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Research Article

Immune Checkpoint Inhibitor Associated Kidney Transplant Rejection: A Real World Pharmacovigilance Analysis Using the FAERS Database

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Abstract

Objectives: This study aims to characterize kidney transplant rejection events associated with immune checkpoint inhibitor (ICI) therapy using real-world pharmacovigilance data from the FDA Adverse Event Reporting System (FAERS).

Methods: We conducted a retrospective pharmacovigilance analysis using the FAERS to identify cases of kidney transplant rejection associated with ICIs reported between January 1, 2012, and March 30, 2025. Reports were included if an FDA-approved ICI was the primary suspect and "kidney transplant rejection" was listed as the adverse event.

Results: Among 215,907 ICI-related adverse event reports reports, 99 cases (0.04%) of kidney transplant rejection were identified. The median age was 68 years; 63.6% were male. Nivolumab (54.5%) and pembrolizumab (24.2%) were the most frequently reported ICIs. Malignant melanoma was the most common underlying malignancy (41.4%). Most patients (86.9%) received single-agent ICI therapy, while 13.1% received combination therapy with CTLA-4 inhibitors. Death due to adverse events occurred in 25.3% of cases.

Conclusion: Our findings align with previous literature, which reports high rejection rates, particularly among patients with melanoma.

Keywords: Adverse drug reaction, Allograft rejection, Kidney transplantation; Kidney transplant rejection, Immune checkpoint inhibitors, Pharmacovigilance, FAERS (FDA Adverse Event Reporting System)

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Immune checkpoint inhibitors (ICIs) are humanized monoclonal antibodies that have transformed the landscape of cancer immunotherapy by enhancing T cell–mediated antitumor responses through the blockade of inhibitory receptors such as PD-1 (programmed cell death protein 1), PD-L1 (programmed death-ligand 1), CTLA-4 (cytotoxic T-lymphocyte–associated protein 4), and LAG-3 (lymphocyte activation gene-3). Under normal physiological conditions, these checkpoints are essential for maintaining immune homeostasis by limiting excessive immune activation and promoting self-tolerance.[1,2] The clinical use of ICIs has become standard in the treatment of various malignancies including melanoma, lung cancer, renal cell carcinoma, and gastric cancer resulting in significant improvements in patient outcomes and survival. However, with their expanding use, there has been a significant increase in immune-related

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adverse events (irAEs), encompassing a broad spectrum of complications, including endocrinopathies, pneumonitis, and neurological, cutaneous, and renal toxicities.[3,4]

Kidney transplant recipients (KTRs) are at a higher risk of developing cancer compared to the general population, which makes malignancy a major cause of morbidity and mortality in this group.[5] Several factors contribute to the increased risk of de novo or recurrent malignancies, including long-term immunosuppression, oncogenic viral infections, and impaired T-cell–mediated immune surveillance.[6] Despite the demonstrated survival benefits of ICIs in immunocompetent individuals, their efficacy in KTRs remains uncertain. Randomized clinical trials assessing the effectiveness of ICIs have typically excluded KTRs with either early-stage or advanced-stage malignancies, primarily due to safety and efficacy concerns—most notably, the risk of allograft rejection and potentially diminished therapeutic response resulting from chronic immunosuppression.[7,8] In the literature, several retrospective clinical studies and meta-analyses have reported limited efficacy of immune checkpoint inhibitors in kidney transplant recipients. Renal allograft rejection rates among KTRs treated with ICIs have been reported to range from 36% to 42%.[9,10] Pharmacovigilance databases, such as the FDA Adverse Event Reporting System (FAERS), further contribute to this evidence by providing real-world data on the incidence, clinical spectrum, and outcomes of ICI-related adverse events. These large-scale resources are instrumental in identifying rare or delayed toxicities not fully captured in clinical trials, thereby informing post-marketing safety surveillance and clinical decision-making in vulnerable populations such as KTRs.[11]

The aim of our study is to investigate the characteristics and clinical outcomes of kidney transplant rejection events associated with immune checkpoint inhibitor therapy through a retrospective pharmacovigilance analysis using data from FAERS.

