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The rate of occurrence, healthcare resource use and costs of adverse events among metastatic non-small cell lung cancer patients treated with first- and second-generation epidermal growth factor receptor tyrosine kinase inhibitors

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ABSTRACT

Objectives: Clinical trials with first- and second-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) reported severe adverse events (SAEs) in 6%–49% of patients with EGFR-mutated non-small cell lung cancer. This study describes incremental healthcare resource utilization (HRU) and costs associated with real-world management of AEs in this population, with a focus on SAEs.

Materials and methods: Patients receiving erlotinib, gefitinib, or afatinib as first-line (1L) monotherapy were identified from IQVIA™ Real-World Data Adjudicated Claims–US database (04/01/2012–03/31/2017). Relevant AEs were selected from corresponding prescribing information; SAEs were identified from hospitalization claims. HRU and cost per-patient-per-month (PPPM) were assessed during 1L treatment and compared for patients with and without each AE using multivariate Poisson and linear regression, respectively, adjusting for baseline characteristics.

Results: Of 1646 patients, 86.9% were treated with erlotinib, 12.1% with afatinib, and 1.0% with gefitinib. In 1L, 12.2% of patients had ≥1 acute SAE (220.1/1000 patient-years). Patients with any SAE had higher PPPM costs than patients without SAEs (cost difference = $4700, $p < 0.001$). Incremental costs ranged from $2604 PPPM for diarrhea to $10,143 PPPM for microangiopathic hemolytic anemia (MAHA), and were statistically significant for all SAEs (all $p < 0.001$) except MAHA ($p < 0.0528$). Patients with any SAEs had higher rates of HRU relative to patients without SAEs (hospitalization rate ratio = 6.15; outpatient visits rate ratio = 1.21; all $p < 0.001$).

Conclusion: More than one-tenth of patients experienced SAEs, resulting in sizeable economic burden with respect to HRU and costs. EGFR-TKIs with more favorable safety profiles may reduce the burden of managing this population.

1. Introduction

In the United States (US), approximately 50% of patients with non-small cell lung cancer (NSCLC) are diagnosed with stage IV disease [1]. The 5-year survival rate in patients diagnosed with stage IV NSCLC is approximately 6%, indicating that there remains an unmet need in patients with metastatic NSCLC being treated with traditional therapies [2]. For patients with metastatic NSCLC, current American Society of Clinical Oncology guidelines recommend tumor genomic profiling to identify actionable gene alterations, and this information can guide the selection of appropriate treatment [3]. Patients with activating mutations in the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) gene are responsive to treatment with EGFR-tyrosine kinase inhibitors (TKIs) [4]. Patients with metastatic NSCLC treated

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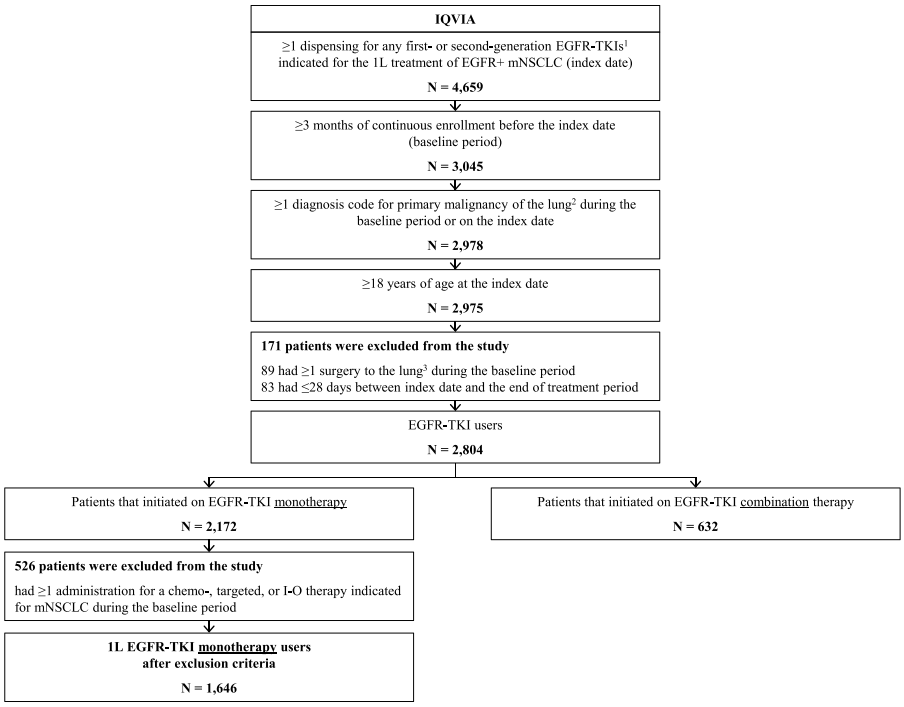


Fig. 1. Patient disposition.
1L, first-line; EGFR, epidermal growth factor receptor; I–O, immuno-oncology; mNSCLC, metastatic non-small cell lung cancer; TKI, tyrosine kinase inhibitor
Notes:
[1]EGFR-TKIs include the following: erlotinib, gefitinib, and afatinib.
[2]Identified using ICD-9-CM codes 162.2–162.5, 162.8, 162.9 and ICD-10-CM codes C34.0-C34.3, C34.8, C34.9.
[3]The index treatment regimen was defined during the 28 days before and after the date of the first TKI dispensing.

with first- and second-generation EGFR-TKIs have been found to have a 5-year survival rate of approximately 15% [5].

