Supportive Care in Cancer (2025) 33:285
https://doi.org/10.1007/s00520-025-09353-5

COMMENT

Receiving immunotherapy for the treatment of advanced renal cell carcinoma is associated with higher burden of illness, coagulopathy, cardiac arrhythmia, and disparities

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Received: 6 August 2024 / Accepted: 10 March 2025

Abstract

Background The adverse outcomes and costs of immunotherapy (IT) have yet to be fully explored. Our study aims to assess the association between the use of IT in patients with metastatic renal cell carcinoma (mRCC) and the burden of illness (BOI), including coagulopathy, arrhythmia, and disparities.

Methods The study used US national data to investigate the association between the use of IT in the mRCC and the BOI. The BOI was measured by total charges and length of stay (LOS). Additionally, we examined coagulopathy, arrhythmia, and disparities in these outcomes. This investigation was conducted using generalized linear models (glm).

Results Of 28,535 patients who had mRCC, 230 had previously received IT. In the adjusted glm, after accounting for other variables, "IT" was found to be associated with higher total charges— (coeff = 7.67; 95% CI 4.86 – 12.09). There was no association with IT and LOS. Coagulopathy (aOR = 5.61; 95% CI 2.40 – 13.14) and arrhythmia (aOR = 4.34; 95% CI 2.20 – 8.55) were associated with IT treatment. Moreover, compared to males, females had a lower cardiac arrhythmia risk (aOR 0.83, 95% CI 0.72–0.98). Non-whites, compared to Whites, had a higher total charge (1.21, 95% CI 1.13–1.29), higher coagulopathies (aOR 1.25; 95% CI 1.01–1.54), but lower cardiac arrhythmia risk (aOR 0.57; 95% CI 0.47–0.69).

Conclusion Although IT has become increasingly important in treating mRCC, this is the first time real-world data on the costs, negative consequences, and disparities of IT are examined. The results may have important implications for creating innovative, supportive care models for this population.

Keywords Immunotherapy · Metastatic renal cell carcinoma · Immune-related adverse events · Burden of illness · Coagulopathy · Cardiac arrhythmia

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Published online: 15 March 2025

Introduction

IT has emerged as a fundamental treatment for mRCC [1, 2]. This advanced treatment enhances cellular immunity, which can sometimes be associated with non-specific targets and harmful effects on normal cells. Nevertheless, the adverse events and expenses related to IT have yet to be thoroughly delineated. Recently, the utilization of IT, specifically immune checkpoint inhibitors (ICIs), has led to a proportional rise in immune-related adverse effects (irAEs) [3, 4]. ICIs could disrupt the immune system's balance and decrease T cell tolerance, further activating and expanding cancer-related T cells [5]. Blocking immunological checkpoints might also cause autoreactive T cells to become activated, leading to the development of diverse irAEs that resemble autoimmune disorders. These irAEs are usually heterogeneous and can occur in many organs. Common adverse effects include gastrointestinal toxicity, endocrine toxicity, and dermatologic toxicity [6]. Neurotoxicity, cardiotoxicity, and pulmonary toxicity are other examples that impact quality of life and have the potential to cause death [7]. Cardiotoxicity caused by ICIs is infrequent, occurring in less than 1% of cases. However, when it does happen, it is typically severe and has the potential to be life-threatening. Studies reported that patients may exhibit symptoms such as cardiac fibrosis, cardiac arrest, autoimmune myocarditis, cardiomyopathy, heart failure, pericardial involvement, and vasculitis [7, 8]. While reports also indicated that adverse effects such as gastrointestinal toxicity, dermatologic toxicity, and hypophysitis are more frequently observed with anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) drugs [8]. Furthermore, adverse effects, including coagulopathy, have been identified in individuals who received ICIs [9]. Hence, our study's objective was to evaluate the relationship between mRCC patients encountering IT and their BOI, coagulopathy, arrhythmia, and disparities.

