirometry values and lung volumes were not associated with ICI pneumonitis grade [18]. Although we did not find underlying pulmonary pathology as a risk factor for ICI pneumonitis severity, when PFTs were available, the odds of higher-grade pneumonitis were related to lower diffusion capacity. Like PFTs, BAL data were space and present primarily in those hospitalized. In those who did not undergo BAL, infection was excluded by the treating clinician either by the absence of infectious symptoms or by noninvasive infectious evaluation. The predominant cell type found in BALs were macrophages. These findings may represent the initial course of the disease process in which macrophage activation initiates the immune response and stimulates T lymphocytes [23]. Moreover, a macrophage predominant cell count likely rules out an infectious etiology for the imaging findings. This finding can also help differentiate between radiation-induced pneumonitis in which the cell count is typically lymphocytic [24, 25]. Prospective studies are needed to identify the role of PFTs and BAL in ICI pneumonitis.

Although multiple society guidelines recommend corticosteroids at varying doses based on severity grade as the mainstay of therapy, our data demonstrate that corticosteroid dosing varies widely in clinical practice [26, 27]. The practice of corticosteroid dosing varies, as evidenced by our data. In our cohort, the median dose of initial prednisone was 60 mg with 89% clinical

improvement and 61% radiographic partial or complete improvement. Higher grade pneumonitis often was treated initially with intravenous prednisone equivalents. Only 3% of patients were administered steroid-sparing agents and represented difficult to treat or refractory cases, predominantly in grade 4 pneumonitis. Rechallenge with ICI occurred in 30% of patients, with 45% experiencing recurrent pneumonitis. Recurrent adverse events after rechallenging in our cohort were similar to other studies showing a 30–50% rate of recurrent irAEs [28]. Rechallenged patients had significantly improved survival, especially in grade 2 cases. Prompt recognition of pneumonitis is important to avoid ≥ grade 3 complications, while further studies should be done to validate whether all patients with ≤ grade 2 pneumonitis should undergo rechallenge. Clinicians should be mindful of pneumonitis recurrence but should not consider it an absolute contraindication when considering rechallenging a patient with ICI.

This study is one of the largest single-center investigation focusing on confirmed cases of ICI pneumonitis in a diverse patient cohort undergoing ICI therapy for various solid tumors. Its extensive scope enhances the potential generalizability of findings. The research identifies notable risk factors associated with severity of pneumonitis and employs predictive modeling to assess mortality risks. However, there are several limitations of this study to address. The retrospective design presents challenges due to variability in documentation practices among healthcare providers. Additionally, using the keywords "pneumonitis" and "immunotherapy" in clinical documentation to identify patients may have inadvertently excluded some patients with ICI pneumonitis. However, in the absence of a specific ICD code to accurately identify these patients, this approach, after review by an informatics specialist and a statistician, was deemed the most effective way to generate a pure cohort of ICI pneumonitis cases.

The nonrandomized nature may have also unintentionally introduced selection bias. As with all retrospective studies, there are potential inconsistencies or limitations in data. For example, ECOG (Eastern Cooperative Oncology Group) status, a scale commonly used to assess a patient's level of functioning, was not collected as a variable due to inconsistences in updating it documentation. Presumably, though, patients in our cohort had performance status amenable to receiving systemic treatment. Similarly, corrected diffusion capacity was unavailable for most patients so uncorrected diffusion capacity was used instead. While this served as a surrogate marker for underlying lung disease, it could have been influenced by other non-pulmonary factors such as anemia or pulmonary hypertension. PD-L1 testing was collected only on patients with NSCLC, another limitation, though most patients in the cohort had NSCLC and analyses have been adjusted for NSCLC.

While our heterogenous of cohort of patients, in terms of cancer type, is more representative of real-world practice, this study's findings focusing on patients with solely confirmed ICI pneumonitis does not allow for extrapolation to patients who may have other concurrent diagnoses or when the diagnosis of ICI pneumonitis is uncertain. Additionally, the absence of well-defined diagnostic and treatment guidelines limits comprehensive insights into best practices, and the evolving landscape of ICI pneumonitis diagnostics and treatments adds complexity to the interpretative framework. Finally, external validation is required to confirm the results of the predictive modeling.

This study on ICI pneumonitis highlights valuable insights into its clinical characteristics and outcomes. We demonstrate that commonly available clinical data can accurately identify high-risk patients at the time of ICI pneumonitis diagnosis, emphasizing the need for standardized diagnostic tests and treatment. Moreover, the heterogenous population allows for some generalization of our findings. Future research should prioritize prospective studies to further delineate malignancy-related risk factors and enhance patient-specific risk assessment.

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Declarations

Conflict of interest The authors declare no competing interests.

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