The first-generation EGFR-TKIs erlotinib (Tarceva®) and gefitinib (Iressa®) were approved by the US Food and Drug Administration (FDA) in May 2013 and July 2015, respectively, as first-line (1 L) therapies for patients with EGFR positive metastatic NSCLC. The second-generation EGFR-TKI afatinib (Gilotrif®) was approved for the same indication in July 2013, while dacomitinib (Vizimpro®) received FDA approval in 2018. Tumors harboring EGFR mutations that initially respond to these first- and second-generation EGFR-TKIs may eventually become resistant to these therapies within a median time of 9–16 months after treatment initiation [6–8]. A third-generation EGFR-TKI, osimertinib, recently received FDA approval for 1 L treatment of patients with EGFR exon 19 deletion (Ex19del)/L858R mutation-positive metastatic NSCLC, as detected by FDA-approved tests. There are additional EGFR-TKIs currently under development [9,10].

When evaluating therapies in this rapidly changing treatment landscape for metastatic NSCLC, it is important to note that first- and second-generation EGFR-TKIs are associated with several treatment-related adverse events (AEs). Because of the concentration of EGFR in skin and mucosa, these tissues are commonly the source of AEs, such as diarrhea and skin rashes and infections [11]. While EGFR-TKIs are, in general, less toxic than traditional anti-neoplastic agents, such as chemotherapy, previous studies have found that the AEs associated with EGFR-TKIs can be severe in some cases, and may substantially impair quality of life [11]. The treatment of AEs in clinical practice can contribute to higher healthcare resource utilization (HRU), which contributes to increased costs to the healthcare system [12]. Therefore, clinicians will have to consider not only treatment efficacy data, but also the potential toxicities when selecting appropriate EGFR-TKIs for their patients. Although trial data describe the extent of AEs experienced by patients treated with erlotinib, afatinib, and gefitinib, there is limited real-world evidence regarding the burden of AE management, especially with respect to healthcare cost, associated with these agents. Thus, to contribute to the understanding of this burden, this study assessed the rate of AE occurrence and estimated the incremental HRU and healthcare costs associated with AE management (of any severity), with a specific focus on severe AEs (SAEs), in patients with metastatic NSCLC treated with first- or second-generation EGFR-TKIs as 1 L monotherapy.

2. Materials and methods

2.1. Data source

Claims data from the IQVIA™ Real-World Data Adjudicated Claims–US (IQVIA RWD Adjudicated Claims–US) database were used. The IQVIA RWD Adjudicated Claims–US database is the largest non-payer owned integrated claims database of commercial insurers and employer-provided Medicare Supplemental plans covered by large employers in the US. The database includes medical and pharmacy claims for more than 80 million members from more than 100 health plans across the US. Records in the IQVIA RWD Adjudicated Claims–US database are representative of the US national commercially insured population, and include demographic measures such as age, gender, and plan type.

2.2. Study design

The index date was defined as the initiation date (i.e., the date of first dispensing) of first- or second-generation EGFR-TKIs used as 1 L monotherapy and approved at time of study. The 3-month period of continuous enrollment prior to the index date served as the baseline period. HRU and costs were assessed over the 1 L treatment period, which was defined as the period from the index date to the end of 1 L treatment. End of treatment was defined as the earliest of treatment discontinuation (i.e., the last day of supply before a gap of 90 or more consecutive days without the EGFR-TKI initiated on the index date), change in treatment (i.e., before the initiation of a therapeutic agent other than the index EGFR-TKI), or end of data availability (i.e., 03/31/2017).

The select AEs analyzed in this study were: cardiac events (i.e., arrhythmia, congestive heart failure, and myocardial infarction) and cerebrovascular accident (CVA); interstitial lung disease (ILD); diarrhea; renal failure; skin and ocular disorders (i.e., bullous and other exfoliating skin disorders, paronychia, and ocular disorders); hepatotoxicity (i.e., hepatic necrosis, non-alcoholic cirrhosis, hepatic encephalopathy, hepatorenal syndrome, hepatitis, or jaundice); microangiopathic hemolytic anemia (MAHA); and gastrointestinal perforation. These AEs were selected as the most relevant with respect

Table 1
Patient baseline characteristics.

