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Impact of Checkpoint Inhibitor Pneumonitis on Survival in NSCLC Patients Receiving Immune Checkpoint Immunotherapy

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ABSTRACT

With increasing use of immune checkpoint inhibitors (ICIs) for advanced NSCLC, there is increasing recognition of immune-related adverse events associated with ICI use. We recently reported increased incidence of checkpoint inhibitor pneumonitis (CIP) in ICI-treated NSCLC patients. Since development of immune-related adverse events in other organ systems has been associated with either no change or even improvement in tumor response/cancer outcomes, we sought to better understand the impact of CIP development on overall survival in ICI-treated NSCLC patients. Using baseline and follow-up data collected on a cohort of 205 ICI-treated NSCLC patients, we used a multi-state modeling approach to understand the effect of developing CIP on the risk of death. We observed time-dependent changes in risk of developing and recovery from CIP, with an increased risk of both developing and recovering from CIP in the first year after initiating ICI. We found that developing CIP independently increased the risk of transitioning to death in both adjusted and unadjusted models. In the multivariate model, we found that the increase in mortality associated with CIP was only seen in patients with adenocarcinoma tumor histology. Collectively, these findings suggest that in NSCLC, development of CIP worsens survival in patients receiving immunotherapy.

Introduction

Use of immune checkpoint inhibitors (ICIs) has significantly improved overall survival in advanced stage NSCLC.[1–6] Initially approved primarily for patients who

failed conventional cytotoxic chemotherapy, recent trials have established the efficacy of ICIs both alone and in combination with chemotherapy in patients with newly diagnosed advanced NSCLC, as well as in stage III disease, based on improvements in recurrence-free survival.[7] In addition to approvals for multiple indications in NSCLC, ICIs have also shown improved outcomes in a variety of tumor types including head and neck squamous cell carcinoma, malignant melanoma, Hodgkin's lymphoma, renal cell carcinoma, NSCLC, cervical carcinoma, esophagogastric carcinoma, urothelial carcinoma, and microsatellite-unstable colorectal carcinomas.[8] This has led to a dramatic increase in ICI usage. Increased use along with use of combination therapy with other immune modulators has led to an increased awareness of ICI-related toxicities, collectively labeled immune-related adverse events (irAEs).[9]

As part of a multidisciplinary irAE toxicity team effort at our center, we sought to better understand the incidence of, risk factors for, and survival impact on checkpoint inhibitor pneumonitis (CIP) in NSCLC patients treated with ICIs (either with a programmed death 1 [PD-1] inhibitor or with PD-1/secondary agent).[10] We recently reported that (1) the incidence of CIP was significantly higher (19%) in our cohort than previous clinical trials (which have ranged from 3% to 5%); (2) almost all of the higher grade (i.e., grade 3 or higher) CIP cases occurred early (within the first 6 months) of ICI initiation; and (3) adenocarcinoma tumor histology (compared to non-adenocarcinoma histology, including squamous cell NSCLC) was associated with a decreased risk of developing CIP (odds ratio: 0.38; 95% confidence interval [CI]: 0.17–0.82).[11,12] The purpose of this study was to determine whether (1) development of CIP increased mortality risk and (2) demographic and/or tumor/treatment-related factors affected the relationship between CIP development and mortality. We hypothesized that CIP independently increased mortality in ICI-treated NSCLC patients.

Methods
Study Population

Following institutional review board and ethical approval, we performed a retrospective cohort study of patient outcomes of individuals diagnosed with advanced NSCLC and treated with ICI either as standard-of-care or part of a clinical trial at Johns Hopkins Hospital between January 1, 2007, and July 31, 2017. Patient demographics, tumor histology, treatment regimen and outcomes (development of CIP, recovery from CIP, and death) were abstracted from electronic medical records. Therapies included ICI agent(s) and choice of additional agent (a second ICI, chemotherapy, or other) and use of prior systemic chemotherapy. Individuals were followed from the time of initiation of ICI until death or last in-person clinical visit before December 31, 2017. Follow-up data via in-patient admission, telephone call, or in-person clinic visit was available for all patients.

