The Oncologist®

Health Outcomes and Economics of Cancer Care

The Impact of Adverse Events on Health Care Resource Utilization, Costs, and Mortality Among Patients Treated with Immune Checkpoint Inhibitors

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Key Words. Immune checkpoint inhibitors • Adverse events • Survival • Cost • Health care resource utilization

Abstract

Background. We investigated the association between adverse events (AEs) suspected to be immune-related and health care resource utilization, costs, and mortality among patients receiving programmed cell death 1/programmed cell death ligand 1 immune checkpoint inhibitor (ICI) monotherapy for urothelial carcinoma, renal cell carcinoma, non-small cell lung cancer, or Merkel cell carcinoma.

Patients and Methods. We conducted a retrospective cohort study using medical and pharmacy claims and enrollment information from U.S. commercial and Medicare Advantage with Part D enrollees in the Optum Research Database from March 1, 2014, through April 30, 2019. Claims were linked with mortality data from the Social Security Death Index and the National Death Index. Eligible patients had at least one ICI claim between September 1, 2014, and April 30, 2019.

Results. After adjusting for potential confounding variables, we found patients with AEs had more than double the risk of an inpatient stay (hazard ratio [HR], 2.2; 95% confidence interval [CI], 1.9–2.5) and an 80% higher risk of an emergency visit (HR, 1.8; 95% CI, 1.6–2.1) than patients without AEs. Adjusted 6-month total costs were $24,301 higher among patients with an AE versus those without ($99,037 vs. $74,736; 95% CI, $18,828–29,774; $p < .001$). Mean ± SD AE-related medical costs averaged $2,359 ± $7,496 per patient per month, driven by inpatient visits, which accounted for 89.9% of AE-related costs. Adjusted risk of mortality was similar in patients with and without AEs.

Conclusion. Patients with AEs had higher risks of hospitalizations, emergency room visits, and higher health care costs, driven by inpatient stays, than patients without AEs. The adjusted risk of mortality was similar between the two cohorts. ***The Oncologist*** 2021;26:e1205–e1215

Implications for Practice: Patients taking immune checkpoint inhibitors (ICIs) who had adverse events (AEs) had significantly higher health care costs and utilization, driven by inpatient stays, compared with patients who did not. Given this high cost associated with AEs and the differences in the side effect profile of ICIs versus traditional chemotherapy, it is important for physicians to be cognizant of these differences when treating patients with ICIs. Ongoing evaluation, earlier recognition, and more effective, multidisciplinary management of AEs may improve patient outcomes and reduce the need for costly inpatient stays.

Introduction

Identification of the molecular pathways by which cancer cells evade the immune system has led to immunotherapy, arguably one of the greatest advancements in cancer treatment over the past decade. Using monoclonal antibodies to block the immune checkpoint protein programmed cell death 1 (PD-1) and its ligand (PD-L1) overcomes cancer's ability to evade the immune system, restoring the immune response against tumor cells. Since 2014, several

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immunotherapeutic agents that block PD-1/PD-L1 receptors have been approved by the U.S. Food and Drug Administration for use in patients with numerous cancer types, including urothelial carcinoma (UC), renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), and Merkel cell carcinoma (MCC), among others. Immune checkpoint inhibitor (ICIs), which include PD-1/PD-L1 inhibitors, have shown durable responses with overall response rates ranging from 30% to ≥50% in patients with PD-L1 expression, even among subgroups with poor prognostic factors [1–10].

Sensitization of the immune system comes with a unique side effect profile. The exact pathophysiology of immune-related adverse events (irAEs) remains unknown, but evidence suggests they may result from a combination of autoreactive T cells, autoantibodies, and proinflammatory cytokines [11, 12]. The incidence of irAEs in patients taking ICIs in clinical trials has ranged from 15% to 90% among monotherapy users based on the agent, but estimates on the lower end are likely underestimated as a result of unreliable reporting in clinical trials [13–19]. Only a fraction of irAEs (0.5%–13%) have been severe enough to require immunosuppression or discontinuation of treatment [14]. A meta-analysis of PD-1/PD-L1 inhibitors in a variety of cancer types noted any-grade and severe irAEs occurred in 27% and 6% of patients, respectively [20]. The reported incidences of irAEs varied by cancer and drug but were not related to the dose of the PD-1/PD-L1 inhibitor.

Immunotherapy agents and systemic chemotherapy are both approved treatment options for patients with advanced cancer. A meta-analysis comparing toxic effects from ICIs versus chemotherapy found that ICI treatment was better tolerated [21]. The risk of any all-grade (risk ratio [RR], 0.82; $p < .001$) or high-grade adverse events (AEs; RR, 0.32; $p < .001$) was significantly lower with PD-1/PD-L1 inhibitors than chemotherapy. Additionally, treatment discontinuation was more frequent among patients receiving chemotherapy than those receiving PD-1/PD-L1 inhibitors (11.1% vs. 4.5%; RR, 0.44; $p < .001$). Compared with chemotherapy, PD-1/PD-L1 inhibitors are associated with significantly lower risks of sensory neuropathy, diarrhea, hematologic toxicities, all-grade anorexia, nausea, constipation, high-grade AEs, all- and high-grade fatigue, and treatment discontinuation but higher risks of all-grade rash, pruritis, colitis, aminotransferase elevations, hypo- and hyperthyroidism, and high-grade pneumonitis [21].

Despite the growing knowledge surrounding irAEs from ICIs, key gaps remain. The relationship between irAEs and antitumor efficacy of immunotherapy is controversial, with some studies suggesting improved response and survival rates [22–25], although others found no association [26, 27]. Additionally, there are limited data on health care resource utilization (HCRU) and costs associated with irAEs from ICIs.