Characteristics		Cohorts		
	EGFR-TKI users (N = 1646)	EGFR-TKI users with SAEs (N = 234)	EGFR-TKI users without SAEs (N = 1082)	p-value[a]
Treatment period, months, mean [median] (SD)	7.6 [5.0] (7.3)	8.7 [5.3] (8.3)	7.6 [5.0] (7.4)	0.057
Time from first lung cancer diagnosis to index date, months, mean [median] (SD)	1.7 [1.7] (0.9)	1.8 [2.0] (0.9)	1.8 [1.7] (0.9)	0.169
Demographics				
Age, years, mean [median] (SD)	60.8 [61] (9.7)	60.5 [61] (10.0)	60.7 [60] (9.7)	0.748
Gender, female, n (%)	1034 (62.8)	146 (62.4)	673 (62.2)	0.956
Region, n (%)				
South	557 (33.8)	82 (35.0)	364 (33.6)	0.681
Midwest	405 (24.6)	60 (25.6)	268 (24.8)	0.780
Northeast	397 (24.1)	55 (23.5)	263 (24.3)	0.795
West	266 (16.2)	35 (15.0)	171 (15.8)	0.747
Unknown	21 (1.3)	2 (0.9)	16 (1.5)	0.456
Insurance plan type, n (%)				
Preferred provider organization	1236 (75.1)	177 (75.6)	806 (74.5)	0.714
Health maintenance organization	275 (16.7)	39 (16.7)	183 (16.9)	0.927
Point of service	59 (3.6)	5 (2.1)	47 (4.3)	0.116
Indemnity/Traditional	48 (2.9)	8 (3.4)	27 (2.5)	0.426
Consumer-driven healthcare	9 (0.5)	1 (0.4)	7 (0.6)	0.695
Unknown	19 (1.2)	4 (1.7)	12 (1.1)	0.447
Year of index date, n (%)				
2012	200 (12.2)	33 (14.1)	132 (12.2)	0.425
2013	368 (22.4)	62 (26.5)	231 (21.3)	0.086
2014	362 (22.0)	61 (26.1)	229 (21.2)	0.101
2015	354 (21.5)	51 (21.8)	232 (21.4)	0.905
2016	329 (20.0)	24 (10.3)	235 (21.7)	**< 0.001**
2017	33 (2.0)	3 (1.3)	23 (2.1)	0.400
Index EGFR-TKI agent, n (%)				
Erlotinib	1431 (86.9)	213 (91.0)	940 (86.9)	0.081
Afatinib	199 (12.1)	20 (8.5)	131 (12.1)	0.121
Gefitinib	16 (1.0)	1 (0.4)	11 (1.0)	0.390
Quan-Charlson comorbidity index	6.1 [6] (1.9)	6.0 [6] (2.0)	5.8 [6] (1.9)	0.133
Select Elixhauser's comorbidities, n (%)				
Hypertension	622 (37.8)	97 (41.5)	364 (33.6)	**0.023**
Chronic pulmonary disease	465 (28.3)	81 (34.6)	248 (22.9)	**< 0.001**
Cardiac arrhythmias	297 (18.0)	39 (16.7)	103 (9.5)	**0.001**
Fluid electrolyte disorders	260 (15.8)	33 (14.1)	91 (8.4)	**0.007**
Liver disease	243 (14.8)	35 (15.0)	141 (13.0)	0.433
Diabetes, uncomplicated	198 (12.0)	34 (14.5)	104 (9.6)	**0.026**
Depression	170 (10.3)	24 (10.3)	99 (9.1)	0.598
Hypothyroidism	166 (10.1)	33 (14.1)	91 (8.4)	**0.007**

Abbreviations: EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; SAE, severe adverse event; SD, standard deviation.
[a] p-values are from *t*-test of means for continuous variables and chi-square tests for equality for proportions for categorical variables. Bold text indicates p-values less than or equal to 0.05.

to prevalence and clinical importance based on a review of the prescribing information for first- and second-generation EGFR-TKIs approved at the time of study (i.e., erlotinib, gefitinib, and afatinib).

SAEs were identified from hospitalization claims using all diagnosis variables, and cohorts of patients with and without SAEs were defined. As a sensitivity analysis, a conservative definition of SAEs, where only the first or admission diagnosis of hospitalization claims was used to identify SAEs, was conducted. Cohorts of patients with and without all AEs (i.e., of any severity) were also defined, and consisted of patients with AEs identified from all diagnosis variables of hospitalization claims or only the first diagnosis or admission diagnosis (i.e., "primary" diagnoses) from non-inpatient claims.

For each select AE, each patient's 1 L treatment period was classified as either "with AE" or "without AE" based on whether or not a diagnosis for the specific AE was recorded during the patient's treatment period. 1 L therapy periods that were classified as "with AE" for the analysis of a given AE may have been classified as "without AE" in the analysis of another AE. For example, if a patient had diarrhea, their treatment period would have been classified as "with AE" in the analysis for diarrhea, but could also have been classified "without AE" for all other studied AEs (e.g., ILD). This methodology was applied separately for patients with and without SAEs (including the sensitivity analysis of SAEs) and patients with and without AEs of any severity.

2.3. Study population

The study population consisted of patients with metastatic NSCLC aged 18 years and above who were treated with first- or second-generation EGFR-TKIs as 1 L monotherapy, had 3 or more months of continuous enrollment prior to the index date to define the baseline period, and had one or more claims for primary malignancy of the lungs during baseline. Since cancer stage and EGFR mutation status information are not available in claims data, it was assumed that patients with a diagnosis code for primary malignancy of the lung with one or more claims for a first- or second-generation EGFR-TKI in the 1 L were likely to be patients with EGFR mutation-positive metastatic NSCLC, as EGFR-TKIs are indicated for the 1 L treatment of this specific population (as patients who do not have EGFR positive metastatic NSCLC are not recommended for treatment with EGFR-TKIs in 1 L). Patients were excluded if they had any claims for lung cancer-related surgery during baseline, 28 or fewer days between the index date and the end of the 1 L treatment period, or any claims for a chemo-, targeted, or immuno-

Table 2
SAEs and all AEs identified during first-line treatment period.