CIP Diagnosis and Management

CIP diagnosis was determined clinically by the treating oncologist (P.F., D.E., K.M., R.K., C.H., B.L., J.F., J.B., or J.N.) in consultation with a multidisciplinary irAE team consisting of pulmonologists (S.D. or K.S.), a radiologist (C.L.), and a second medical oncologist (J.N.) as previously described.[12] Briefly, using a combination of clinical (history and exam, pulse oximetry, and pulmonary function testing), radiographic (presence or absence of tumor progression and pattern of parenchymal infiltrates), and biologic parameters (sputum cultures and/or bronchoscopy, respiratory viral cultures, and routine labs), we excluded alternative etiologies such as heart failure, infection, and tumor progression. ICI therapy was discontinued in all cases when a patient was diagnosed with symptomatic CIP (Common Terminology Criteria for Adverse Events [CTCAE] grade 2 or higher).[13] All patients diagnosed with CIP were treated with high-dose corticosteroids as per current guidelines.[14,15] Following initiation of steroid therapy, clinical improvement (recovery) was defined as a decrease in oxygen requirement, an increase in exercise capacity (improved walking distance), and a decrease in radiographic infiltrates (as assessed by the radiologist) following commencement of CIP treatment. Conversely, worsening was defined as a lack of improvement in oxygen requirement, exercise capacity, and/or radiographic infiltrates after 72 hours of corticosteroid therapy. Patients who continued to require supplemental oxygen had persistent infiltrates and therefore were unable to be fully weaned off steroids were defined as having chronic pneumonitis.

Statistical Analysis

Demographic and clinical characteristics of patients who remained alive at study completion were compared to those who died during follow-up using chi-squared or Student's *t* tests for categorical and continuous variables, respectively.

As CIP was a time-varying event from which recovery could occur, we used a continuous time Markov multistate model to describe the clinical transitions of those alive with and without CIP to death.[16] Such models have traditionally been used to study the effect of transitory states of illness (or interventions such as transplantation) on progression to death.[16-18] Figure 1 shows the Markov model describing the transient states of individuals without CIP (state 1) and those
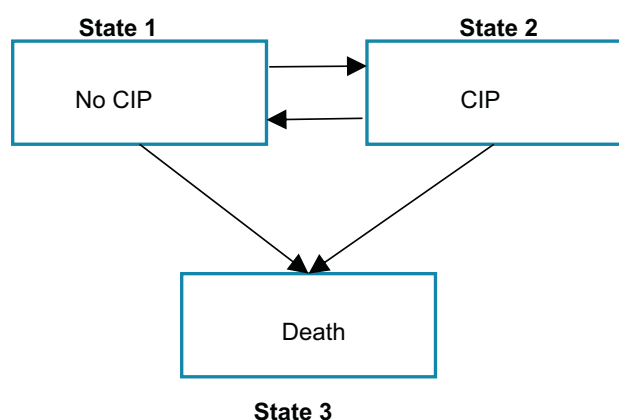
Figure 1. Diagram showing the multistate model used for modeling the impact of CIP on survival in ICI-treated NSCLC patients. CIP, checkpoint inhibitor pneumonitis; ICI, immune checkpoint inhibitor.

with CIP (state 2) along with the absorbing state (i.e., a final state from which no outward transitions are allowed), death (state 3). The transition time from state 1 to state 2 was defined as the difference between date of initiation of ICI therapy and date of onset of pneumonitis (defined as the date of clinical annotation of the diagnosis of CIP). If recovery occurred (i.e., transition from state 2 to state 1), the time between onset of pneumonitis and onset of recovery (defined as the first clinic or inpatient visit where improvement in oxygenation and symptoms was documented) was used. Similarly, death (or transition to state 3) was taken as the date from the last entry into either state 1 or state 2 to date of death. Importantly, as individuals were allowed to transition between no-CIP and CIP and back to no-CIP, individuals could contribute multiple observations to either the CIP free or CIP states. For example, a patient who develops CIP, recovers, and then dies would be considered to have transitioned from state 1 to state 2, followed by state 2 back to state 1, and finally from state 1 to state 3. Patients who never leave state 1 represent patients who neither developed CIP nor died during the follow-up period. From the Markov model estimates for both transition intensities (TIs) and probabilities (TPs) from one state to another were obtained. The former summarizes the instantaneous risk of transition between any two states and is analogous to a hazard rate whereas the latter is an estimate of the probability of transitioning to a different state or time.[16]

Initially an unadjusted Markov model was used to summarize the TI and TP with CIs for TPs estimated by sampling maximum likelihood estimates of the log transformed transition intensity.[17] We present

detailed results of this model which describes the experience of patients treated at our center, focusing on describing the transition throughout time in each stage. Next, a multivariable model adjusted for covariates including sex, histology (adenocarcinoma, squamous, or other), receipt of chemotherapy (yes versus no), and ICI therapy received (nivolumab, pembrolizumab, or other), and receipt of combination ICI therapy (yes vs. no) was fitted and covariate-specific hazard ratios (HRs) were produced which were used to evaluate the association between individual-level characteristics and transition between states (i.e., risk factors). Finally, we explored differences of TIs within the subgroups of patients defined by the previously described covariates (e.g., differences between transition to death with and without CIP in males versus females). A *p* value less than 0.05 was considered statistically significant. All analyses were performed using the R statistical environment with multistate models implemented using the *msm* R package.[19,20]