Filling these critical knowledge gaps would facilitate decision-making based on risk-benefit assessments and elucidate the economic burden of managing irAEs. Thus, the purpose of this study was to examine all-cause and irAE-related HCRU and costs and to characterize the association between AEs and mortality among patients receiving ICI monotherapy (PD-1 or PD-L1 inhibitors) for advanced UC, RCC, NSCLC, or MCC. Immune-related adverse events were selected based on guidelines from the National Comprehensive Cancer Network (NCCN) [28] and the American Society of Clinical Oncology (ASCO) [29], as well as clinician guidance; however, given the complexity of diagnosing irAEs using claims, this study employed a conservative approach to classify irAEs as AEs. Thus, costs and other absolute values are an underestimate of all AEs because this study focused on AEs that were plausibly immune-related. We hypothesized that AEs in patients receiving ICIs would be positively associated with costs and HCRU but inversely associated with mortality.

Materials and Methods

Data Sources

This was a retrospective cohort study using medical and pharmacy claims and enrollment information from commercial and Medicare Advantage with Part D (MAPD) enrollees in the Optum Research Database (ORD) from March 1, 2014, to April 30, 2019 (study period). Claims data from the ORD were linked with mortality data from the Social Security Death Index (SSDI) and the National Death Index (NDI).

ORD

The ORD contains medical and pharmacy claims data (including linked enrollment) for Commercial and Medicare Advantage patients, collected from all sites of health care (inpatient and outpatient hospital, emergency room, physician's office, surgery center, etc.), with the associated paid amounts. Medical claims included International Classification of Diseases (ICD), Ninth Revision, Clinical Modification (ICD-9-CM)/ICD 10th Revision, Clinical Modification (ICD-10-CM) diagnosis codes; ICD-9-CM/ICD-10-CM procedure codes; Current Procedural Terminology codes; or Healthcare Common Procedure Coding System codes. Pharmacy claims are from the database of outpatient filled prescriptions. In 2018, the ORD represented 19% of the U.S. commercially insured population, 21% of the Medicare Advantage population (with medical and pharmacy claims), and 22% of the Medicare Part D (with pharmacy claims only) population.

SSDI

Medical and pharmacy claims data were linked with data from the SSDI Master File to obtain more complete information on mortality. After patients' files were linked, their data were used to inform sample selection. That is, patients who might otherwise have been removed from the study because of insufficient continuous enrollment were included if they were determined to have been disenrolled because of death. These data were also used to estimate the association between AEs and mortality.

NDI

Because of missingness in the SSDI, gold-standard NDI mortality data were also used. After approval from the New England Independent Review Board, medical and pharmacy claims data were linked with data from the NDI, which is a central computerized index of death record information on

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file in each state's vital statistics office. Patients were eligible for linkage to the NDI if they were allowed by compliance (70% of the study population). After patients were linked, these data were used to estimate the association between AEs and mortality.

Study Sample Selection

To be eligible for study inclusion, patients must have had at least two nondiagnostic claims for either UC, RCC, NSCLC (without driver mutations), or MCC >30 days apart, in any position on the claim during the study period (supplemental online Table 1). The date of the earliest cancer claim was the disease diagnosis date. Eligible patients also had at least one claim for an ICI (cemiplimab, nivolumab, pembrolizumab, atezolizumab, avelumab, or durvalumab) between September 1, 2014, and April 30, 2019, and after the disease diagnosis date. The date of the first ICI claim was the index date. Additionally, patients had to be ≥18 years of age (≥12 years of age for patients with MCC) as of the index year and have continuous health plan enrollment with medical and pharmacy benefits for ≥6 months prior to the index date, between the disease diagnosis date and the index date, and for ≥3 months following the index date, unless death occurred earlier.

Patients were excluded from the study if they had evidence of more than one cancer diagnosis; at least one claim related to pregnancy; at least one procedure code indicating clinical trial participation; missing demographic data; claims for UC, RCC, NSCLC, or MCC in the 90 days prior to the disease diagnosis date (i.e., evidence of left truncation of data); evidence of other anticancer agents in addition to ICIs; and/or at least one claim during the pre-index period for any condition considered an AE during the follow-up period. Additionally, patients with NSCLC were excluded if they had at least one claim for a drug associated with small cell lung carcinoma or at least one claim for therapy targeting driver mutations during the study period.

Study Measures

Demographic and Clinical Characteristics

Age, sex, insurance type, geographic region, and rural residency were obtained from enrollment information. Autoimmune disease, cardiovascular disease, obesity, dyslipidemia, and hypertension were defined as at least one claim with an ICD code, in any position, during the pre-index period. Metastatic disease at ICI initiation was defined as at least one claim with a metastatic code between the disease diagnosis date and index date. Radiation was defined as at least one claim with a procedure code during the pre-index period. Line of therapy (LOT) was estimated using a well-defined algorithm, as previously published [30, 31]. The index LOT started on the index date and ended on whichever was earliest from the following: (a) end of study period, (b) start of a subsequent LOT, (c) death, (d) disenrollment from health plan, or (e) discontinuation (i.e., 60 days after runout date) of the ICI.

AE Ascertainment

Adverse events were selected a priori based on guidelines for the management of irAEs from NCCN [28] and ASCO [29], as well as clinician guidance (supplemental online Table 2). The presence of any of the 21 selected AEs that resulted in a medical encounter during the AE observation period was identified using the first or second position on the claim. The AE observation period started on the index date and ended on whichever was earliest of the following: (a) end of study period, (b) start of a new LOT, (c) death, (d) disenrollment from the health plan, or (e) 180 days after discontinuation of the ICI. The period of 180 days was chosen to capture the lasting effects that ICIs can have on the body.