Cohorts		Patients with AE during treatment period n (%)[a]	Rate per 1000 patient-years[a]	N cases	N controls
SAEs	**Any AEs**	–	–	**234**	**1082**
	Any non-chronic AEs	**200 (12.2)**	**220.1**	**169**	**1281**
	Cardiac events and CVA	–	–	141	1341
	ILD	131 (8.0)	139.6	106	1373
	Diarrhea	74 (4.5)	78.6	72	1560
	Renal failure	–	–	62	1547
	Skin and ocular disorders	38 (2.3)	37.8	38	1592
	Hepatotoxicity	–	–	27	1573
	MAHA	8 (0.5)	10.7	8	1632
	Gastrointestinal perforation	3 (0.2)	2.9	3	1640
All AEs	**Any AEs**	–	–	**385**	**613**
	Any non-chronic AEs	**549 (33.4)**	**870.9**	**375**	**853**
	Cardiac events and CVA	–	–	177	1209
	ILD	240 (14.6)	279.3	159	1138
	Diarrhea	125 (7.6)	137.7	120	1495
	Renal failure	–	–	70	1535
	Skin and ocular disorders	289 (17.6)	482.9	277	1321
	Hepatotoxicity	–	–	58	1487
	MAHA	18 (1.1)	25.2	17	1617
	Gastrointestinal perforation	3 (0.2)	2.9	3	1640

Abbreviations: SAE, severe AE; AE, adverse event; CVA, cerebrovascular accident; ILD, interstitial lung disease; MAHA, microangiopathic hemolytic anemia.
[a] Patients diagnosed with the specific AE during the 3-month baseline period were not excluded for these analyses.

oncology therapy indicated for metastatic NSCLC within 28 days of the index date or during baseline.

For the analysis of healthcare cost and HRU, patients who had a claim for the select AE during the 3-month baseline period were excluded from the analysis for that specific AE only. For example, a patient who had diarrhea in the baseline period was not included in analyses for diarrhea regardless of the occurrence of diarrhea during the treatment period.

2.4. Study outcomes and statistical analysis

Baseline demographic and clinical characteristics were assessed for patients with and without SAEs, and patients with and without AEs of any severity (i.e., all AEs). The following analyses were conducted separately to evaluate SAEs and all AEs.

2.4.1. Rate of occurrence of AEs

Of the select AEs, ILD, diarrhea, skin and ocular disorders, MAHA, and gastrointestinal perforation were acute in nature. The remaining AEs (cardiac events and CVA, renal failure, and hepatotoxicity) were considered to be chronic and long-lasting in nature, and could not be quantified based on the number of claims observed. Thus, the calculation of a rate of occurrence is not applicable to those chronic AEs.

The rate of occurrence of each acute AE was assessed during the 1 L treatment period only. For the analysis of this specific objective, patients with the specific AE during the 3-month baseline period were not excluded to ensure that rates of AEs were calculated in the total study population, and to ensure that a consistent denominator was used across AEs.

Outcomes used to describe AE rate of occurrence included rate of each acute AE, defined as the number of non-consecutive claims for AE events per 1000 patient-years. AEs were considered as distinct events if there was a gap of at least 14 days between claims with the corresponding diagnosis. In addition, the proportion of patients who experienced at least one acute AE over the treatment period was also reported.

2.4.2. Healthcare cost

For each select AE cohort, total healthcare cost was assessed over the entire 1 L treatment period and reported on a PPPM basis to account for different lengths of treatment durations. Total all-cause healthcare costs were estimated from a US payer's perspective and represented the sum of pharmacy cost and medical service cost, and were evaluated at the value of the US dollar in 2017 (the Medical Care component of the 2017 Consumer Price Index from the US Bureau of Labor statistics was used to inflate all costs to 2017 US dollars). Mean cost differences comparing patients with and without specific AEs were obtained using multivariable linear regressions adjusted for age, gender, region, insurance type, year of index date, index EGFR-TKI, time from first lung cancer diagnosis to index date, most prevalent baseline comorbidities (overall prevalence ≥10%), Quan-Charlson comorbidity index, baseline healthcare costs, and baseline HRU. Confidence intervals and p-values were obtained using non-parametric bootstrap estimation with 499 replications.

2.4.3. Healthcare resource utilization

For each AE, crude rates of HRU were calculated based on the occurrence of hospitalization, emergency room (ER), and outpatient visit events during the 1 L treatment period. Results were reported as the number of HRU events per patient-year. Rate ratios (RR) comparing patients with and without specific AEs were obtained using multivariate generalized linear models with a log link and a Poisson distribution. A separate regression was performed for each studied AE, and adjusted for the same baseline demographic and clinical characteristics as in the analysis of healthcare costs.