Table 1. Baseline Characteristics

	Overall (N = 204)	Alive (n = 118)	Dead (n = 86)	p
Median age (IQR), y	68 (14)	69.5 (15)	68 (13)	0.83
Female, n (%)	91 (44)	53 (45)	38 (44)	1
Race, n (%)				1
Caucasian	162 (79)	94 (79.6)	68 (79)	
African American	35 (17)	20 (16.9)	15 (17.4)	
Other	8 (3.9)	4 (3.3)	3 (3.4)	
Smoking, n (%)				0.42
Current	15 (7)	11 (9)	4 (5)	
Former	151 (74)	86 (73)	64 (74)	
Never	39 (19)	21 (18)	18 (21)	
Tumor histology, n (%)				0.76
Squamous	57 (27)	33 (41)	24 (24.6)	
Adenocarcinoma	131 (64)	76 (46)	55 (68.6)	
Other[a]	16 (9)	9 (13)	7 (6.6)	
Initial cancer stage, n (%)				0.766
I	17 (8.7)	11 (9)	6 (7)	
II	16 (8.3)	11 (9)	5 (6)	
III	57 (27.8)	28 (24)	29 (34)	
IV	109 (53.1)	65 (55)	44 (51)	
Unknown	5 (2)	3 (2)	2 (2)	
Enrolled in ICI trial				
Prior chemotherapy, n (%)	151 (74)	86 (73)	65 (75)	0.61
Prior surgery, n (%)	47 (23)	30 (25)	17(20)	0.4
ICI agent, n (%)				0.02
Nivolumab	163 (78)	86 (73)	73 (84)	
Pembrolizumab	23 (11)	19 (16)	4 (5)	
Other	22 (11)	13 (11)	9 (11)	
Combination ICI	63 (30)	30 (25)	33 (38)	0.05

[a]Other: large cell neuroendocrine carcinoma, mesothelioma, atypical carcinoid, sarcomatoid carcinoma.
IQR, interquartile range; ICI, immune checkpoint inhibitor.

Table 2. Number of Transitions and Transition Intensities in Unadjusted Multistate Model of CIP

From State	To State					
	State 1		State 2		State 3	
	n	TI (95% CI)	n	TI (95% CI)	n	TI (95% CI)
State 1[a]	126	−0.0015 (−0.0018 to −0.0012)	38	0.00057 (0.0004 to 0.0007)	62	0.00094 (0.0007 to 0.0012)
State 2[b,c]	8	0.00082 (0.0004 to 0.0016)	6	−0.0034 (−0.0047 to −0.0024)	25	0.00256[d] (0.0017 to 0.0037)
State 3	0		0		0	

State 1: alive, No CIP. State 2: alive, CIP. State 3: death.
[a]The average length of stay in state 1 before transitioning to either state 2 (CIP) or state 3 (death) was 727.6 d.
[b]The average length of stay in state 2 before transition either back to state 1 or to death was 116.6 d.
[c]One patient developed pneumonitis at 0 d, and thus began in state 2.
[d]Fold increase in transition intensity to death after developing CIP ($q_{2,3}$ / $q_{1,3}$) = 2.73 (95% CI: 1.71 to 4.34)
CIP: Checkpoint inhibitor pneumonitis; TI, transition intensity; CI, confidence interval.

Results

A total of 204 patients met inclusion criteria and comprised the study population of whom 38 (19%) developed CIP during follow-up. Patients were followed for a median of 8.2 months (interquartile range [IQR]: 1 year) and progression to CIP occurred at a median of 6.3 months (IQR: 9.9 months). Baseline characteristics of individuals who died during follow-up (n = 86) and those who were alive (n = 118) at study completion are presented in Table 1. The median age of subjects was 68 years (IQR: 14 years) and the majority of patients were male (56%) and white (79%). Demographic and clinical characteristics were similar between the groups, including the distributions of cancer histology and stage. However, the proportion of patients who received pembrolizumab or other non-nivolumab ICI was greater in among survivors (27%) compared to the nonsurvivor group (16%). In addition, combination ICI therapy was received more frequently among nonsurvivors (33 of 86; 38%) than survivors (30 of 118; 25%).

Overall, 61% (n = 126) of patients remained CIP free (state 1) during follow-up. Of the patients who transitioned to state 2 (n = 38), 8 (21%) returned to state 1 (recovered), whereas 6 (15%) remained in state 2 (chronic pneumonitis) and 25 (65%) transitioned to death.