Outcomes

Health Care Resource Utilization. Per patient per month (PPPM) AE-related HCRU during the AE observation period was calculated. HCRU was measured as a claim for ambulatory care (office and outpatient visits), emergency department care, or inpatient care. HCRU was considered AE-related if the claim had a diagnosis code for an AE in position 1 or 2. Person-years at risk for Kaplan-Meier and Cox analyses were calculated as time elapsed from the index date to whichever came first of the following: (a) HCRU event of interest, (b) end of study period, (c) start of a subsequent LOT, (d) death, (e) disenrollment from the health plan, or (f) 180 days after discontinuation of the ICI.

Health Care Costs. Health care costs were calculated as the PPPM combined health plan and patient-paid amounts in the AE observation period, adjusted to 2019 U.S. dollars using the annual medical care component of the Consumer Price Index [32]. Payments from Medicare (and other payers) were estimated based on coordination of benefits information. Cost categories included ambulatory (office and outpatient), emergency, inpatient, and other medical costs (i.e., durable medical equipment). Costs were considered AE-related if the claim had a diagnosis for an AE in position 1 or 2.

Mortality. The month and year of death were captured from the SSDI Master File, NDI, or Centers for Medicare & Medicaid Services for Medicare Advantage data and insurance claims with a diagnosis code indicating death, a discharge or disenrollment status field indicating death, and/or a hospice code. Notably, hospice care does not always result in death. When the death date differed between the claims or SSDI data and the NDI, the NDI date of death was used. Person-years of follow-up for patients eligible for NDI linkage were calculated as time elapsed from the index date to whichever of the following came first: (a) death or (b) end of the study period. Person-years of follow-up for patients not eligible for NDI linkage were calculated as time elapsed from the index date to whichever of the following came first: (a) death, (b) end of study period, or (c) disenrollment from the health plan.

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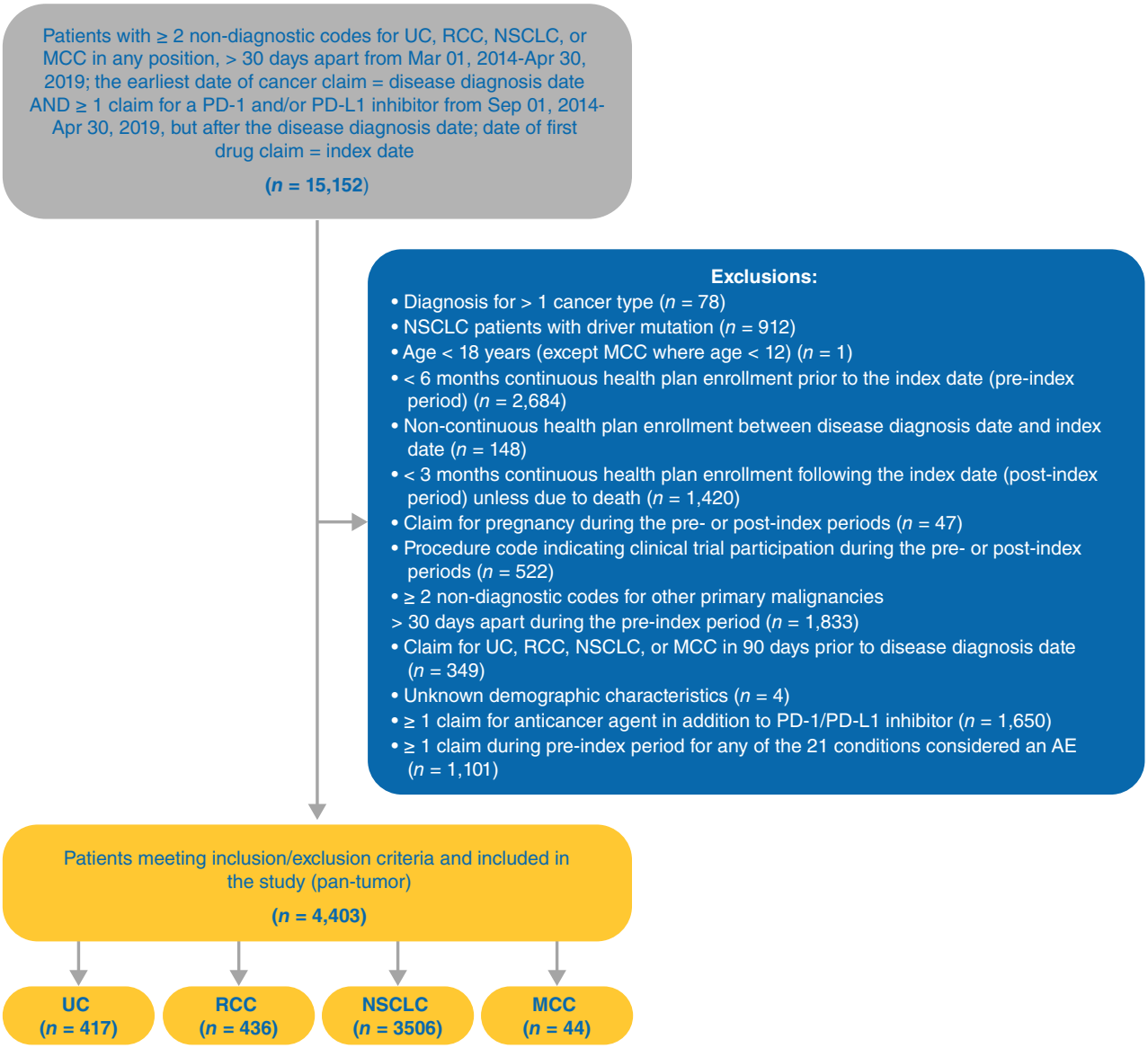

Figure 1. Study sample selection.
Abbreviations: AE, adverse event; MCC, Merkel cell carcinoma; NSCLC, non-small cell lung cancer; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; RCC, renal cell carcinoma; UC, urothelial carcinoma.