3. Results

3.1. Baseline characteristics

Of 4659 patients with one or more claims for any first- or second-generation EGFR-TKI indicated for the 1 L treatment of EGFR positive metastatic NSCLC, 1646 met the study eligibility criteria (Fig. 1). In the total study population, 1431 (86.9%) patients were treated with erlotinib, 199 (12.1%) with afatinib, and 16 (1.0%) with gefitinib (Table 1). The mean age was 60.8 years and 1034 (62.8%) were female. The average 1 L treatment period was 7.6 months and the average time from first lung cancer diagnosis to the initiation of index EGFR-TKI was 1.7

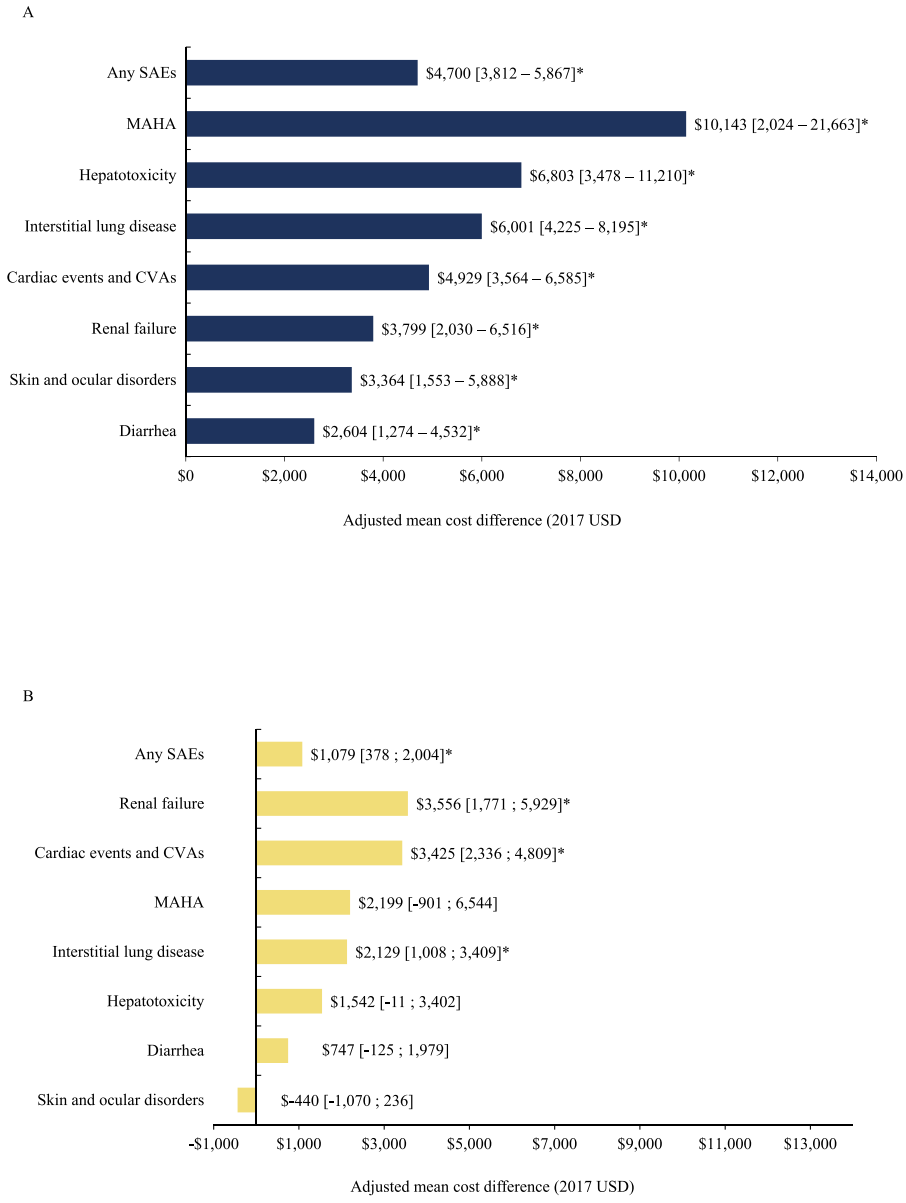


Fig. 2. Adjusted mean cost differences (and 95% CIs) comparing patients A) with versus without SAEs, B) with versus without all AEs.
*Indicates statistical significance at the 5% level.
CI, confidence interval; SAE, severe AE; AE, adverse event; MAHA, microangiopathic hemolytic anemia; CVA, cerebrovascular accident; PPPM, per-patient-per-month

months. The three most frequent comorbidities recorded were hypertension (37.8%), chronic pulmonary disease (28.3%), and cardiac arrhythmias (18.0%). A total of 330 (20.0%) EGFR-TKI users had at least one SAE during the baseline period. The most frequent SAEs during the baseline period were ILD (10.1%), cardiac events and CVA (10.0%), and hepatotoxicity (2.8%).