Methods

We conducted a retrospective pharmacovigilance analysis using data from the publicly accessible FAERS. Adverse event reports submitted between January 1, 2012, and March 30, 2025, were retrieved and analyzed. The FAERS database was queried for reports involving ICIs that had received approval from the U.S. Food and Drug Administration (FDA) as of March 30, 2025. These ICIs included anti-PD-1 agents (nivolumab, pembrolizumab, cemiplimab, dostarlimab, toripalimab, retifanlimab, and tislelizumab), anti-PD-L1 agents (atezolizumab, avelumab, durvalumab), anti-CTLA-4 agents (ipilimumab, tremelimumab), and the anti-LAG-3 agent relatlimab.

The primary objective of this study was to characterize kidney transplant rejection events associated with ICIs, as reported in the FAERS database. Adverse events were identified using the Preferred Term "kidney transplant rejection" from MedDRA Version 28.0.[12] Only reports in which an ICI was identified as the primary suspect drug were included in the analysis. Cases of kidney transplant rejection not associated with ICI use, as well as those attributed to other causes, were excluded to ensure specificity.

A total of 215,907 adverse event reports were initially retrieved from the FAERS database. After data cleaning and application of inclusion criteria, 99 cases of kidney transplant rejection associated with ICI use were identified and included in the final analysis.

Statistical Analysis

Categorical variables were compared using either the Chi-square test or Fisher's exact test, based on the size of the sample and the distribution of expected values within contingency tables. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA), with a two-sided p-value <0.05 considered indicative of statistical significance.

Results

A total of 215,907 adverse event reports related to ICIs were analyzed, identifying 99 (0.04%) cases of ICI-associated kidney transplant rejection. The median age was 68 years (range: 40–84). A total of 43 patients (43.4%) were 65 years of age or older. The majority of patients were male (63.6%). The most frequently reported immune checkpoint inhibitor was nivolumab (54.5%), followed by pembrolizumab (24.2%) (Fig. 1a). The most common underlying malignancy was malignant melanoma (41.4%) (Fig. 1b). Regarding reporter characteristics, most reports were submitted by healthcare professionals (91.9%), while 8.1% were submitted by consumers. In terms of geographic distribution, 44.4% of reports originated from North America, 40.4% from Europe, and 15.2% from other regions. Reports were most commonly submitted in or before 2019 (58.7%), followed by the period between 2020 and 2022 (33.3%), and 2023 to 2024 (8%). Adverse event-related death was reported in 25 cases (25.3%). Baseline characteristics are summarized in Table 1.

A total of 86 patients (86.9%) received single-agent ICI therapy, while 13 patients (13.1%) were treated with a combination of ICI and CTLA-4 inhibitors. In the single-agent ICI group, the median age was 69 years (range: 46–84), and 38 patients (62.0%) were aged 65 or older. In comparison, the ICI plus CTLA-4 inhibitor group had a median age of 60

