Immune-Related Adverse Events (irAEs) Associated with Immune Checkpoint Inhibitor (ICI) Therapy in Bladder Cancer: An Analysis of the FDA Adverse Event Reporting System (FAERS)

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# 1. Summary/Abstract

Background: Bladder cancer is the ninth most common type of cancer worldwide. Treatment options include surgery, chemotherapy, and immunotherapy. Immune checkpoint inhibitors (ICIs) are a class of immunotherapeutic agents recommended for the treatment of bladder cancer. ICIs have been associated with certain immune-related adverse events (irAEs)

Methods: Reports in the FAERS dashboard through December 2024 were analyzed for irAEs to four ICIs recommended in bladder cancer: atezolizumab, avelumab, nivolumab, and pembrolizumab. Standardized queries were used to identify cases of rash, pruritus, hypothyroidism, hyperthyroidism, colitis, hepatitis, and nephritis. Descriptive and disproportionality analyses were performed to detect safety signals.

Results: Out of 2948 cases identified from FAERS, 365 cases with irAEs were analyzed. The largest number of cases was reported for pembrolizumab (n=307), followed by atezolizumab (n = 91), avelumab (n = 41), and nivolumab (n =37). Pembrolizumab was found to have safety signals for all irAEs considered together (PRR: 1.8 (1.52, 2.14), ROR: 2.07 (1.69, 2.55), IC: 0.36 (0.29, 0.44)). A safety signal was also found for rash (PRR: 2.11 (1.17, 3.8), ROR: 2.14 (1.18, 3.9), IC: 0.44 (0.17, 0.71)). Safety signals for atezolizumab included hyperthyroidism and nephritis, while hypothyroidism was identified as a concern for avelumab.

Conclusion: Immune-related adverse events are found to be associated with immune checkpoint inhibitor therapy in bladder cancer. Pembrolizumab appears to have the highest risk, though this may be due to its early approval (2014). Appropriate treatment guidelines must be developed to address the management of irAEs associated with ICI therapy in bladder cancer.

# 2. Introduction

## 2.1 General Background Information

Bladder cancer is the ninth most common type of cancer, according to a 2022 report published by the International Agency for Research on Cancer1. The American Cancer Society estimates approximately 85,000 new bladder cancer cases and approximately 17,000 bladder cancer deaths in the United States in 2025.

The cancer is more common in males than in females, with a male-female ratio of about 4:12. Risk factors for bladder cancer include smoking and occupational chemical exposures (in particular, aromatic amines and polycyclic aromatic hydrocarbons). Certain dietary factors, impaired microbiome, and pelvic radiotherapy may also increase the risk of bladder cancer3.

Treatment of bladder cancer is multifaceted and depends on the type of tumor. Surgical resection, adjuvant and intravesical chemotherapy, Bacillus Calmette–Guérin (BCG) immunotherapy, and systemic chemotherapy are the different treatment options available2.

According to the National Comprehensive Cancer Network (NCCN) guidelines, immunotherapy with immune checkpoint inhibitors (ICIs) is recommended at various stages of bladder cancer treatment. ICIs such as pembrolizumab, atezolizumab, nivolumab, and avelumab are FDA-approved and recommended for the adjuvant and first and second-line treatment of bladder cancer4.

ICIs are associated with various adverse effects, particularly with immune-related adverse events (irAEs) such as pneumonitis, hepatitis, colitis, hypothyroidism, dermatitis, and others5. This study aims to analyze real-world adverse event data from the FDA Adverse Event Reporting System associated with ICI therapy in bladder cancer.

## 2.2 Description of data and data source

The United States Food and Drug Administration (FDA) maintains a dashboard of adverse event reports in the FDA Adverse Event Reporting System (FAERS)6. FAERS is a publicly available dashboard of safety reports submitted by patients, healthcare professionals, and pharmaceutical companies.

Since FAERS consists of self-reported data from multiple sources, there may be duplicates, missing data as well as various errors. The findings of this study should be considered in context of this data limitation.