Statistical Analysis

Time to first AE and AE-related inpatient stay were calculated using Kaplan-Meier curves. To control for possible confounding of the relationship of AEs with inpatient stays, emergency room visits, and mortality, adjusted hazard ratios (HRs) and 95% confidence intervals [CIs] were calculated using Cox regression. Models were adjusted for ICI LOT; sex; region; insurance type; age, metastatic disease, cardiovascular disease, hypertension, or dyslipidemia as of the index date; and radiation during the 6 months prior to the index date. Additionally, models with inpatient stay or emergency room visit as the outcome were adjusted for inpatient stays or emergency department visits during the 6 months prior to ICI initiation, and models with mortality as the outcome were also adjusted for the Charlson comorbidity score. Whether a patient had an AE was modeled as a time-varying exposure in order to yield results not biased for immortal time and retain statistical efficiency [33, 34]. Because of the association between tumor type and mortality, pan-tumor results were not presented when mortality was the outcome. As a sensitivity analysis, mortality models were also run restricted to those eligible for NDI mortality data. Also, an interaction term between time-varying AEs and ICI LOT number was tested for significance in a model with mortality as the outcome.

Because follow-up time in this study was censored, estimating health care costs adjusting for covariates using standard methods (e.g., general linear model) may be inefficient or biased. To control for censoring and possible confounding of the relationship of AEs with all-cause total health care costs, we used Lin's weighted regression [35] to

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Table 1. Pre-index demographic and clinical characteristics

Pre-index characteristics	Total ($n = 4,403$)	AE ($n = 955$)	No AE ($n = 3,448$)	p value
Age, years, mean ± SD	70.7 ± 9.2	71.2 ± 9.0	70.5 ± 9.3	.049
Male sex, *n* (%)	2,523 (57.3)	511 (53.5)	2,012 (58.4)	.007
Insurance type, *n* (%)				
Commercial	1,030 (23.4)	199 (20.8)	831 (24.1)	.035
Medicare	3,373 (76.6)	756 (79.2)	2,617 (75.9)	
Region, *n* (%)				
Northeast	614 (14.0)	160 (16.8)	454 (13.2)	.005
Midwest	1,372 (31.2)	312 (32.7)	1,060 (30.7)	.255
South	2,118 (48.1)	420 (44.0)	1,698 (49.3)	.004
West	299 (6.8)	63 (6.6)	236 (6.8)	.788
Rural residence, *n* (%)	3,414 (77.5)	764 (80.0)	2,650 (76.9)	.039
Comorbidities, *n* (%)				
Autoimmune disease	226 (5.1)	55 (5.8)	171 (5.0)	.322
Cardiovascular disease	2,986 (67.8)	679 (71.1)	2,307 (66.9)	.014
Obesity	588 (13.4)	135 (14.1)	453 (13.1)	.422
Dyslipidemia	2,375 (53.9)	586 (61.4)	1789 (51.9)	<.001
Hypertension	3,148 (71.5)	721 (75.5)	2,427 (70.4)	.002
Baseline Quan-Charlson comorbidity score, mean ± SD	6.5 ± 2.2	6.4 ± 2.3	6.6 ± 2.2	.046
Treatment and disease characteristics				
Metastatic disease at index date, *n* (%)	3,198 (72.6)	638 (66.8)	2,560 (74.3)	<.001
Radiation during pre-index, *n* (%)	1,703 (38.7)	342 (35.8)	1361 (39.5)	.040
Months diagnosed with cancer before index date, mean ± SD	10.7 ± 9.8	10.6 ± 9.5	10.7 ± 9.9	.780
Index medication, *n* (%)				
PD-1	3,566 (81.0)	766 (80.2)	2,800 (81.2)	.487
PD-L1	837 (19.0)	189 (19.8)	648 (18.8)	.487
ICI LOT, *n* (%)				
ICI was first line	1,239 (28.1)	296 (31.0)	943 (27.4)	.027
ICI was second line	2,476 (56.2)	506 (53.0)	1,970 (57.1)	.022
ICI was third line	537 (12.2)	120 (12.6)	417 (12.1)	.694
ICI was fourth line or higher	151 (3.4)	33 (3.5)	118 (3.4)	.960
Duration of ICI therapy, mean ± SD, days	179.1 ± 173.4	249.6 ± 211.6	159.6 ± 155.8	<.001
Systemic steroids within 30 days prior to PD-1/PD-L1 initiation, *n* (%)	1,341 (30.5)	267 (28.0)	1,074 (31.2)	.06

Abbreviations: AE, adverse event; ICI, immune checkpoint inhibitor; LOT, line of therapy, PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1.

calculate predicted 6-month all-cause total costs by AE group and 95% CIs surrounding the cost difference between the two groups. Models were adjusted for the same variables as the Cox inpatient stay model.

A p value of <.05 on a two-tailed test was considered statistically significant, and all analyses were conducted using SAS statistical software version 9.4 (SAS Institute, Cary, NC). Unless otherwise stated, all analyses were presented both pan-tumor and stratified by tumor type.

Results

Baseline Demographics and Clinical Characteristics

This study included 4,403 patients, including 417 patients with UC, 436 with RCC, 3,506 with NSCLC, and 44 with MCC (Fig. 1). The mean age was 70.7 years, 57.3% of patients were male, and most patients had MAPD coverage (76.6%) (Table 1). The majority of patients had hypertension (71.5%) and cardiovascular disease (67.8%), more than half had dyslipidemia (53.9%), and approximately 13% and 5% had obesity and autoimmune disease, respectively. The majority of patients had metastatic disease at index, and more than one third had prior radiation therapy. Cancer diagnoses occurred an average of 10.7 months prior to the index date, and patients averaged 5.9 months of ICI therapy. Most patients (81.0%) had a PD-1 inhibitor as their index medication, and more than half of patients received their index medication as second-line treatment (56.2%). Steroid use in the 30 days prior to PD-1/PD-L1 initiation was common (30%).