EGFR-TKI users experiencing any SAEs during the 1 L treatment period (N = 234) were generally comparable to those without any SAEs (N = 1082 [Table 2]). Notably, they were similar in terms of age (mean = 60.5 years vs 60.7 years), the proportion that were female (62.4% vs 62.2%), and Quan-Charlson comorbidity index (mean = 6.0 vs 5.8). Patients with SAEs had a higher incidence of medical comorbidities compared to patients with no SAEs (e.g., hypertension: 41.5% vs 33.6% [p = 0.023], chronic pulmonary disease: 34.6% vs 22.9% [p < 0.001], cardiac arrhythmias: 16.7% vs 9.5% [p = 0.001]). Baseline characteristics were generally similar in patients with AEs of any severity (N = 385) and patients without any AEs (N = 613).

3.2. Rates of acute SAEs and AEs of any severity

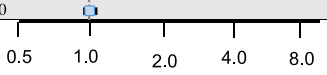
During the treatment period, 200 EGFR-TKI users had one or more acute SAEs (12.2%, 220.1 per 1000 patient-years) and 549 EGFR-TKI users had one or more acute AEs (33.4%, 870.9 per 1000 patient-years) (Table 2). Among SAEs, ILD was the most common (8.0%, 139.6 per 1000 patient-years), followed by diarrhea (4.5%, 78.6 per 1000 patient-years), and skin and ocular disorders (2.3%, 37.8 per 1000 patient-years). Across all AEs (of any severity), skin and ocular disorders were most common (17.6%, 482.9 per 1000 patient-years), followed by ILD (14.6%, 279.3 per 1000 patient-years) and diarrhea (7.6%, 137.7 per 1000 patient-years).

3.3. Incremental healthcare costs over the 1 L treatment period due to SAEs and all AEs of any severity

All-cause healthcare costs over the 1 L treatment period were

A

		With SAEs	Without SAEs	Adjusted RR (95% CI)
Hospitalizations	**Any SAE**	2.23	0.35	6.15 [5.16–7.31]*
	MAHA	4.28	0.76	4.21 [2.68–6.63]*
	Cardiac events and CVA	2.41	0.56	4.03 [3.41–4.76]*
	Interstitial lung disease	2.49	0.60	3.94 [3.27–4.75]*
	Renal failure	2.32	0.70	3.08 [2.48–3.83]*
	Hepatotoxicity	2.85	0.75	2.98 [2.14–4.15]*
	Diarrhea	2.37	0.69	2.94 [2.40–3.59]*
	Skin and ocular disorders	2.13	0.74	2.68 [2.06–3.48]*
Outpatient visits	**Any SAE**	46.25	38.17	1.21 [1.18–1.24]*
	MAHA	55.84	39.63	1.34 [1.19–1.51]*
	Interstitial lung disease	48.99	38.85	1.20 [1.16–1.25]*
	Diarrhea	51.64	39.08	1.18 [1.13–1.23]*
	Cardiac events and CVA	44.55	38.17	1.17 [1.13–1.21]*
	Renal failure	43.75	39.70	1.12 [1.07–1.17]*
	Hepatotoxicity	45.04	39.70	1.08 [1.00–1.17]
	Skin and ocular disorders	37.58	39.60	1.01 [0.95–1.07]



B

		With AEs	Without AEs	Adjusted RR (95% CI)
Hospitalization	**Any AE**	0.96	0.51	1.86 [1.52–2.27]*
	Cardiac events and CVA	1.72	0.57	2.92 [2.46–3.46]*
	Renal failure	2.08	0.70	2.80 [2.26–3.48]*
	Diarrhea	1.46	0.70	2.04 [1.69–2.46]*
	Interstitial lung disease	1.31	0.66	2.01 [1.67–2.42]*
	MAHA	1.32	0.77	1.56 [1.03–2.37]*
	Hepatotoxicity	1.05	0.75	1.44 [1.09–1.92]*
	Skin and ocular disorders	0.57	0.87	0.69 [0.58–0.82]
Outpatient visits	**Any AE**	37.79	36.44	1.06 [1.03–1.09]*
	Cardiac events and CVA	43.59	37.32	1.21 [1.18–1.25]*
	Renal failure	43.89	39.68	1.14 [1.09–1.19]*
	MAHA	45.47	39.62	1.12 [1.04–1.20]*
	Diarrhea	44.55	39.28	1.05 [1.02–1.09]*
	Skin and ocular disorders	42.94	38.05	1.05 [1.03–1.08]*
	Hepatotoxicity	39.95	39.58	1.02 [0.98–1.07]
	Interstitial lung disease	38.45	39.81	0.99 [0.96–1.02]

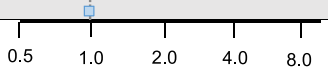


Fig. 3. Adjusted RR (and 95% CI) comparing the rate of HRU between patients A) with versus without SAEs, B) with versus without all AEs.
*Indicates statistical significance at the 5% level.
RR, rate ratio; CI, confidence interval; HRU, healthcare resource utilization; SAE, severe AE; AE, adverse event; MAHA, microangiopathic hemolytic anemia; CVA, cerebrovascular accident

significantly higher in the cohort of EGFR-TKI users with any SAEs compared to the cohort of EGFR-TKI users without SAEs (Fig. 2A). Notably, the adjusted all-cause healthcare cost difference between EGFR-TKI users with and without any SAEs was $4700 PPPM ($p < 0.001$). Adjusted cost differences for specific SAEs ranged from $2604 PPPM for diarrhea to $10,143 PPPM for MAHA, and were statistically significant for all specific AEs (all $p < 0.05$). The sensitivity analysis identifying SAEs based on only the first or admission diagnosis of a hospitalization claim showed similar results.