Results of the unadjusted Markov multistate model summarizing the TIs between states are presented in Table 2. From state 1, individuals had a positive risk of transitioning to CIP (TI = 0.00057) and death (TI = 0.00094) and, over time, were less likely to remain CIP-free and alive (TI = -0.0015). Those in state 2 were more likely to transition to death (TI = 0.00256) or CIP-free (TI = 0.00082) than to remain with CIP (TI = -0.0034). A significantly higher risk (2.7-fold) of transition to death was seen in CIP+ patients compared to patients who did not develop CIP; with a correspondingly favorable survival for patients without CIP (Fig. 2). The probability of remaining in state 2 (i.e., CIP) is highest immediately following ICI with the probabilities of both development of and recovery from CIP peaked at approximately 1 year following CIP diagnosis (Fig. 3A). Importantly, the TP for death with CIP was significantly different compared to death without CIP (Fig. 3B). Table 3 presents the transition probabilities at various follow-up times for: (1) development of CIP (state 1 to 2), recovery from CIP (state 2 to 1), death without CIP (state 1 to 3), and death following CIP (state 2 to 3). Over time, the probability of death increased; however, at all times patients with CIP had a higher probability of death compared to patients without CIP.
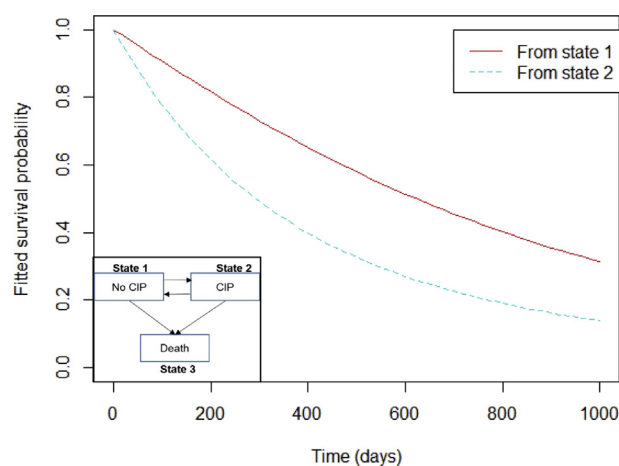
Figure 2. Fitted survival probability curves based on transition intensities from state 1 to state 3 (i.e., transitioning to death without developing CIP) and state 2 to 3 (i.e., transitioning to death after developing CIP) in the unadjusted multistate model. CIP, checkpoint inhibitor pneumonitis.

A

B
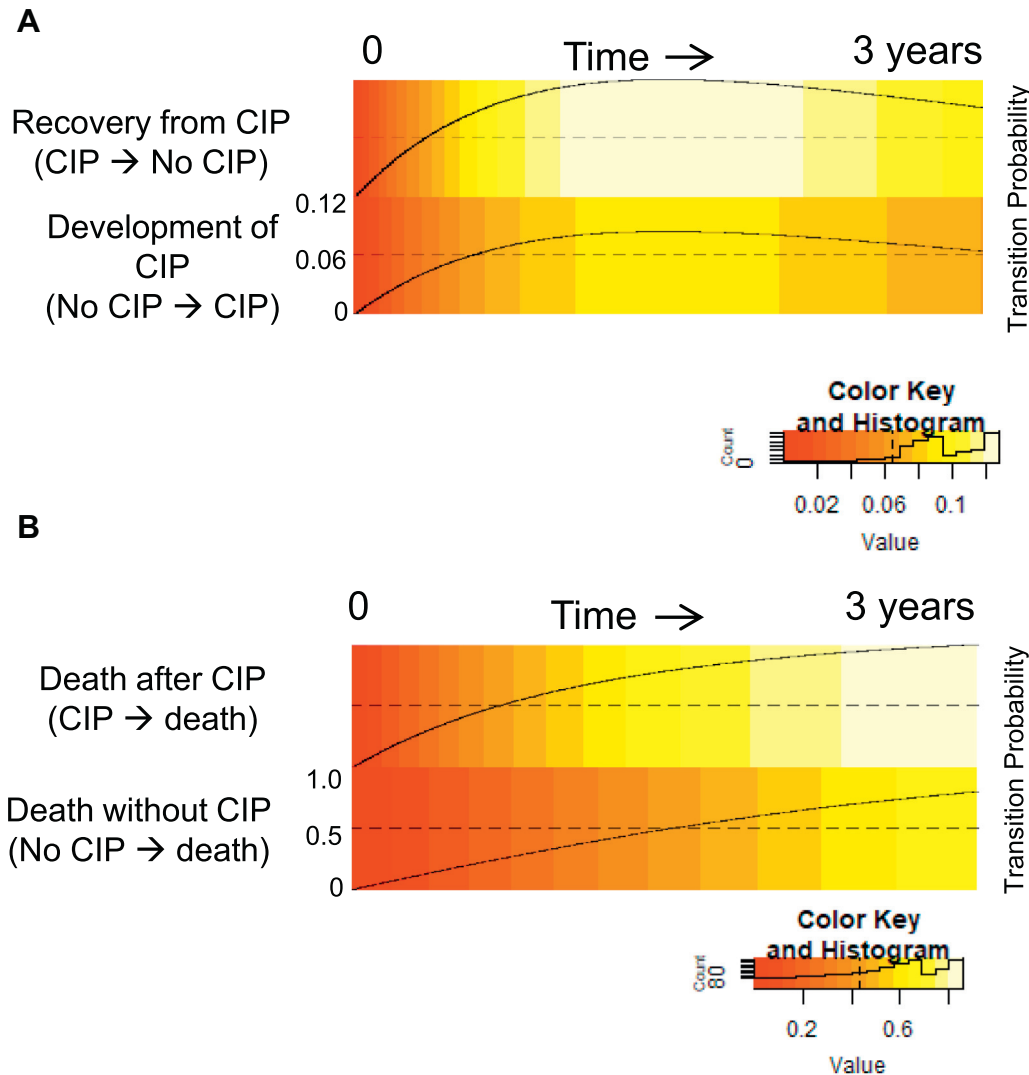
Figure 3. State-specific transition probabilities over time. Heatmaps showing change transition probabilities over time in (*A*) patients who develop CIP and patients who recover from CIP, and in (*B*) patients who die with and without CIP. CIP, checkpoint inhibitor pneumonitis.