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Table 2. Cox regression models of the association between adverse events (modeled as time-varying [28], adverse event vs. none) and emergency room visits, inpatient stays, and mortality

	Tumor type				
	Pan-tumor (n = 4,403)	**UC (n = 417)**	**RCC (n = 436)**	**NSCLC (n = 3,506)**	**MCC (n = 44)**
Emergency visits					
No. of visits	2,565	263	242	2,040	20
Person-years at risk	1,635.9	138.5	195.4	1,282.2	19.7
Unadjusted HR (95% CI)	1.8 (1.6–2.1)	1.5 (1.0–2.3)	1.4 (0.9–2.0)	2.0 (1.7–2.3)	1.0 (0.3–3.7)
Adjusted HR (95% CI)[a]	1.8 (1.6–2.1)	1.6 (1.0–2.5)	1.3 (0.9–2.0)	2.0 (1.8–2.3)	—
Inpatient stays					
No. of stays	2,097	227	188	1,664	18
Person-years at risk	1,948.7	165.5	228.6	1,535.2	19.5
Unadjusted HR (95% CI)	2.2 (1.9–2.5)	2.1 (1.4–3.3)	2.0 (1.4–3.0)	2.3 (1.9–2.6)	1.1 (0.3–3.8)
Adjusted HR (95% CI)[a]	2.2 (1.9–2.5)	2.6 (1.7–4.0)	1.9 (1.3–2.9)	2.3 (2.0–2.7)	—
Mortality					
Overall					
No. of deaths	—	285	229	2,246	19
Person-years at risk	—	313.5	505.8	2,920.4	48.4
Unadjusted HR (95% CI)	—	1.3 (0.9–1.7)	1.3 (1.0–1.8)	1.0 (0.9–1.1)	1.4 (0.5–3.8)
Adjusted HR (95% CI)[b]	—	1.2 (0.9–1.6)	1.2 (0.9–1.7)	1.0 (0.9–1.1)	—
Patients with metastatic disease		(n = 288)	(n = 389)	(n = 2,487)	—
No. of deaths		198	212	1,668	
Person-years at risk		209.0	443.5	1,977.3	
Unadjusted HR (95% CI)		1.4 (1.0–2.0)	1.3 (1.0–1.8)	1.0 (0.9–1.2)	
Adjusted HR (95% CI)[b]		1.3 (0.9–1.9)	1.2 (0.9–1.7)	1.0 (0.9–1.2)	
Patients without metastatic disease		(n = 129)	(n = 47)	(n = 1,019)	
No. of deaths		87	17	578	
Person-years at risk		62.3	505.8	943.2	
Unadjusted HR (95% CI)		1.0 (0.6–1.7)	1.5 (0.5–4.4)	1.0 (0.8–1.3)	
Adjusted HR (95% CI)[b]		0.9 (0.5–1.5)	0.9 (0.2–4.0)	1.0 (0.8–1.2)	

[a]Adjusted for treatment line number of immune checkpoint inhibitor (ICI) therapy; age; sex; region; insurance type; presence of metastatic disease, cardiovascular disease, hypertension, or dyslipidemia at time of ICI initiation; and radiation, inpatient stay, or emergency room visit during the 6 months prior to ICI initiation.
[b]Adjusted for treatment line number of ICI therapy; age; sex; region; insurance type; Charlson comorbidity score; presence of metastatic disease, cardiovascular disease, hypertension, or dyslipidemia at time of ICI initiation; and radiation during the 6 months prior to ICI initiation.
Abbreviations: CI, confidence interval; HR, hazard ratio; MCC, Merkel cell carcinoma; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; UC, urothelial carcinoma.

The time to onset of any AE is shown in supplemental online Figure 1. Patients with an AE were slightly older (71.2 years vs. 70.5 years; $p = .049$), were more likely to be female (46.5% vs. 41.6%; $p = .007$), had higher rates of cardiovascular disease (71.1% vs. 66.9%; $p = .014$), and were less likely to have metastatic disease at index (66.8% vs. 74.3%; $p < .001$) or to have received radiation treatment during the pre-index period (35.8% vs. 39.5%; $p = .040$). Patients with an AE were more likely to be on first-line ICI therapy (31.0% vs. 27.4%; $p = .027$) and patients without AEs were more likely to be on second-line therapy (53.0% vs. 57.1%; $p = .022$). Additionally, patients with an AE had a longer duration of ICI therapy (8.2 vs. 5.2 months; $p < .001$). Demographic characteristics stratified by cancer type are shown in supplemental online Table 3.

All-Cause Total HCRU and Costs

After adjustment for potential confounding variables, patients with AEs had more than double the risk of an inpatient stay (HR, 2.2; 95% CI, 1.9–2.5) and an 80% higher risk of an emergency visit (HR, 1.8; 95% CI, 1.6–2.1) than patients without AEs (Table 2). Unadjusted hazard ratios and 95% CIs for the association between AEs and inpatient stays or emergency visits were identical to the adjusted values (data not shown).