## 2.3 Questions/Hypotheses to be addressed

The study aims to analyze whether irAEs associated with ICIs generate a signal of disproportionate reporting (SDR). The goal is to determine whether irAEs associated with ICIs in bladder cancer are greater than expected, and thus, further research and strategies to deal with these adverse events are required.

# 3. Methods

The FAERS dashboard was searched by product to obtain cases related to the use of ICIs in bladder cancer. This data was then filtered to retain only irAE cases. Other adverse events and duplicate cases were removed. Following this, the demographic and drug characteristics were summarized.

To assess whether an ICI has a safety signal associated with a particular irAE, three metrics were used:

1. Proportional reporting ratio (PRR): This approach compares the proportion of reports for a specific adverse event with a drug of interest to the proportion of the same event reported for all other drugs.
2. Reporting odds ratio (ROR): This metric is obtained by comparing the ratio of a drug’s adverse event reports to all other reports for that drug against the same ratio across all drugs.
3. Information component (IC): For this metric, the observed vs. expected reporting of a drug-adverse event combination is compared.

The association between severity of reactions and age and sex was assessed using logistic regression. Three machine learning models (logistic regression, decision tree, and random forest) were used to distinguish between serious and non-serious reactions.

## 3.1 Data acquisition

In order to obtain the FAERS data, the ICIs were used to search by product. Pembrolizumab, atezolizumab, avelumab, and nivolumab were the keywords used. Previously, durvalumab and ipilimumab were also approved for bladder cancer treatment. However, this indication has since then been removed by the manufacturers. As such, these were not considered. Following this, the search was limited to cases of bladder cancer. A total of 2948 reactions were obtained.

## 3.2 Data import and cleaning

The file was downloaded as an Excel file. Then, in R, the columns were renamed so as to make them easier to use in code. Then, products with concomitant drugs were removed so as to focus only on cases associated with ICIs. Then, cases that also had other drugs as the suspect active ingredients were removed. This was followed by retaining only the irAEs. A list of common irAEs was used. This list is available in the supplementary material. This list was informed by common irAEs reported in various clinical trials7 89 10. Any reactions that had the same age, weight, FDA received date, country of occurrence, suspected active ingredient, and reported reaction were considered duplicates and were removed. Following this, the reactions were coded according to the MedDRA Preferred Terms (PTs) and classified according to the System Organ Class (SOC). The age values were converted to numeric, and the countries were reclassified as US, outside US, and not specified. The code for the analysis would involve loading the file, removing duplicates, assessing missing data, and deciding whether to remove it. The details are available in the processing code file.

The processing was done according to [Figure 1](#fig-processing1).

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| Figure 1: Study Flowchart |

## 3.3 Statistical analysis

Firstly, descriptive statistics were used to describe the demographic and other characteristics. This was followed by creating some descriptive figures. Two logistic regression models were fit to assess the association by severity with sex and age. The PRR, ROR, and IC (along with their 95% CI) were then calculated to assess the drug signal. Three different machine learning models were used to distinguish severity on the basis of sex, age, and type of ICI. Due to missing values, the patient age values were imputed. First, the data was split into training and testing data (70/30 split). A 5-fold cross-validation was used.

# 4. Results

## 4.1 Exploratory/Descriptive analysis

[Table 1](#tbl-summarytable) provides the patient characteristics, and summary of reactions by type of immune checkpoint inhibitor, and organ system affected.

The mean age reported was 66.94±17.65. A large percentage of the reactions occurred in males (70.2%). This may be because bladder cancer is much more common in males than in females.

Over 60% of the reactions were associated with pembrolizumab. A majority of the reactions were serious (83.7%).

Most of the reactions were reported by healthcare professionals. Since FAERS is a US-based dashboard, many reactions were reported from the US.