Similarly, probability of developing CIP (state 1 to state 2) or recovering from CIP (state 2 to state 1) increased gradually throughout the first year in each state and then decreased in subsequent years.

Table 4 presents the TIs after adjustment for individual level demographic and clinical characteristics (prior chemotherapy, ICI agent, tumor histology, use of combination ICI, and sex). Results were similar to those

Table 3. Transition Probabilities From Individual States[a] at Various Follow-Up Times

Time	State 1 – State 2		State 1 – State 3		State 2 – State 1		State 2 – State 3	
	TP	95% CI	TP	95% CI	TP	95% CI	TP	95% CI
1 mo	0.01	(0.011-0.021)	0.028	(0.022-0.035)	0.022	(0.011-0.045)	0.073	(0.050-0.10)
2 mo	0.02	(0.022-0.040)	0.056	(0.044-0.071)	0.042	(0.02-0.08)	0.14	(0.097-0.20)
3 mo	0.04	(0.029-0.055)	0.084	(0.06-0.10)	0.059	(0.02-0.11)	0.20	(0.14-0.28)
6 mo	0.06	(0.047-0.09)	0.16	(0.13-0.20)	0.09	(0.04-0.18)	0.35	(0.25-0.47)
1 y	0.08	(0.06-0.12)	0.31	(0.26-0.37)	0.12	(0.06-0.22)	0.56	(0.44-0.69)
2 y	0.07	(0.05-0.11)	0.55	(0.47-0.63)	0.11	(0.05-0.20)	0.78	(0.67-0.88)
3 y	0.05	(0.03-0.08)	0.71	(0.63-0.78)	0.08	(0.04-0.15)	0.87	(0.78-0.93)

[a]State 1: alive, no CIP; state 2: alive, CIP; state 3: death.
TP, transition probability; CI, confidence interval.

Table 4. Transition Intensities in Adjusted[a] Multistate Model of CIP

	To State		
	State 1 TI (95%CI)	State 2 TI (95% CI)	State 3 TI (95% CI)
From State			
State 1	−0.0015 (−0.0018, −0.0012)	0.0005 (0.0004, 0.0008)	0.00094 (0.0007, 0.0012)
State 2	0.0002 (−Inf, Inf)[b]	−0.0033 (−0.18, −0.00006)	0.003[c] (0.002, 0.0046)
State 3	0	0	0

State 1: alive, no CIP. State 2: alive, CIP. State 3: death.
[a]Adjusted for prior chemotherapy, ICI use, tumor histology, combination ICI, sex.
[b]Given the small number (n = 8) of patients who transitioned from state 2 (CIP) back to state 1 (no CIP), the CIs were very wide in the adjusted model.
[c]Fold increase in transition intensity to death after developing CIP ($q_{2,3}$ / $q_{1,3}$) = 3.26 (95% CI: 1.99-5.35).
CIP, checkpoint inhibitor pneumonitis; CI, confidence interval; TI, transition intensity; Inf, infinity.

in the unadjusted model; for example, the baseline increase in death TI in CIP patients (i.e., state 2 to state 3) was unchanged in the adjusted model. The fold increase in state 2–to–state 3 TI was similar in both the unadjusted (2.37 [95% CI: 1.71–4.34]) and adjusted (3.26 [95% CI: 1.99–5.35]) models.