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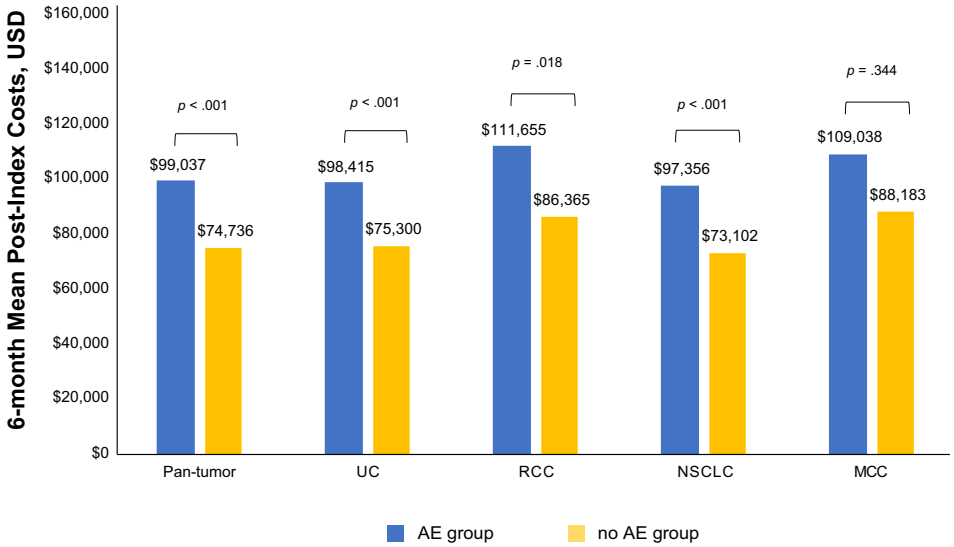

Figure 2. Per patient per month mean AE-related post-index medical costs, adjusted for treatment line number of immune checkpoint inhibitor (ICI) therapy; age; sex; region; insurance type; radiation; inpatient stay or emergency department visit during the 6 months prior to ICI initiation; presence of metastatic disease at time of ICI initiation; and cardiovascular disease, hypertension, or dyslipidemia during the 6 months prior to ICI initiation. An unadjusted estimate is presented for MCC because of low sample size.
Abbreviations: AE, adverse event; ICI, immune checkpoint inhibitor; MCC, Merkel cell carcinoma; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; UC, urinary carcinoma.

In Lin's regression analyses, predicted all-cause total costs over 6 months were significantly higher among patients with AEs versus without (Fig. 2). Among all patients, adjusted 6-month total costs were $24,301 higher among patients with an AE than without ($99,037 vs. $74,736, 95% CI, $18,828–29,774; $p < .001$). Patients with UC, RCC, and NSCLC who had AEs had 6-month predicted all-cause total costs $23,115 (95% CI, $11,615–34,615; p < .001), $25,289 (95% CI, $4,321–46,258; $p = .018$), and $24,254 (95% CI, $18,598–$29,909; $p < .001$) higher, respectively, than patients without AEs. Unadjusted all-cause total costs were similar to adjusted costs across all cohorts (data not shown) and were estimated at $97,571 for patients with an AE and $74,065 for those without (cost difference = $23,506; 95% CI, $17,456–29,556; $p < .001$).

AE-Related HCRU and Medical Costs

Among patients who had an AE during the post-index period ($n = 955$), ambulatory visits averaged 0.23 visits PPPM, emergency room visits averaged 0.03 visits PPPM, and inpatient stays averaged 0.09 stays PPPM (Table 3). Patients with UC had slightly higher utilization than the average (0.3 ambulatory stays, 0.06 emergency visits, and 0.16 inpatient stays), whereas patients with RCC had slightly lower utilization than the average (0.21 ambulatory visits, 0.03 emergency visits, and 0.08 inpatient stays). By 6 and 12 months after ICI initiation, 26% and 34% of patients, respectively, required an AE-related inpatient stay (Fig. 3).

Mean ± SD AE-related medical costs averaged $2,359 ± $7,496 PPPM among all patients with an AE. Patients with UC had the highest AE-related medical costs at $4,195 ± $12,699 PPPM and patients with MCC had the lowest at $563 ± $1,219 PPPM (Fig. 4). AE-related medical costs were driven by costs for inpatient care, which accounted for 79.1%–91.3% of the cost total, depending on the cancer type.

Mortality

Patients with an AE had a mortality risk similar to that in patients without an AE (Table 2). Adjusted HR estimates ranged from 1.0 (95% CI, 0.9–1.1) to 1.2 (95% CI, 0.9–1.6), whereas unadjusted HR estimates ranged from 1.0 (95% CI, 0.9–1.1) to 1.4 (95% CI, 0.5–3.8), depending on the cancer type. Results did not change when restricted to patients who were eligible for NDI linkage (data not shown). The interaction terms between AE and ICI LOT number were not

Table 3. Mean per patient per month post-index[a] adverse event–related health care resource use[b]

	Tumor type				
Health care resource	**Pan-tumor ($n = 955$)**	**UC ($n = 90$)**	**RCC ($n = 127$)**	**NSCLC ($n = 722$)**	**MCC ($n = 16$)**
Ambulatory, mean ± SD	0.23 ± 0.57	0.30 ± 1.14	0.21 ± 0.28	0.23 ± 0.50	0.28 ± 0.27
Emergency, mean ± SD	0.03 ± 0.14	0.06 ± 0.22	0.03 ± 0.11	0.03 ± 0.13	0.03 ± 0.06
Inpatient, mean ± SD	0.09 ± 0.23	0.16 ± 0.43	0.08 ± 0.16	0.09 ± 0.20	0.02 ± 0.05

[a]During the immune checkpoint inhibitor line and, if no subsequent therapy was started, up to 180 days after.
[b]Among patients who had an adverse event.
Abbreviations: MCC, Merkel cell carcinoma; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; UC, urothelial carcinoma.