Methods

Analysis was conducted utilizing the National Inpatient Samples Database to examine patients hospitalized with mRCC. The study group was stratified based on whether they previously encountered antineoplastic IT. Both univariate and multivariate survey-weighted generalized linear models (glm) were utilized to assess the association between IT in mRCC and the BOI — length of stay (LOS), total charges, and additionally, coagulopathy, arrhythmia, and disparities while controlling for patient and clinical characteristics. This analysis utilized the 2017 National Inpatient Sample (NIS) database from the Healthcare Cost and Utilization Project (HCUP) at the Agency for Healthcare Research and Quality [10]. This study exclusively involved adults aged over 18 years.

The NIS dataset encompasses patient demographics, medical history, outcomes during hospitalization, hospital specifics, and associated expenditures. This study comprised individuals hospitalized for the treatment of renal cell carcinomas (RCC). The cancer type was determined by ICD-10-CM billing codes (S1 file).

Ethics statement

The HCUP does not mandate that users obtain IRB review from their institutions; hence, it has not submitted to the Institutional Review Board (IRB) as this study utilized publicly available de-identified data or comprised a limited dataset. In addition, obtaining patient permission is unfeasible.

Measures

The main independent variables comprised the administration of antineoplastic IT in patients with RCC. The outcome variables are BOI (in-hospital length of stay (LOS) and total charges/expenses), coagulopathy, and cardiac arrhythmias. The phrase "total charges" refers to the comprehensive expenses associated with a hospital stay. Generally, professional fees and non-reimbursable expenses are omitted from the overall charges. Professional fees and other expenses are deducted during processing, and the total charge is then adjusted for the current year. We used log transformation to total costs and length of stay (LOS) and reported the geometric mean because of the non-normal distribution. To prevent a negative logarithm, a length of stay (LOS) of 0 days was assigned a value of 0.0001. Coagulopathy and cardiac arrhythmias were identified using the Elixhauser comorbidity index program.

Patient and clinical variables were incorporated as covariates. Patient characteristics included age, gender, primary payer (Medicare, Medicaid, private insurance, and others), median household income by zip code (first to fourth quartile), and urban/rural status (utilizing a six-category urban–rural classification system for US counties established by the National Center for Health Statistics). Additional factors encompassed the kind of hospitalization (elective versus non-elective) and comorbidity status, assessed using the Elixhauser comorbidity index [11].

Statistical analysis

mRCC with and without IT demographic and clinical features were described using descriptive statistics (Table 1). Furthermore, we employed survey-weighted generalized linear models [11] (svyglm) to examine the correlation

Table 1 Baseline characteristics of metastatic renal cell carcinoma (RCC) patients stratified with or without encountering immunotherapy

	Metastatic RCC without immunotherapy (weighted)	Metastatic RCC with immunotherapy (weighted)	*P* value
n	28,305	230	
AGE (mean (SD))	65.80 (12.18)	54.50 (8.67)	< 0.001
Sex (%)			0.54
Female	9245 (32.7)	65 (28.3)	
RACE (%)			0.37
White	20,490 (71.5)	190 (81.0)	
Non-white	7815 (28.5)	40 (19.0)	
Median household income (based on current year)			0.1
0–25th percentile	7530 (27.0)	30 (13.3)	
26th to 50th percentile	7325 (26.2)	95 (42.2)	
51st to 75th percentile	6915 (24.8)	45 (20.0)	
76th to 100th percentile	6145 (22)	55 (24.4)	
Expected primary payer (%)			< 0.001
Medicare	15,730 (55.5)	40 (17.4)	
Non-Medicare	12,575 (44.5)	190 (82.6)	
Patient location: NCHS urban–rural code (%)			0.53
"Central" counties of metro areas of > = 1 million population	8010 (28.4)	75 (32.6)	
"Fringe" counties of metro areas of > = 1 million population	6900 (24.4)	35 (15.2)	
Counties in metro areas of 250,000–999,999 population	5655 (20)	45 (19.6)	
Counties in metro areas of 50,000–249,999 population, micropolitan counties, and not metropolitan	7685 (27.2)	75 (32.6)	
Elective admission	6060.0 (20.6)	170.0 (73.9)	< 0.001
Weighted Elixir score mean (SD))	24.66 (8.10)	22.78 (5.63)	0.02
Length of stay (geometric mean)	3.92 days	4.6 days	0.03
Total charge (geometric mean)	$44,762	$181,549	< 0.001
Cardiac arrhythmia (%)	5740 (20.3)	85 (37.0)	0.003
Coagulopathy (%)	2725 (9.6)	60 (26.1)	0.001