Results for all AEs of any severity were similar to those for SAEs, though the magnitude of cost differences was slightly smaller (Fig. 2B). PPPM total healthcare costs in patients with any AEs were higher than in patients without any AEs (cost difference = $1079 PPPM, $p < 0.001$). The greatest statistically significant incremental PPPM cost was observed for renal failure (adjusted cost difference = $3556 PPPM, $p < 0.001$), followed by cardiac events and CVA (adjusted cost difference = $3425 PPPM, $p < 0.001$) and ILD (adjusted cost difference = $2129 PPPM, $p < 0.001$). In the analysis of all AEs, incremental PPPM costs associated with management of diarrhea, skin and ocular disorders, hepatotoxicity, and MAHA were not statistically significant.

3.4. Incremental healthcare resource utilization over the 1 L treatment period due to SAEs and all AEs of any severity

All-cause HRU over the 1 L treatment period for EGFR-TKI monotherapy users was significantly higher in the cohort with any SAEs compared to the cohort without SAEs (Fig. 3A). Notably, the HRU rate per patient-year for EGFR-TKI users with any SAEs compared to those without any SAEs was 2.23 versus 0.35 for hospitalizations (adjusted RR = 6.15, $p < 0.001$), 1.39 versus 0.65 for ER visits (adjusted RR = 2.16, $p < 0.001$), and 46.25 versus 36.71 for outpatient visits (adjusted RR = 1.21, $p < 0.001$). Similar results were observed for most of the specific SAE cohorts. For example, EGFR-TKI users with severe diarrhea had a higher rate of hospitalizations (adjusted RR = 2.94, $p < 0.001$), ER visits (adjusted RR = 2.13, $p < 0.001$), and outpatient visits (adjusted RR = 1.18, $p < 0.001$), compared to EGFR-TKI users without severe diarrhea during the 1 L treatment period. Results were consistent in sensitivity analysis of SAEs considering only the first diagnosis or admission diagnosis of a hospitalization claim.

Results from the analysis of all AEs of any severity were similar (Fig. 3B). The rate per person-year for EGFR-TKI users with any AEs compared to those without any AEs was 0.96 versus 0.51 for hospitalizations (adjusted RR = 1.86, $p < 0.001$), 0.99 versus 0.64 for ER visits (adjusted RR = 1.40, $p < 0.001$), and 37.79 versus 36.44 for outpatient visits (adjusted RR = 1.06, $p < 0.001$).

4. Discussion

Treatment options for EGFR-mutated metastatic NSCLC may be associated with considerable toxicity, which can lead to higher HRU and associated healthcare expenditure. Although clinical trial data describe the extent of AEs experienced by patients treated with erlotinib, afatinib, and gefitinib, there is limited real-world evidence regarding the burden of managing AEs associated with these agents. This retrospective study is among the first using real-world data to assess the rate of AE occurrence and to quantify HRU and costs of AE management in patients with metastatic NSCLC receiving first- or second-generation EGFR-TKIs as 1 L monotherapy.

In this study, more than a tenth of all patients had at least one AE that resulted in hospitalization. ILD and diarrhea were the SAEs with the highest rate of occurrence during the 1 L treatment period. Findings

from this study also demonstrated that the incremental costs associated with the specific treatment-related SAEs were high. Specific SAEs with the largest economic burden in terms of total healthcare costs were MAHA, hepatotoxicity, and ILD.

When considering all AEs of any severity, skin and ocular disorders, which can be quite burdensome to patients, had the highest rate of occurrence during the 1 L treatment period. While the incremental costs of this specific AE during the 1 L treatment period were not significant, the rate of outpatient visits in these patients was higher than in patients without this AE, suggesting that less costly AEs are still burdensome and can affect patients' quality of life. A similar trend was also observed with patients who experienced diarrhea.

Generally, the rates of AEs found in this study were different from AE rates from clinical trials, which themselves varied across therapies and studies. For instance, a Phase III randomized clinical trial of erlotinib for 1 L treatment of advanced NSCLC found that 90% of patients treated with erlotinib experienced an AE of any severity [13], which is higher than the proportion observed in the current study, likely due to the fact that AEs would be included in the current study only if the patient obtained medical care that resulted in an insurance claim. The lower proportion of patients with skin and ocular disorders in the current study compared to those with rash in the clinical trial may be explained by fewer patients seeking treatment for skin and ocular disorders in the real-world setting versus potentially close monitoring in clinical trials. Additionally, skin and ocular disorders may not be well documented in claims.