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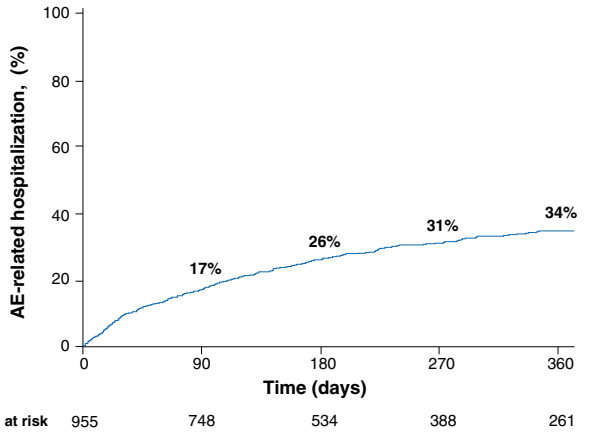

Figure 3. Time to AE-related inpatient stay among patients with all tumor types who had an AE.
Abbreviation: AE, adverse event.

statistically significant in models with mortality as the outcome ($p = .423$ for RCC, .668 for UC, and .984 for NSCLC).

Discussion

This study assessed the real-world economic burden and mortality associated with AEs in patients with advanced UC, RCC, NSCLC, or MCC who received ICI monotherapies. Patients with AEs had twice the risk of inpatient stays and emergency room visits and 30% higher all-cause total health care costs over the 6-month time period following ICI initiation than patients without AEs. AE-related medical costs were driven by inpatient stays, with one third of patients with an AE requiring an AE-related inpatient stay within 1 year of initiating ICIs. The risk of mortality was similar in patients with and without AEs.

Patients with AEs required additional HCRU, resulting in significantly higher costs than those incurred by patients without AEs. Over 6 months, 26% of patients had an inpatient hospitalization for an AE, a rate similar to those previously reported [36, 37]. In a study in patients admitted to an academic oncology center, 23% treated with an ICI were hospitalized with a confirmed irAE [36]. In another study of patients with UC, RCC, NSCLC, or MCC, 38% of patients had an irAE-related inpatient stay during a 90-day period [37]. AE-related costs observed in this study averaged $2,359 PPPM, with inpatient hospitalizations accounting for 90% of AE-related costs. Engel-Nitz et al. found irAE-related costs to be almost double those in patients with metastatic NSCLC at $4,259 PPPM, likely driven by inpatient and emergency costs [31]. One potential explanation for the cost differential is that the Engel-Nitz study included only first-line initiators of immunotherapy, who are known to have a higher risk of any-grade and severe irAEs [38].

Despite the economic burden of AEs among patients receiving ICI therapy, patients receiving chemotherapy have more AEs and higher costs, comparatively [31, 39]. In a study in patients with metastatic NSCLC, those receiving chemotherapy had 1.4 times more AEs, had 48% higher PPPM AE-related costs, and were 40% more likely to have high costs than patients receiving immunotherapy [31] Additionally, a meta-analysis among patients with advanced solid organ malignancies found those receiving chemotherapy were more likely to have an AE and had more treatment discontinuations and deaths because of AEs compared with patients receiving immunotherapy [39].

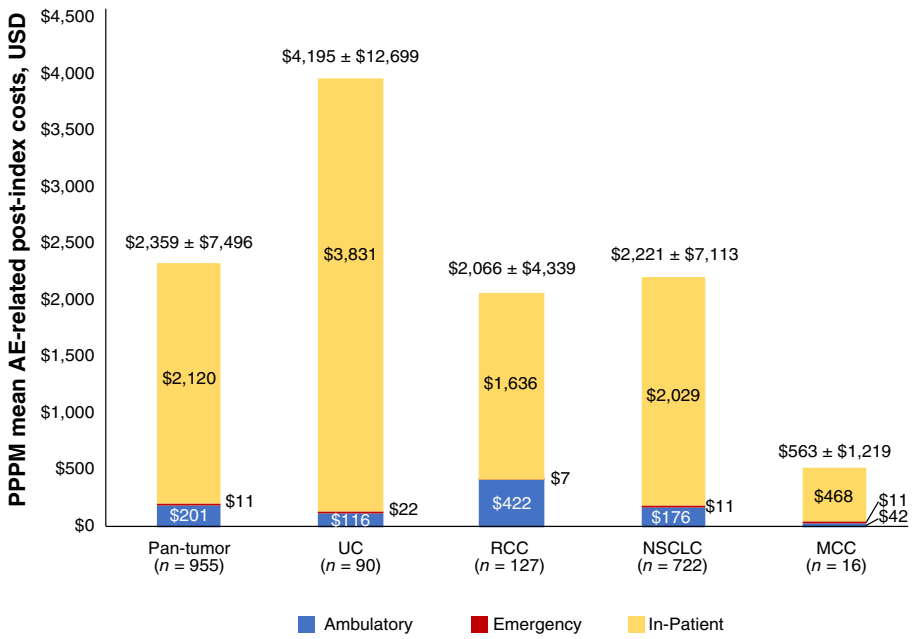

Figure 4. Per patient per month mean AE-related post-index medical costs among patients who had an AE. Post-index costs were incurred during line of treatment with a programmed cell death 1 or programmed cell death ligand inhibitor and, if no subsequent therapy was started, up to 180 days after.
Abbreviations: AE, adverse event; MCC, Merkel cell carcinoma; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; UC, urothelial carcinoma; USD, U.S. dollars.

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Several studies have noted improved outcomes, including overall response rate, progression-free survival, and overall survival in patients who develop irAEs while receiving ICIs compared with patients who do not [23, 40–47]. This issue is still somewhat controversial as several studies have had conflicting results [22, 27, 45, 48–51]. A lack of a significant association between the development of irAEs because of PD-1 inhibitor therapy and overall survival has been noted in some studies [27, 45, 48, 50], with some even documenting worse survival in patients with colitis [49] or pneumonitis [51]. In Ksienski et al., 20.7% of patients with irAEs experienced a treatment interruption, which was associated with decreased overall survival at 6 and 12 weeks [49].