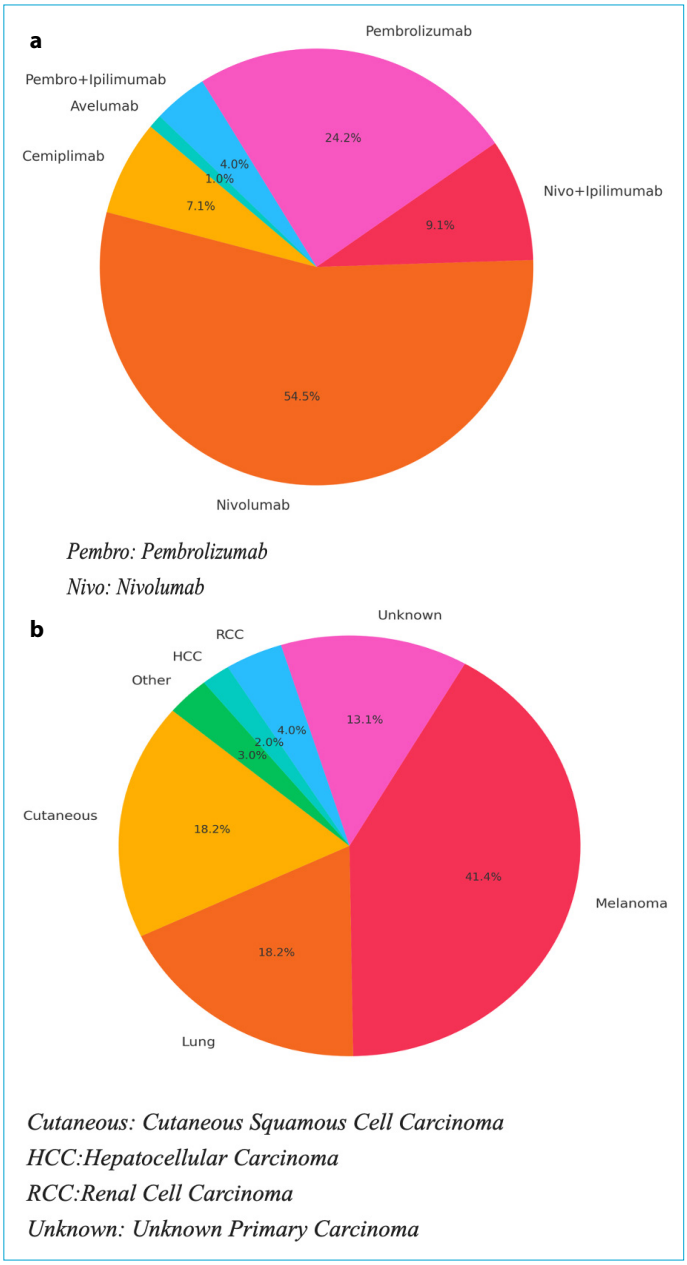

Figure 1. (a) Distribution of cases by immune checkpoint inhibitors. **(b)** Frequency of Cancer Types in Cases with ICI-Associated Allograft Rejection.

Table 1. Baseline Demographic and Clinical Characteristics of Patients With ICI-Associated Kidney Transplant Rejection

Variables	n=99 (%)
Age	
Median (range)	68 (40-84)
≥ 65	43 (43.4)
Gender	
Female	11 (11.1)
Male	63 (63.6)
Not specified	25 (25.3)
Immune checkpoint inhibitors	
Cemiplimab	7 (7.1)
Nivolumab	54 (54.5)
Nivolumab + Ipilimumab	9 (9.1)
Pembrolizumab	24 (24.2)
Pembrolizumab + Ipilimumab	4 (4)
Avelumab	1 (1)
Malignancy Types	
Cutaneous Squamous Cell Carcinoma	18 (18.2)
Lung Carcinoma	18 (18.2)
Malignant Melanoma	41 (41.4)
Renal Cell Carcinoma	4 (4)
Hepatocellular Carcinoma	2 (2)
Other	3(3)
Unknown Primary Carcinoma	13 (13.2)
Reporter Type	
Healthcare worker	91 (91.9)
Consumer	8 (8.1)
Region of Report	
North America	44 (44.4)
Europe	40 (40.4)
Other	15 (15.2)
Year of Report	
2023-2024	8 (8)
2020-2022	33 (33.3)
≤2019	58 (58.7)
Adverse Event-Related Death	25 (25.3)

years (range: 40–70), with 5 patients (45.5%) aged 65 or older. The difference in median age was statistically significant (p=0.017), whereas the proportion of patients aged 65 or older did not differ significantly between groups (p=0.29). There was no significant difference in gender distribution between the two groups (p=0.21). Malignant melanoma was the most frequently reported underlying malignancy in both treatment groups, observed in 11 patients (84.6%) in the ICI plus CTLA-4 group and in 30 patients (34.8%) in the single-agent ICI group. In the single-agent ICI group, the second most common malignancy was cutaneous squamous cell carcinoma, reported in 18 patients (20.9%) (Fig. 2). Although melanoma was more prevalent in the combination therapy group, the difference in the overall distribution of malignancy types between the groups was not statistically significant (p=0.06), but a trend was observed. The distribution of reported cases by year of receipt showed a higher proportion of ICI plus CTLA-4 inhibitor use in more recent years. Between 2023 and 2024, 3 out of 8 cases (37.5%) involved combination therapy, compared to 5 cases (62.5%) with single-agent ICI. From 2020 to 2022, 5 of 33 cases (15.2%) received combination therapy and 28 (84.8%) received single-agent ICI. For cases reported in or before 2019, only 5 of 58 cases (8.6%) involved combina-