A few previous US studies investigated the cost of adverse events in patients with metastatic NSCLC, though not among patients treated with EGFR-TKIs specifically. A study with a similar design estimated the average incremental costs (in 2015 US dollars) of the following AEs (all grades) during lung cancer treatment episodes: arrhythmia ($6159), heart failure ($6464), and diarrhea ($4246) [12]. Another study investigating costs associated with SAEs in Medicare patients with advanced NSCLC who were largely treated with second-line chemotherapy-based regimens reported that patients with SAEs had an incremental cost PPPM of $8588 (in 2014 US dollars), which was largely attributed to inpatient costs [14], and exceeds the incremental costs observed in the current study. In addition, compared to the current study, a greater proportion of Medicare patients experienced SAEs (40.9% vs 12.2%), which is in line with the literature suggesting EGFR-TKIs are a safer alternative to chemotherapy [11].

While EGFR-TKIs are favorable compared to chemotherapies with respect to safety, the current study demonstrated that first- and second-generation EGFR-TKIs still present an economic burden with regards to AE management. Treatment options with further improved safety profiles may help decrease healthcare costs and resource utilization in the treatment of metastatic NSCLC. Given its recent approval by the FDA in April 2018, osimertinib is an alternative to first- and second-generation EGFR-TKIs for the first-line treatment of advanced EGFR-mutated NSCLC. Third-generation EGFR-TKIs, such as osimertinib, are active against EGFR sensitizing and T790 M resistance mutations but lower potency against EGFR wild type [15]. Lower activity against wild type EGFR may reduce related toxicities and improve tolerability; activity against wild type EGFR has been associated with AEs including rash and diarrhea [15,16]. This was observed in the FLAURA trial, where 34% of patients treated with osimertinib had AEs of grade 3 or higher compared to 45% of patients treated with standard EGFR-TKIs (i.e. gefitinib or erlotinib) [17]. Further research into the rates, costs, and HRU of AEs among patients with metastatic NSCLC treated with third-generation EGFR-TKIs are needed to determine if improvements over first- and second-generation EGFR-TKIs in trials are also observed in real-world settings.

The strengths of the study are related to the data source used, as the IQVIA RWD Adjudicated Claims–US database includes information from various healthcare providers with whom a patient may interact regardless of healthcare system or location. In addition, the database is representative of the US commercially insured population, allowing for the generalizability of results to the majority of patients in the US. In addition, a sizeable number of patients with metastatic NSCLC treated with EGFR-TKIs was studied, ensuring that relatively rare AEs were observed in the study.

However, results of the study should be interpreted with caution given its limitations. Although adjusted regression analysis was used to compare HRU and cost outcomes, potential bias may remain due to unmeasured confounders since certain variables that influence the choice of metastatic NSCLC therapy, the occurrence of adverse events, and costs, such as performance status and smoking history, are not included in the database. In addition, the study relies on diagnosis codes from medical claims to identify patients with NSCLC and to determine the presence of each AE. However, there is no specific ICD-9-CM or ICD-10-CM code for NSCLC. Patients with lung cancer treated with erlotinib, gefitinib, or afatinib were assumed to have non-small cell histology. Coding errors may also result in misclassification of the patients with NSCLC and patients who experience AEs. Due to limitations of using administrative claims data to conduct this study and a lack of data on underlying causes of disease, the occurrence of AEs could not be specifically attributed to the treatments under study or characterized as "treatment-related". Rather, diagnoses related to AEs were studied without consideration of a definitively ascertained underlying cause. Furthermore, the reliance on claims data to estimate the rate of occurrence of acute SAEs and AEs (of any severity) in patients with NSCLC may yield different estimates than those from population-based studies. For example, billing codes may provide a less accurate disease definition than clinical criteria. It is challenging to ensure that the occurrence of an AE is truly incident to current treatment, rather than a reoccurrence of a prior condition. While claims with diagnoses for the select AE in baseline were relied upon to exclude patients from the analysis of HRU and cost associated with that specific AE during the observation period, inaccuracies in diagnosis coding may result in misclassification of patients with the AEs during baseline. Therefore, in order to be as accurate as possible in the terminology used, we refer to rate of occurrence rather than incidence rate of AEs. AEs that did not require medical care which resulted in an insurance claim are not represented in the data. As a result, there is the potential for AEs that are underrepresented to appear less common and costly. Similarly, only AEs included on the prescribing information for first- and second-generation EGFR-TKIs were considered in this study. As such, other AEs that present frequently in patients but are not noted on the prescribing information, which may be of interest to clinicians, are excluded.

5. Conclusion

The current study, which analyzed data from 04/01/2012 to 03/31/2017, found that 12.2% and 33.4% of patients with EGFR mutation-positive metastatic NSCLC treated with first- or second-generation EGFR-TKIs suffered from acute SAEs and acute AEs of any severity during the course of the 1 L treatment period, respectively. This is comparable to clinical trials of EGFR-TKIs which have reported SAEs and treatment-related AEs of grade 3 or 4 in 6%–49% of patients, although acute AEs represent only a portion of AEs reported in these trials [7,18,19].

Our study findings highlight both the economic burden of SAEs and AEs of any severity associated with first- or second-generation EGFR-TKIs and the need for awareness about the risk of SAEs in this population among treating oncologists. The substantial economic burden associated with SAEs underscores the need for EGFR-TKIs with safety profiles that could reduce the economic burden in this population.

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Declaration of competing interest

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