Results of adjusted multistate models evaluating risk factors for transition are presented in Table 5. Sex, chemotherapy, ICI agent, or combination ICI use were not associated with an increased risk of death from either CIP or non-CIP state (i.e., state 1 to state 3 or state 2 to state 3). Similarly, no covariate was associated with an increased or decreased risk of transition from state 2 to state 1. However, squamous histology (compared to adenocarcinoma) was associated with a significantly higher risk (HR: 2.63; 95% CI: 1.34–5.19) for transitioning to CIP (i.e., state 1 to state 2). The covariate-specific TIs between state 1–to–state 3 and state 2–to–state 3 are presented in Figure 4 with

differences observed both at baseline and by presence/absence of prior chemotherapy, use of combination ICI, and sex. Corresponding to the TPs shown in Figure 5, state 2–to–state 3 TI was not significantly different in patients with nonadenocarcinoma pathology. As shown in the TP plots (with computed CIs) in Figure 4 and fitted survival plots in Supplemental Figure 1, increased mortality with CIP was significantly higher in patients with adenocarcinoma histology but not in patients with nonadenocarcinoma histology (squamous or other).

Discussion

In this study, we described the relationship between development of pneumonitis and survival in ICI-treated NSCLC patients using a multistate model of illness and death and report that development of CIP at any point after initiation of ICI therapy is associated with an increased risk of death. The effect of irAEs on disease progression has been studied in other malignancies and development of (primarily nonpulmonary) irAEs has been associated with improved responses to therapy as well as improved survival in some cases.[21-24] Specifically, in a cohort of 134 ICI-treated NSCLC patients, Haratani et al.[25] used landmark analyses to show that development of irAE by 4 or 6 weeks (but not 8 weeks) of ICI initiation was associated with improved overall survival and progression-free survival; however, the incidence of pneumonitis was low in this cohort (4%). In contrast, our data suggest development of CIP decreases survival in NSCLC. One explanation for our findings is that individual irAEs may have differing effects on survival. Unlike irAEs in other organ systems, hypoxia from pneumonitis is poorly tolerated and can often precipitate failure of other organs due to decreased oxygenation; thus, CIP, especially when at higher grade, may be unique among irAEs with regards to its impact on particularly NSCLC patient mortality. A recent report noted decreased survival in nivolumab-treated NSCLC patients who received steroids for

Table 5. Hazard Ratios From the Adjusted Multistate Model

	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Female	1.66	(0.85-3.23)	1.1	(0.64-1.88)	2.88	(0.51-16.2)	0.55	(0.20-1.47)
Histology (compared to adenocarcinoma)								
Squamous	2.63	(1.34-5.19)	0.92	(0.49-1.73)	2.18	(0.35-13.5)	0.61	(0.23-1.54)
Other	1.63	(0.38-7.0)	1.87	(0.73-4.80)	0.68	(0.04-11.0)	0.36	(0.03-3.4)
Chemotherapy	0.70	(0.32-1.52)	1.04	(0.55-1.98)	4.36	(0.30-62.4)	0.60	(0.19-1.82)
ICI therapy (compared to nivolumab)								
Pembrolizumab	0.96	(0.27-3.43)	1.13	(0.39-3.30)	4.0	(0.32-50.1)	2.68	(0.54-13.2)
Other	0.14	(0.01-1.09)	0.80	(0.35-1.78)	0.00077	(−Inf, Inf)	4.6	(0.5-42)
Combination ICI	1.09	(0.52-2.2)	1.22	(0.70-2.12)	2.36	(0.28-19.45)	1.93	(0.64-5.87)