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| Table 1: Descriptive Statistics   | **Attribute** | **Atezolizumab** | **Avelumab** | **Nivolumab** | **Pembrolizumab** | | --- | --- | --- | --- | --- | | Age, mean years ± SD | 67.6 ± 13.2 | 71.8 ± 8.7 | 70.4 ± 10.6 | 67.9 ± 18.6 | | Sex |  |  |  |  | | Male | 72 | 37 | 36 | 257 | | Female | 29 | 11 | 11 | 70 | | Not Specified (Sex) | 12 | 2 | 9 | 9 | | Severity of reaction |  |  |  |  | | Serious | 98 | 47 | 44 | 287 | | Non-Serious (Reaction) | 15 | 3 | 12 | 49 | | Outcomes |  |  |  |  | | Died | 11 | 7 | 3 | 39 | | Hospitalized | 54 | 18 | 19 | 128 | | Disabled | 1 | 0 | 0 | 7 | | Life Threatening | 2 | 1 | 1 | 11 | | Non-Serious (Outcome) | 15 | 3 | 12 | 49 | | Other Outcomes | 30 | 21 | 21 | 102 | | Reporter type |  |  |  |  | | Healthcare Professional | 103 | 46 | 43 | 280 | | Consumer | 10 | 4 | 13 | 56 | | Country |  |  |  |  | | US | 37 | 6 | 37 | 133 | | Outside US | 47 | 30 | 18 | 198 | | Not Specified (Country) | 29 | 14 | 1 | 5 | |

[Table 2](#tbl-summarytable1) shows the number of reactions by organ system and the ICI.

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| Table 2: Reactions by Organ System and Drug   | **Reaction** | **Atezolizumab** | **Avelumab** | **Nivolumab** | **Pembrolizumab** | | --- | --- | --- | --- | --- | | Cardiovascular | 6 (1.1%) | 8 (1.4%) | 5 (0.9%) | 23 (4.1%) | | Endocrinological | 16 (2.9%) | 11 (2%) | 9 (1.6%) | 65 (11.7%) | | Gastrointestinal | 33 (5.9%) | 10 (1.8%) | 11 (2%) | 60 (10.8%) | | Neurological | 9 (1.6%) | 3 (0.5%) | 6 (1.1%) | 33 (5.9%) | | Other | 23 (4.1%) | 21 (3.8%) | 18 (3.2%) | 120 (21.6%) | | Renal | 13 (2.3%) | 5 (0.9%) | 7 (1.3%) | 20 (3.6%) | | Respiratory | 8 (1.4%) | 2 (0.4%) | 3 (0.5%) | 17 (3.1%) | | Skin | 33 (5.9%) | 8 (1.4%) | 14 (2.5%) | 101 (18.2%) | |

Pembrolizumab has the highest number of reactions. The largest percentage of reactions are classified as “Other”. These include reactions that do not belong to the other organ classes, such as myositis.

## 4.2 Basic statistical analysis

[Figure 2](#fig-result) shows the number of reactions by drug, along with the seriousness of the reaction.

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| Figure 2: Association of severity with sex |

The probability of serious outcomes is highest for sex not specified, followed by males, then females. There are more cases for males than females, so it is expected that more males report severe cases. However, it is surprising that even with a low percentage of non-specified sex reports, the severity can be high. This may indicate underlying issues with the data reporting. However, sex is not a significant predictor of severity.

[Figure 3](#fig-result2) shows the association between severity and age.

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| Figure 3: Association of severity with age |

The predicted severity decreases with age. However, this relationship is also not significant.

## 4.3 Full analysis

For the disproportionality analysis, we need 4 different values: a: Number of reports reporting both the drug and the adverse event. b: Number of reports reporting the drug but not the adverse event. c: Number of reports reporting the adverse event but not the drug. d: Number of reports reporting neither the drug nor the adverse event.

For PRR, the formula used is: (a/(a+c)) / (b/(b+d))

For ROR: (a/c)/(b/d)

For IC: log2((a+b+c+d)/(a+c)\*(a+b)/n)

The following tables show the results of the disproportionality analysis.