Note: All frequencies and percentages are weighted

SD, standard deviation; *NCHS*, National Center for Health Statistics; *$*, United States' dollar

between IT status and outcomes such in-hospital length of stay (LOS) and total charges, coagulopathy, and cardiac arrhythmias. Through univariate and multivariate analysis, we examined the study groups to ascertain the relationship between variables and the outcome. Patient demographics (gender, age, payer type, geography, race, and median household income) and clinical variables (comorbidities score, hospital discharge status, and median household income) were all included in our multivariate models. For models with binary outcomes, we fitted the svyglm using a quasibinomial. Our investigations consistently utilized two-tailed probability distributions, with a *P* value less than 0.05 established as the cutoff for statistical significance. The R Foundation statistical computing environment R 4.3.0, was used for all statistical analyses.

Results

A sample of 230 (who encountered IT) out of 28,535 mRCC patients in the NIR database was analyzed (Table 1). Patients who received IT treatment had a mean age of 54.50 years (SD 8.67), while those who did not receive IT treatment had a mean age of 65.80 years (SD 12.18). The IT recipients were predominantly White, accounting for 81.0% of the total. The majority (82.6%) of IT-treated patients did not receive Medicare. The total charge for IT patients was $181,549 (geometric mean), whereas non-IT patients had average total charges of $44,762 (geometric mean). The LOS for IT patients was 4.6 days (geometric mean), compared to 3.92 (geometric mean) days for non-IT patients. The incidence of

coagulopathy in patients with IT-treated mRCC was 26.1% vs. 9.6% for non-IT mRCC patients, while the incidence of cardiac arrhythmia was 37.0% for IT mRCC vs. 20.3% for non-IT mRCC. In the adjusted glm, after accounting for other variables, the IT treatment was associated with increased total charges; the estimated effect size (coeff) was 7.67 (95% confidence interval (CI) 4.86 to 12.09). In addition, IT among mRCC was associated with a higher likelihood of coagulopathy (adjusted odds ratio [aOR] = 5.61; 95% CI 2.40 – 13.14) and cardiac arrhythmia (aOR = 4.34; 95% CI 2.20 – 8.55). Non-whites, compared to Whites, had higher coagulopathies (aOR 1.25; 95% CI 1.01–1.54). However, non-whites, compared to Whites, had a lower cardiac arrhythmia (aOR 0.57; 95% CI 0.47–0.69). Compared to males, females had a lower cardiac arrhythmia (aOR 0.83, 95% CI 0.72–0.98). Non-whites, compared to Whites, had a higher total charge; the estimated effect size (Coeff) was 1.21, 95% CI 1.13–1.29 (Fig. 1). None of the IT recipients died in the hospital compared to mRCC without IT (2225.0 (7.6) vs. mRCC with IT 0(0).

Discussion

mRCC patients who received IT had a higher likelihood of coagulopathies and cardiac arrhythmia, which impacted total charges. While IT has played a vital role in treating mRCC in recent years, this is the first analysis using "real-world" data to assess irAEs and cost of care. The findings may have substantial implications for new supportive care in this population. The report examines emerging toxicities and contributes additional data to previous investigations. The findings of this study will facilitate the analysis, strategizing, and emphasis on initiatives to identify further unknown irAEs and their financial implications and disparities. The study outcomes have the potential to greatly influence the manner in which IT group receives and derives advantages from additional assistance and supportive care needs.