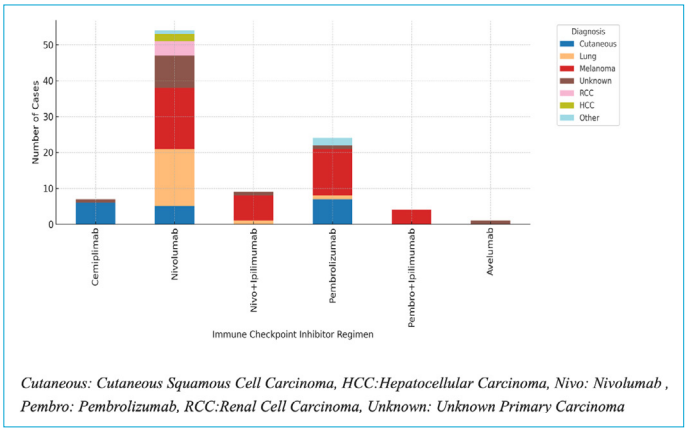

Figure 2. Distribution of Cases by Immune Checkpoint Inhibitor and Diagnosis.

tion therapy, while 53 (91.4%) were treated with single-agent ICI. Although the proportion of combination therapy cases appeared to increase over time, the difference was not statistically significant (p=0.07). The incidence of adverse event-related death was lower in the combination therapy group (7.7% vs. 27.9%), although the difference was not statistically significant (p=0.11).

Discussion

In this study, we identified 99 (0.04%) cases of renal transplant rejection associated with immunotherapy among 215,907 ICI-related adverse event reports, based on a large-scale pharmacovigilance analysis of the FAERS database. Among the 99 identified cases of ICI-associated renal transplant rejection, the majority of patients were male, with 43.4% aged 65 or older, and nivolumab was the most commonly reported agent. Malignant melanoma was the most frequent underlying malignancy, with most reports submitted by healthcare professionals and primarily originating from North America and Europe; adverse event-related death occurred in 25.3% of cases.

Current evidence regarding the efficacy of immunotherapy in KTRs is scarce and predominantly based on retrospective cohort studies, early-phase (phase I–II) clinical trials, and pooled data from meta-analyses. In a multicenter study, Murakami et al. evaluated the use of immune checkpoint inhibitors in 69 kidney transplant recipients. The most common underlying malignancies were malignant melanoma and cutaneous squamous cell carcinoma. Acute allograft rejection occurred in 42% of patients, and graft loss was reported in 65%. The objective response rate was 36.4% in the squamous cell carcinoma subgroup and 40% in the melanoma subgroup.[9] Furthermore, several case reports have reported acute allograft rejection events following the use of immune checkpoint inhibitors in KTRs.[13,14] In the meta-analysis conducted by Nida Saleem et al., 128 studies involving 343 solid organ transplant recipients treated with immune checkpoint inhibitors were included. Of the included patients, 76.9% were male and 70.9% were kidney transplant recipients. The median age was 63 years (interquartile range: 14–88), and PD-1 inhibitors were the most frequently administered agents, used in 72.9% of cases. At one year, acute allograft rejection was observed in 36.2% of patients (95% CI: 30.7%–41.7%), with the majority of cases (33.7%; 95% CI: 28.3%–39.0%) occurring within the first six months. Similarly, graft loss was reported in 18.4% of patients at one year (95% CI: 13.7%–23.1%), and 16.5% (95% CI: 12.1%–20.8%) experienced graft loss within the initial six-month period. The authors concluded that the risk of acute allograft rejection among solid organ transplant recipients treated with ICIs varies by cancer type, being significantly higher in patients with melanoma compared to those with cutaneous squamous cell carcinoma. Furthermore, the concurrent use of corticosteroids and mTOR inhibitors during ICI therapy was associated with a lower risk of rejection, suggesting a potential protective effect of this immunosuppressive regimen.[10] Based on data obtained from the FAERS database, our analysis revealed that malignant melanoma was the most frequently reported malignancy, and PD-1 inhibitors were the most commonly used agents, particularly among elderly patients and males—findings that are consistent with previously published literature.