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| Table 3: Atezolizumab Reactions by Organ System   | **Reaction** | **Atezolizumab PRR (95% CI)** | **Atezolizumab ROR (95% CI)** | **Atezolizumab IC (95% CI)** | | --- | --- | --- | --- | | All irAEs | 0.73 (0.62, 0.86) | 0.66 (0.53, 0.81) | -0.36 (-0.55, -0.16) | | Rash | 0.71 (0.39, 1.29) | 0.7 (0.38, 1.29) | -0.39 (-1.09, 0.31) | | Pruritus | 1.22 (0.64, 2.3) | 1.22 (0.64, 2.34) | 0.21 (-0.45, 0.86) | | Hypothyroidism | 0.15 (0.02, 1.11) | 0.15 (0.02, 1.11) | -2.39 (-5.15, 0.36) | | Hyperthyroidism | 3.49 (1.18, 10.36) | 3.52 (1.18, 10.51) | 1.11 (0.39, 1.83) | | Colitis | 1.23 (0.57, 2.65) | 1.23 (0.56, 2.68) | 0.21 (-0.57, 1) | | Hepatitis | 2.25 (0.78, 6.45) | 2.26 (0.78, 6.53) | 0.78 (-0.09, 1.64) | | Nephritis | 3.59 (1.1, 11.74) | 3.62 (1.1, 11.89) | 1.12 (0.35, 1.9) | |

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| Table 4: Avelumab Reactions by Organ System   | **Reaction** | **Avelumab PRR (95% CI)** | **Avelumab ROR (95% CI)** | **Avelumab IC (95% CI)** | | --- | --- | --- | --- | | All irAEs | 0.87 (0.7, 1.08) | 0.83 (0.62, 1.11) | -0.18 (-0.47, 0.11) | | Rash | 0.52 (0.19, 1.42) | 0.52 (0.19, 1.43) | -0.86 (-2.22, 0.5) | | Pruritus | 0.6 (0.19, 1.91) | 0.59 (0.18, 1.92) | -0.68 (-2.25, 0.89) | | Hypothyroidism | 2.61 (0.96, 7.07) | 2.64 (0.96, 7.26) | 1.16 (0.06, 2.25) | | Hyperthyroidism | 0.7 (0.09, 5.34) | 0.7 (0.09, 5.37) | -0.47 (-3.19, 2.24) | | Colitis | 0.28 (0.04, 2.03) | 0.28 (0.04, 2.03) | -1.73 (-4.51, 1.05) | | Hepatitis | 1.39 (0.31, 6.19) | 1.4 (0.31, 6.27) | 0.42 (-1.43, 2.26) | | Nephritis | 1.86 (0.4, 8.55) | 1.86 (0.4, 8.66) | 0.77 (-1.04, 2.57) | |

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| Table 5: Nivolumab Reactions by Organ System   | **Reaction** | **Nivolumab PRR (95% CI)** | **Nivolumab ROR (95% CI)** | **Nivolumab IC (95% CI)** | | --- | --- | --- | --- | | All irAEs | 0.7 (0.57, 0.87) | 0.63 (0.48, 0.83) | -0.44 (-0.73, -0.16) | | Rash | 0.61 (0.26, 1.39) | 0.6 (0.26, 1.39) | -0.64 (-1.74, 0.45) | | Pruritus | 0.96 (0.41, 2.26) | 0.96 (0.4, 2.29) | -0.05 (-1.11, 1.02) | | Hypothyroidism | 1.04 (0.31, 3.52) | 1.04 (0.31, 3.56) | 0.05 (-1.45, 1.56) | | Hyperthyroidism | 0.52 (0.07, 4) | 0.52 (0.07, 4.01) | -0.84 (-3.55, 1.87) | | Colitis | 0.67 (0.2, 2.19) | 0.67 (0.2, 2.21) | -0.51 (-2.06, 1.04) | | Hepatitis | 1.71 (0.48, 6.09) | 1.71 (0.48, 6.17) | 0.64 (-0.8, 2.08) | | Nephritis | 0 (0, NaN) | 0 (0, NaN) | -Inf (-Inf, NaN) | |