While this study examining 2017 data in healthcare research, it provides a historical context for health trends related to immunotherapy-associated adverse events. Additionally, it shows significant potential irAEs that should be thoroughly examined and potentially prevented or managed. Ongoing analysis should assess the effects of intervention and demographic shifts over time, especially concerning mRCC among hospitalized patients. It may also disclose annual patterns that fluctuate based on guideline recommendations, which short-term datasets may overlook following the approval of immunotherapy for mRCC. It is crucial to recognize the potential limits of each dataset, including outdated diagnostic codes, changes in treatment methodologies, and biases in data collection methods over the years. Current drug approvals suggest that integrating historical findings may be beneficial. "Real-world evidence" is essential to comprehend, particularly for irAEs, as well as their

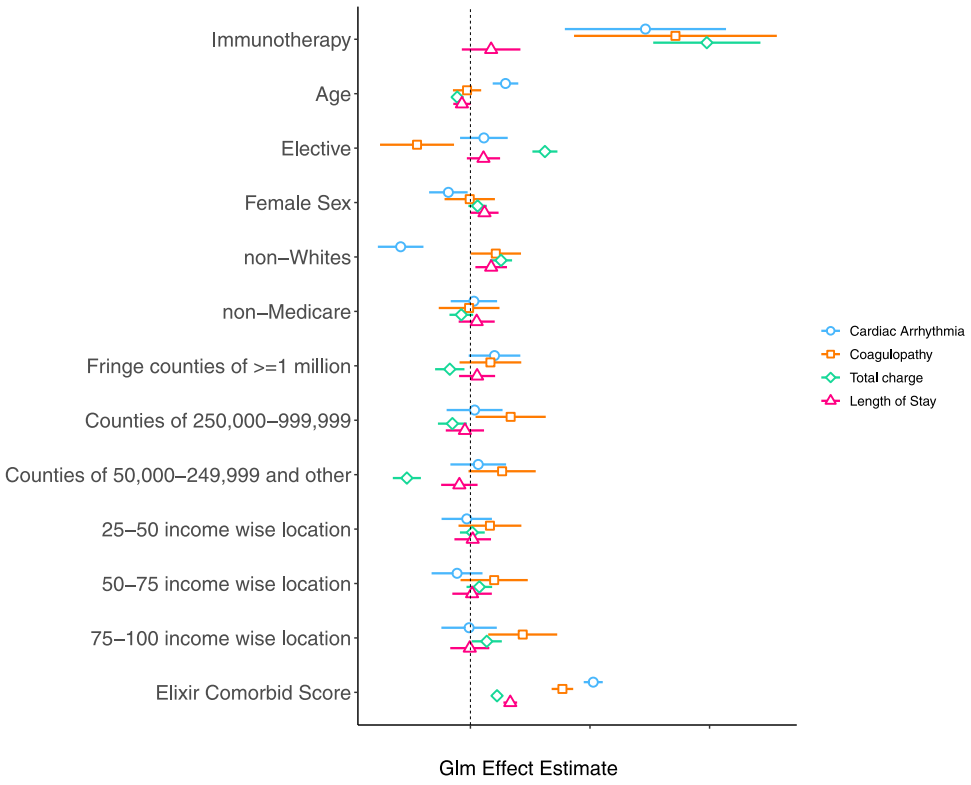

Fig. 1 Plotted regression estimate and confidence intervals for all adjusted generalized linear models

consequences in clinical trials, adverse event documentation, and beneficial for supportive care recommendations. As IT becomes more commonly employed and may be utilized over extended periods of time, comprehensive evaluation of irAEs are essential.

Most information from the clinical trials are derived from Whites, with very little information from the non-white populations [12]. RCC, urothelial cancer, and head and neck malignancies, the occurrence of irAEs correlated with enhanced treatment efficacy [13]. However, according to our reports, cost, length of stay, and cardiac arrhythmias and coagulopathies impact the disease burden and inadvertently the quality of life of patients, while acknowledge the fact that clinical trials frequently lack representation from minority groups. The majority of accessible data originates from research that mostly included White patients, with scant information concerning the non-white population [14]. Further, the important gaps persist despite the expanding body of information about irAEs caused by ICIs. Some research has shown a link between irAEs and increased response and survival rates, whereas other studies have shown no association [15].