Early-phase clinical studies are being conducted to investigate strategies aimed at reducing the risk of acute allograft rejection associated with immune checkpoint inhibitor therapy in this population. A multicenter Phase 1 study was conducted to assess the risk of allograft rejection associated with ICI therapy—specifically nivolumab—while maintaining baseline immunosuppression in kidney transplant recipients. Among the 17 patients enrolled, continued immunosuppression did not appear to diminish the antitumor efficacy of ICI treatment, and the incidence of allograft rejection was lower than previously reported. Irreversible rejection occurred in only one patient (6%), while another (6%) experienced a rejection episode that was successfully managed with plasma exchange and antithymocyte globulin.[15] In another multicenter Phase 1/2 study, a total of 14 KTRs with advanced cutaneous malignancies were treated with a combination of nivolumab, tacrolimus, and prednisone, with or without ipilimumab. The primary endpoint was disease control rate (DCR) without allograft loss at 16 weeks following initiation of nivolumab therapy. No cases of kidney allograft rejection or loss were observed during the transition to the standardized immunosuppression regimen. Among the eight patients who received nivolumab, tacrolimus, and prednisone alone, all experienced pro-

gressive disease , resulting in an objective response rate of 0%.[16] In a single-arm study evaluating cemiplimab in KTRs with advanced cutaneous squamous cell carcinoma, the combination of cemiplimab therapy with mTOR inhibitor–based immunosuppression and dynamic steroid tapering was found to be safe, with no cases of kidney allograft rejection. The treatment achieved an objective response rate of 46% (90% CI, 22 to 73%). These findings support the use of mTOR-based immunosuppressive regimens as a preferred strategy in KTRs undergoing anti–PD-1 therapy.[17]

This study has several limitations specific to the use of the FAERS database. First, as a spontaneous and voluntary reporting system, FAERS is inherently subject to significant underreporting and reporting bias, particularly for less severe or anticipated adverse events. Second, the quality and completeness of the reports are variable, with frequent omissions of critical clinical information such as comorbidities, dosage, timing of onset, and diagnostic confirmation (e.g., biopsy). Lastly, the lack of detailed data regarding immunosuppressive medication use represents an additional limitation in accurately assessing transplant-related outcomes.

Conclusion

We present a large-scale pharmacovigilance analysis utilizing FAERS data to characterize the incidence and clinical features of ICI–associated allograft rejection in kidney transplant recipients. Our findings are consistent with the existing literature, reinforcing that PD-1 inhibitors are the most frequently implicated agents and malignant melanoma is the most commonly reported underlying malignancy. Although retrospective analyses and meta-analyses highlight a substantial risk of allograft rejection and loss in this population, emerging data from early-phase prospective studies suggest that individualized immunosuppressive strategies—especially those incorporating mTOR inhibitors and corticosteroids—may help reduce the risk of rejection without diminishing the antitumor efficacy of ICI therapy. Further research is warranted to optimize immunotherapeutic strategies and to identify reliable predictive biomarkers, thereby facilitating safer and more effective use of immune checkpoint inhibitors in kidney transplant recipients with malignancy.

Disclosures

Ethics Committee Approval: This study used publicly available de-identified data from the FAERS database. Therefore, institutional review board approval and informed consent were not required.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of Interest: No conflict of interest was declared by the authors.

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Authorship Contributions: All authors contributed substantially to the study, including its conception, design, data collection, analysis, and interpretation. They were all involved in drafting, revising, or critically reviewing the manuscript, approved the final version to be published.

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