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| Table 6: Pembrolizumab Reactions by Organ System   | **Reaction** | **Pembrolizumab PRR (95% CI)** | **Pembrolizumab ROR (95% CI)** | **Pembrolizumab IC (95% CI)** | | --- | --- | --- | --- | | All irAEs | 1.53 (1.34, 1.74) | 1.78 (1.49, 2.11) | 0.27 (0.2, 0.33) | | Rash | 1.92 (1.17, 3.15) | 1.95 (1.17, 3.24) | 0.39 (0.15, 0.63) | | Pruritus | 1.02 (0.57, 1.83) | 1.03 (0.57, 1.85) | 0.02 (-0.39, 0.43) | | Hypothyroidism | 1.31 (0.55, 3.09) | 1.31 (0.55, 3.12) | 0.18 (-0.35, 0.71) | | Hyperthyroidism | 0.44 (0.13, 1.41) | 0.43 (0.13, 1.41) | -0.71 (-1.89, 0.46) | | Colitis | 1.36 (0.67, 2.76) | 1.36 (0.66, 2.79) | 0.2 (-0.23, 0.63) | | Hepatitis | 0.27 (0.07, 0.96) | 0.27 (0.07, 0.95) | -1.24 (-2.68, 0.21) | | Nephritis | 0.37 (0.1, 1.38) | 0.37 (0.1, 1.38) | -0.89 (-2.28, 0.5) | |

The PRR and ROR when all irAEs are considered is greater than 1 for pembrolizumab (PRR: 1.8 (1.52, 2.14), ROR: 2.07 (1.69, 2.55)). Similarly, the IC is greater than 0 (0.36 (0.29, 0.44)). Thus, there is a safety signal associated with pembrolizumab for all irAEs.

When considering individual irAEs, pembrolizumab also has a safety signal for rash (PRR: 2.11 (1.17, 3.8), ROR: 2.14 (1.18, 3.9), IC: 0.44 (0.17, 0.71).

Atezolizumab has a safety signal for hyperthyroidism (PRR: 3.51 (1.07, 11.45), ROR: 3.53 (1.07, 11.61), IC: 1.1 (0.33, 1.87). There also may be a signal for nephritis (PRR: 3.65 (0.98, 13.56), ROR: 3.68 (0.98, 13.73), IC: 1.12 (0.29, 1.96), though the 95% CI for PRR and ROR is not greater than 1 (though very close to 1).

Similarly, avelumab may have a safety signal for hypothyroidism (PRR: 3.05 (0.98, 9.51), ROR: 3.08 (0.97, 9.75), IC: 1.32 (0.12, 2.52)).

No significant safety signals were found for nivolumab.

## 4.4 Machine Learning Analysis

[Table 7](#tbl-randomforest) shows the results of the three machine learning models (logistic regression, decision tree, random forest).

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| Table 7: Random Forest Evaluation Metrics   | **Model** | **Accuracy** | **AUC** | **Sensitivity** | **Specificity** | | --- | --- | --- | --- | --- | | Logistic Regression | 0.874 | 0.542 | 0.000 | 1.000 | | Decision Tree | 0.874 | 0.500 | 0.000 | 1.000 | | Random Forest | 0.874 | 0.752 | 0.000 | 1.000 | |

The Random Forest model has an AUC of 0.806. Thus, this model is able to predict between serious and non-serious cases ~81% of the time. The logistic regression model is next, able to distinguish ~60% of the time. The decision tree model performs poorly, possibly due to fitting issues. All the models have the same accuracy. Additionally, sensitivity is 0, and specificity is high, meaning all the models always predict ‘serious’. Such problems arise due to class imbalances, and may require advanced methods to deal with. The random forest model does not perform as well on the test data (AUC=0.56), and is able to distinguish the severity only 56% of the time.

[Figure 4](#fig-result3) shows the feature importance.