Significant discrepancies in the use of immunotherapy were observed across diverse sociodemographic and socioeconomic characteristics among patients diagnosed with non-small cell lung cancer, renal cell carcinoma, and melanoma prior to FDA clearance [12]. Consequently, the impact of race on the incidence of irAEs and the treatment outcomes linked to immune checkpoint inhibitors remain insufficiently explored, with existing studies providing further insights [16–18]. The characteristics of this association warrant an examination concerning access to care, the behaviors associated with healthcare seeking, the reporting of adverse events, the management of these events, the financial burden involved, and the logistics of transportation for reporting adverse events [18–21]. As a result, prioritizing historical evidence that demonstrates association is essential, alongside providing supportive care for patients who exhibit such evidence. Consequently, our comprehensive national study investigates the association between the onset of irAEs and overall, BOI, aiming to clarify the relationship with social demographics.

The specific pattern of AEs linked to immune system sensitization may differ across racial and socioeconomic populations [22]. The exact processes by which irAEs occur are under investigation, encompassing autoreactive T cells, autoantibodies, and proinflammatory cytokines [22]. The immunological tolerance regulators CTLA4, PD1, and PD-L1, and further, the expression of immune checkpoint proteins on cell surfaces is augmented by chronic inflammation, especially interferon-γ, which might mitigate tissue damage are important predictors of irAEs [23]. Nonetheless, inconsistent reporting in clinical research is likely responsible for the underreporting of the incidence of irAEs in patients receiving immune checkpoint inhibitors (ICIs), as documented in clinical trials [24]. Most recently, diabetes and ketoacidosis related with ICIs were identified in the FDA adverse event reporting system through a real-world evidence database analysis [25]. Our ongoing examination integrating electronic health data and national estimates will aid in identifying unrecognized adverse factors, including financial barriers and disparities.

Limitations

The quality of data entry in any extensive database is influenced by the supplied information and is subject to discrepancies in reporting and classification. However, inconsistencies may be substantially reduced by the volume of data incorporated. Also, while NIS data encompasses discharges, it is theoretically feasible for a patient to be readmitted and recorded many times, although this is highly improbable, and there is no data regarding the population of non-admitted patients. Ultimately, in assessing resource consumption, we were constrained to hospital charges rather than actual expenses. Despite controlling for potential confounding factors in the study, it is plausible that there are variables related to exposure status that we could not incorporate into our analysis due to dataset limitations. Furthermore, our studies are limited to a cross sectional assessment of hospitalized cancer patients based on their length of stay; therefore, the findings may not be applicable to a wider population. Nevertheless, the findings are significant in evaluating the characteristics of real-world evidence and its capacity for future investigation.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00520-025-09353-5.

Acknowledgements We thank Ishan S and Vipanchika S for organizing the tables, and Cedrick Ball for the grammatical corrections.

Author contributions SE contributed to the drafting; RP contributed to the design and conception; JE contributed to the design and conception; RR contributed to critical revision of the manuscript; PSSK contributed to the design, conception, acquisition, interpretation of data, drafting, and critical revision of the manuscript.

Funding This study is funded by Kaleida Troup to Poolakkad S Satheeshkumar.

Data availability No datasets were generated or analysed during the current study.

Code availability Non applicable.

Declarations

Ethics approval 1. This study is not required or mandate from the Institutional Review Board approval because it used publicly available data that had been de-identified or contain limited data set (The

Healthcare Cost and Utilization Project (HCUP) does not require that users receive IRB review from their institutions). Hence, a patient consent is not possible. Further this study included only adults > 18 years age.

2. As per the HCUP agreement it is not required that users receive IRB review from their institutions, the HCUP Data Use Agreement (DUA) provide the proof of compliance with the HIPAA privacy rule. In addition, the HCUP databases are consistent with the definition of "limited data sets" (https://privacyruleandresearch.nih.gov/pr_08.asp) under the HIPAA Privacy Rule. They contain no direct patient identifiers, and completion of both the HCUP Data Use Agreement (DUA) training (https://www.hcup-us.ahrq.gov/tech_assist/dua.jsp), and a signed or electronically submitted DUA are required to obtain the HCUP databases.

Consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest We want to disclose the role of one of the co-authors (Joel B Epstein) as an Editor of the journal.

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