State 1: alive, no CIP. State 2: alive, CIP. State 3: death.
ICI, immune checkpoint inhibitor; CIP, ; HR, hazard ratio; CI, confidence interval; Inf, infinity.
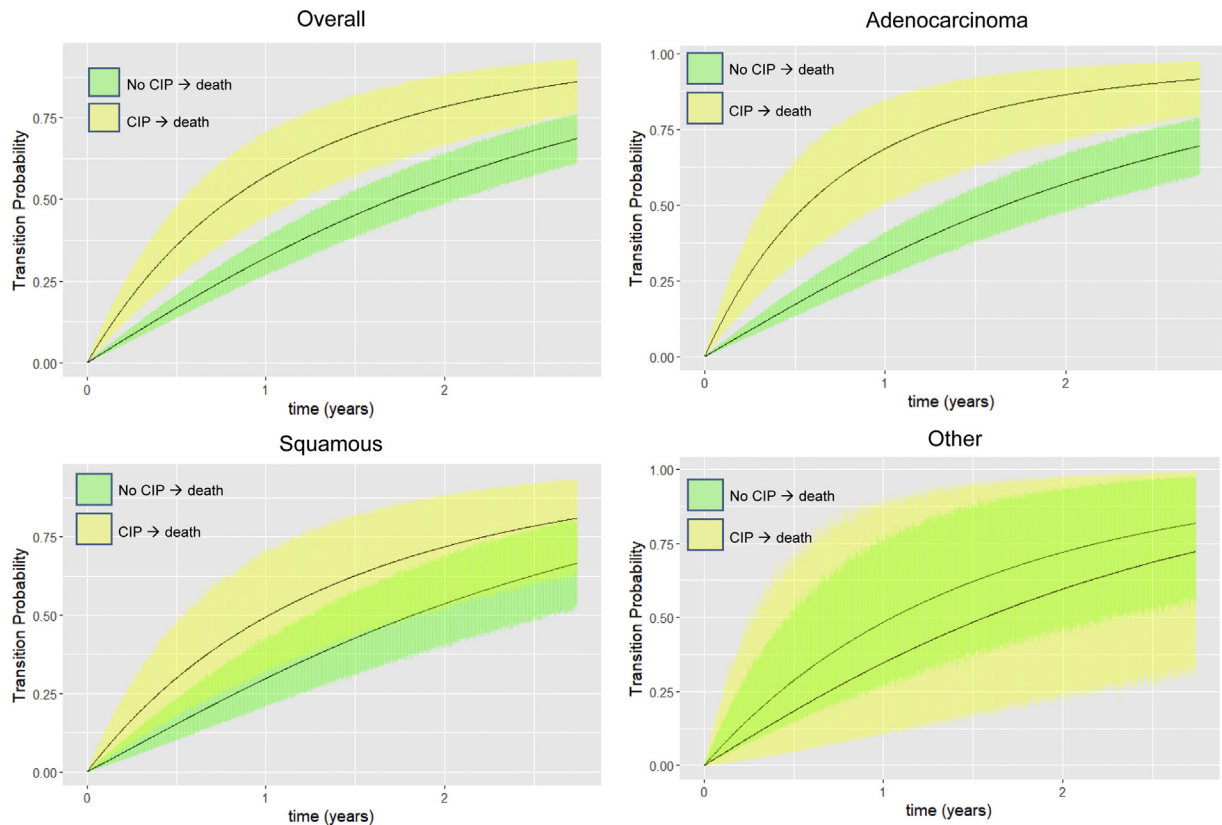
Figure 4. Transition probabilities with computed CIs for probability of death without CIP (*green shading*) and with CIP (*yellow shading*) for all patients (overall) as well as for patients with either adenocarcinoma, squamous or other histology. CI, confidence interval; CIP, checkpoint inhibitor pneumonitis.

nonpneumonitis etiologies (such as exacerbations of chronic obstructive pulmonary disease or brain metastases).[26] Thus, another explanation for our findings is that steroid use (either for CIP or otherwise) may be directly impacting ICI-mediated antitumor activity in the lung.

There are several limitations to our results. This is a single-center retrospective study of NSCLC patients and generalizability of findings may be limited. Importantly, data on pre-existing lung disease (such as obstructive lung disease or interstitial abnormalities) were not recorded; thus, it is possible that comorbid lung conditions affected the risk of CIP development. The majority of patients had adenocarcinoma tumor histology and received nivolumab; therefore, this case mix may not be representative of other centers and the limited numbers of individuals in other covariate-defined subgroups precluded stable estimates for transition. Furthermore, as newer ICIs and combinations are used in NSCLC, such as durvalumab in stage III NSCLC and use of chemotherapy and PD-1/ programmed death ligand 1 (PD-L1)–based ICI combinations become incorporated into standard practice, evaluation of these therapies and their impacts within defined subgroups will be critical for understanding

the etiology of CIP, impact on survival, as well as other patient outcomes.[2,3,27] The transition time to development of CIP reflect the earliest time at which the patient presented with pneumonitis. Thus, it is possible that both development of and recovery from lower grades of CIP could introduce misclassification due to the patient not presenting to clinic with symptoms of CIP or this was not considered when the patient presented with nonspecific CIP symptomatology, such as fatigue. Similarly, in patients who died, CIP diagnosis may not have occurred. In the patients with CIP who died, the exact cause of death was not recorded in our data; thus, it is not clear whether patients died of hypoxia from progressive pneumonitis or from other complications. Finally, the Markov assumption of the models specified that an individual's transition was based solely on the current state and not dependent on the time that was spent in a prior state.