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| Figure 4: Feature importance |

The most important feature is the patient age. However, this variable has imputations and thus may affect the dependability of the model. Overall, the model performs decently on train data, but not on test data. More data and variables can help improve the fit. With this data, this model is not useful in distinguishing between serious and non-serious cases. The ROC curves for the different models are available in the Supplementary Material.

# 5. Discussion

## 5.1 Summary and Interpretation

In this study, the safety signals for the most commonly reported irAEs in clinical trials were assessed.

Pembrolizumab had a safety signal for all irAEs considered together, as well as for rash.

Five clinical trials14 have reported rash as an adverse effect associated with pembrolizumab monotherapy in bladder cancer. The report of rash from both clinical trials and real-world data suggests that this is a significant adverse event. Rash associated with ICIs may be of various grades. For a grade 1 rash, the ICI therapy may be continued. Grade 2 rash may necessitate discontinuation of ICIs, and grade 3 rash requires discontinuation. Based on the grade, treatment with topical or systemic corticosteroids is appropriate. Dermatological consultation is usually suggested15.

Atezolizumab had a safety signal for hyperthyroidism. Two clinical trials16 reported hyperthyroidism associated with atezolizumab monotherapy in bladder cancer.

Avelumab may have a safety signal for hypothyroidism. One clinical trial assessing avelumab monotherapy has reported hypothyroidism as an adverse event10. Thyroid disorders are seen with about 1-15% of patients receiving ICIs17. Risk factors for thyroid dysfunction with ICIs include gender (females are at a higher risk), age (younger age), race (Caucasian and Hispanic individuals are at higher risk), obesity, higher number of treatment cycles, and higher baseline thyroid-stimulating hormone (TSH)18.

It has been suggested that a combination of genetic factors, cellular autoimmunity, and humoral immunity may lead to thyroid dysfunction19. ICI therapy should involve thyroid function tests every 4-6 weeks. Treatment is largely symptomatic and may involve levothyroxine therapy in the case of hypothyroidism20.

Atezolizumab may also have a safety signal for nephritis. Two clinical trials have reported nephritis associated with atezolizumab monotherapy in bladder cancer16. Nephritis is not a common adverse event associated with ICIs, affecting about 2-5% of patients. The mechanism for the development of this adverse event is not well established. Most patients recover with appropriate management. Treatment may involve discontinuation of the ICI, and corticosteroid therapy21.

No prospective trials have defined strategies for effectively managing specific immune-related adverse events; thus, clinical practice remains variable. Committees are working to improve guidelines and to harmonize expert consensus22. In conclusion, irAEs are associated with ICI monotherapy with bladder cancer. More comprehensive guidelines are required for the management of these adverse events. Clinicians should be aware of the potential for such adverse events.

## 5.2 Strengths and Limitations

This study used data from the FAERS dashboard, and thus provides real-world evidence regarding the association of irAEs with ICI use in bladder cancer. To my knowledge, this is the first study using FAERS data to assess this association. However, the findings of this study must be considered in context of certain limitations. Firstly, FAERS data has several limitations. The dashboard cannot provide causal information. This is a voluntary system. In the US, only drug manufacturers are mandated to reported adverse events. This means that all events are not reported. Additionally, the reports may have duplicates, or may be incomplete. Efforts have been made in this study to remove the duplicates, but data completeness cannot be ensured. Pembrolizumab was approved in 2014, while avelumab, nivolumab, and atezolizumab were initially approved in 2017, with additonal approvals in later years for other stages of bladder cancer. As such, the larger number of reports associated with pembrolizumab may simple be due to the larger reporting time. A future analysis with additional data may find different results to the one obtained using data until December 2024.

## 5.3 Conclusions

Immune checkpoint inhibitor therapy are associated with immune-related adverse events (particularly rash, hypothyroidism, hyperthyroidism, and nephritis) in bladder cancer. Currently, no established guidelines exist to manage these adverse events. There is a need to develop centralized guidelines and protocols for managing irAEs associated with ICI therapy.

# 6. References

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