There are a variety of hypotheses for these mixed results, including treatment time, site of irAEs, and irAE severity. It has been suggested that the association between irAEs and improved outcomes may be confounded by immortal-time bias [52], in which patients with irAEs are those who remain on treatment longer and thus have better outcomes. This study has accounted for immortal-time bias. However, contradicting studies have shown that patients who discontinued because of irAEs have lasting anticancer effects leading to increased survival and improved outcomes, despite discontinuing treatment [53, 54]. The site of the irAE may also have an impact on outcomes. In a meta-analysis of head, neck, and lung cancer clinical trials, endocrine irAEs were associated with improved overall survival ($p = .019$) [55], whereas in patients with melanoma dermatologic irAEs resulted in increased survival rates ($p < .001$) [56]. In Ricciuti et al., dermatologic and hepatic-gallbladder reactions did not result in improved overall survival, but pulmonary, endocrine, and gastrointestinal irAEs did in patients with stage IV NSCLC [57]. Although the timing of irAE onset and immunotherapy response has not been well reported, studies in patients with gastrointestinal cancer, NSCLC, and melanoma have failed to show an association between earlier irAE onset and improved treatment efficacy [42, 58, 59]. Similarly, irAE severity has not affected treatment efficacy outcomes in several studies [58]. This may be because patients presenting with severe irAEs often have high rates of morbidity from autoimmune reactions, which may obscure the difference in survival in patients with and without irAEs. As AEs included in this study were severe enough to require a medical encounter, this may partially explain why no association between AEs and survival was found.

Limitations

Claims data allow for efficient examination of real-world HCRU and costs; however, because claims are collected for payment purposes, inherent limitations exist. LOTs were not captured in the claims data, so an algorithm with various assumptions was used. Additionally, the presence of a diagnosis code on a medical claim was not necessarily indicative of the positive presence of disease, as the diagnosis code may have been incorrectly coded or included as rule-out criteria. Tumor histology and cancer stage were not available in the database. Also, this study relied on diagnosis codes in claims data to indicate the presence of AEs, which did not have information on severity. AEs that did not result in a medical encounter were not included in this analysis. This study employed a conservative approach in classifying irAEs as AEs given the complexity of identifying irAEs using claims data. Because AEs measured in this study were plausibly immune-related, costs and absolute values presented are an underestimate of those from all AEs. Also, the connection between the event and ICI use was inferred. To limit this inference, we restricted to a relevant time period (ICI initiation up to 180 days after), excluded patients with evidence of the condition prior to ICI initiation, and required ICI monotherapy. By restricting the time period to 180 days following ICI initiation, HCRU and costs falling outside of this window were not included in the analysis; however, it was expected that the majority of HCRU and costs would fall within this time period and any costs outside of this window may not be attributable to the AE. Additionally, residual confounding may remain. For instance, high costs and utilization could be partially explained if patients who had an AE were a sicker group, regardless of the AE. However, the high AE-related costs and utilization we noted in this study point to an association that cannot be explained away by residual confounding. Gold-standard mortality data (i.e., NDI) were only available for 70% of our population. However, when analyses were restricted to this 70% of data for sensitivity analysis, results did not change, strengthening confidence in our findings. Furthermore, steroid use prior to PD-1/PD-L1 inhibitor initiation was common; patients may have already been immunocompromised. Lastly, this study was conducted in patients with commercial or MAPD coverage and may not be generalizable to patients with other types of coverage or the uninsured. There were likely temporal trends in health care utilization because clinicians were more likely to hospitalize patients with suspected AEs when ICIs were first introduced and AEs were poorly understood. Additionally, there may also be a difference in the management of patients between academic and nonacademic medical centers. Despite these limitations, given the sparsity of real-world data on this topic, it is expected that results of this study will move the field forward.

Conclusion

Patients with AEs severe enough to result in a health care encounter had higher risks of hospitalizations and emergency room visits and higher health care costs, driven by inpatient stays, than patients without AEs. However, the risk of mortality was similar in the two cohorts. Given the high cost of AEs among patients receiving ICIs, it is important for physicians to be cognizant of the unique profile of AEs in order to promptly identify them in patients receiving these medications. Ongoing evaluation, earlier recognition, and more effective, multidisciplinary management of AEs may improve patient outcomes and reduce the need for costly inpatient stays.

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Disclosures

Saby George: Bristol-Myers Squibb, Bayer, Pfizer, Exelixis, Corvus, Genentech, Sanofi/ Genzyme, EMD Serono, Seattle Genetics, Eisai, Merck (C/A), Bristol-Myers Squibb, Pfizer, Corvus, Seattle Genetics, Eisai, Merck, Immunomedics, Agensys, Novartis, Bayer, Astellas/ Seattle Genetics, Calithera, Corvus (RF); **Elizabeth J. Bell:** Optum (E), EMD Serono, Inc., Pfizer (RF); **Ying Zheng:** EMD Serono, Inc. (E); **Ruth Kim:** Pfizer (E), Bristol-Myers Squibb, Exelixis (OI); **John White:** Optum (E), EMD Serono, Inc. (C/A); **Geeta Devgan:** Pfizer (E, OI); **Jodi Smith:** EMD Serono, Inc. (E); **Lincy S. Lal:** Optum (E); **Nicole M. Engel-Nitz:** UnitedHealth Group (Optum) (E), UnitedHealth Group (OI), EMD Serono, Novartis, AstraZeneca, Pfizer, Clovis, Exact Sciences, Adaptive, Alexion, Eli Lilly & Co., GlaxoSmithKline, Genentech (RF—Optum); **Frank X. Liu**: EMD Serono, Inc. (E).

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