Our prior data suggest that the CIP incidence rate was higher in patients with nonadenocarcinoma histology (squamous or other) and the odds of developing pneumonitis were lower for adenocarcinoma pathology. In our current analysis, the HR for transitioning from state 1 to state 2 (i.e., development of CIP) was
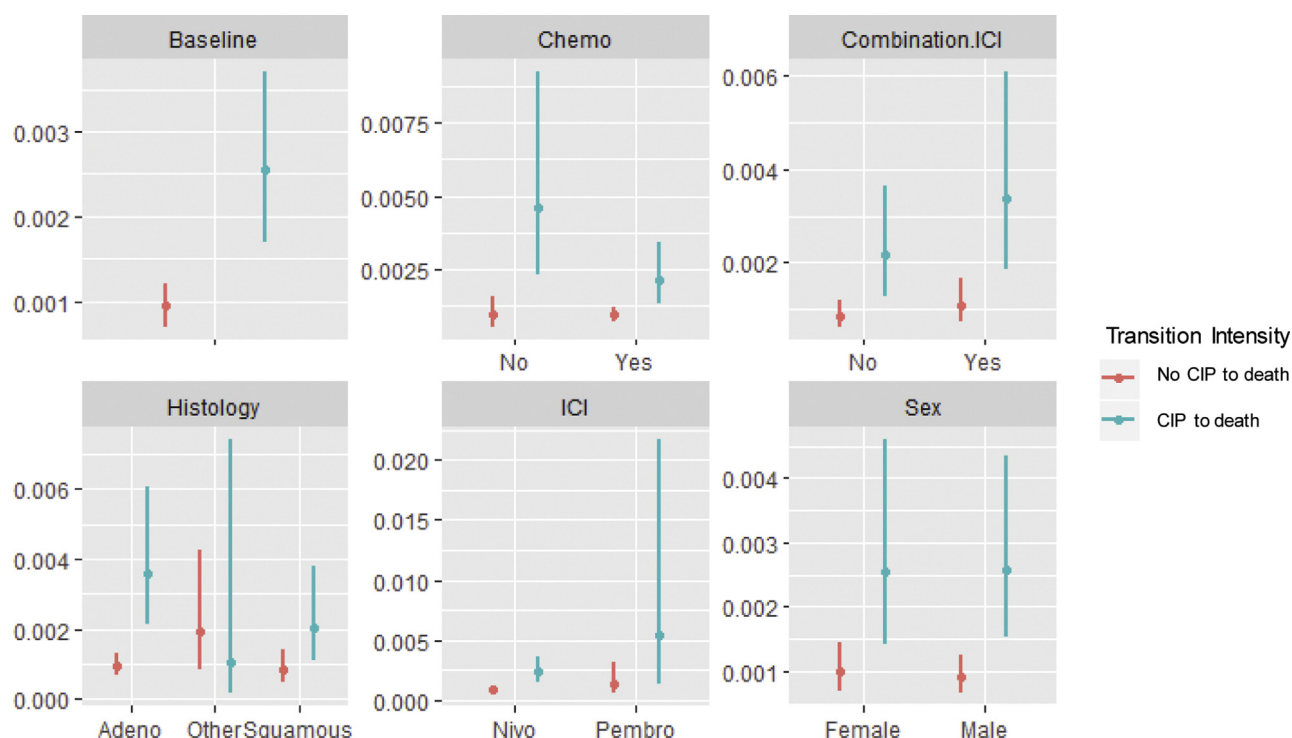
Figure 5. Effect of covariates on transition intensity. Plots showing transition intensity (and 95% CI) for death without CIP (*orange bars*) and death with CIP (*blue bars*) for the unadjusted model (Baseline) and in univariate models adjusted for the listed covariates (presence/absence of prior chemotherapy, use of combination ICI, histology of tumor, ICI agent used, sex). CI, confidence interval; CIP, checkpoint inhibitor pneumonitis; ICI, immune checkpoint inhibitor.

significantly higher in patients with squamous histology, mirroring our earlier incidence analyses. Our current analysis suggests that if CIP does occur in NSCLC patients with adenocarcinoma histology, the risk of dying from CIP is higher compared to squamous NSCLC. One explanation for these findings is that differences in tumor microenvironment (including PD-L1 expression levels) may influence the repertoire of T cells that are present in the adjacent normal interstitium, thus modulating CIP risk. Further preclinical investigations into the effects of tumor histology on PD-L1 expression and T cell migration to the normal lung at baseline and following inflammatory stimuli may prove useful in this regard.

In summary, our data show that development (and lack of recovery) from CIP is associated with increased mortality in ICI-treated NSCLC patients. These data support that pharmacovigilance for irAEs is critical for early detection and treatment of CIP, and that a potentially tailored discussion on the risks for development and mortality from CIP by histology may need to occur.

Acknowledgments

Supplementary Data
Note: To access supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2018.11.016.

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