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Original Article

World J Oncol. 2025;16(5):439-445

Demographic Variations in Immune Checkpoint Inhibitor Adverse Events: A Real-World Study

Shreya Shambhavi[a, e], Mariela DiVanna[a], Shubhangi Sharma[a], Harmanjeet Singh[b], Arushi Gupta[c], Tiffany Pompa[a], Adam Kaplan[a], Jose Iglesias[d]

Abstract

Background: Immune checkpoint inhibitors (ICIs) have caused a paradigm shift in cancer therapy, but the resultant immune activation also precipitates autoimmune toxicities termed immune-related adverse events (irAEs). However, system-specific analyses of irAEs remain limited, particularly their variation with body mass index (BMI), race, sex, age, and type of ICI.

Methods: A retrospective analysis was conducted on 244 patients who developed irAEs after receiving ICI. Among the study population, 58% were female; the racial and ethnic distribution was 84% White, 13% Hispanic, 2% African American, and 1% Asian; and the age breakdown was 23% under 65 years, 38% between 65 and 79 years, and 39% over 80 years. Univariate analysis was performed employing the Chi-square test. Multivariable logistic regression and cluster analyses revealed distinct irAE predictors.

Results: Univariate analysis (Chi-square) showed significant associations between BMI and pneumonitis (P = 0.02) and between race and hepatitis (P = 0.04), but these did not persist in multivariate regression. No significant correlations were found between thyroiditis or colitis and sex, race, BMI, age, or immunotherapy type. Increasing age was protective against neutropenia, with significantly lower risk in patients aged 65 - 79 (odds ratio (OR) 0.38, P = 0.007) and ≥ 80 years (OR 0.18, P < 0.001); African Americans were at higher risk (OR 10.29, P = 0.02), and male sex was protective (OR 0.51, P = 0.03). Anemia was less frequent in those ≥ 80 years (OR 0.48, P = 0.03) and Hispanics (OR 0.4, P = 0.03). Thrombocytopenia risk was reduced in patients aged 65 - 79 (OR 0.41, P = 0.03) and ≥ 80 (OR 0.36, P < 0.001). Cluster analysis showed higher irAE rates in patients treated with nivolumab (alone or with ipilimumab) compared to pembrolizumab.

Conclusion: Advanced age showed a protective effect on cytopenias. Hispanics had reduced anemia and dermatitis risk; African Americans and females had higher neutropenia, and obesity was linked to dermatitis. These findings may aid clinicians in personalizing ICI counseling and recognizing at-risk groups.

Keywords: PDL-1; CTLA-4; Immune checkpoint inhibitors; Immune-related adverse events; Pembrolizumab; Nivolumab

Manuscript submitted May 18, 2025, accepted July 30, 2025
Published online August 19, 2025

[a]Rutgers Health/Community Medical Center, Toms River, NJ, USA
[b]Mahatma Gandhi Memorial Medical College, Jamshedpur, Jharkhand, India
[c]Irvine High School, Irvine, CA, USA
[d]Department of Nephrology, Jersey Shore University Medical Center, Hackensack Meridian School of Medicine, Nutley, NJ, USA
[e]Corresponding Author: Shreya Shambhavi, Rutgers Health/Community Medical Center, Toms River, NJ, USA. Email: shambhavishreya997@gmail.com

doi: https://doi.org/10.14740/wjon2612

Introduction

Immune checkpoint inhibitors (ICIs) such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed death ligand 1 (PD-L1) inhibitors/programmed death 1 (PD-1) inhibitors have revolutionized cancer treatment paradigms by leveraging the host immune system to eradicate tumors, either as an alternative or complementary approach to traditional chemotherapy. ICIs block inhibitory pathways that restrain T-cell activation. CTLA-4 modulates the early phases of T-cell priming in lymphoid organs through a competitive interaction with cluster of differentiation (CD)80/CD86 ligands. Concurrently, the PD-1/PD-L1 interaction also suppresses effector T cells in peripheral tissues by dephosphorylation of CD28 and T-cell receptor (TCR) signaling cascades through Src homology 2 domain-containing protein tyrosine phosphatase 2 (SHP2), the predominant phosphatase [1, 2]. By inhibiting these checkpoints, ICIs rescue anti-tumor immunity, resulting in long-lasting responses across cancer types [3, 4]. However, this immune activation can also cause immune-related adverse events (irAEs), which are adverse effects caused by ICIs and result from ICI's non-specific action, which not only upregulates the anti-tumor immune response but also disrupts the body's normal safeguards against autoimmunity [3, 5-7].

At present, the epidemiological data are almost exclusively restricted to total frequencies of irAEs. For example, gastrointestinal (GI) toxicity ranges from 30% to 40% of patients treated with anti-CTLA-4 agents and hepatotoxicity from 15% to 30%, depending on monotherapy or combination treatments [3, 5]. However, system-specific analyses of irAEs such as hepatitis, colitis, thyroiditis, and hematologic dyscrasias (e.g., anemia, thrombocytopenia, leukopenia) remain limited [8, 9]. Preliminary data indicate that high body mass index (BMI) may be associated with an increased risk of irAEs, which might be related to chronic inflammation and altered immune metabolism,

although it still needs to be validated across different ethnic populations [9]. Similarly, although racial differences in irAEs are suspected to reflect genetic polymorphisms in immune pathways, the majority of studies are based on racially or ethnically homogenous study populations (mostly Caucasians) and may be confounded by ethnic diversity. Moreover, the susceptibility to irAEs about age is not well defined, even though aging-related immunosenescence leads to changes in T-cell responses [3, 10].

Prior studies on irAEs from PD-L1/CTLA-4 inhibitors have often been limited in scope, focusing on specific organ systems or lacking comprehensive analyses across diverse patient populations. Addressing these limitations, this real-world analysis provides a comprehensive evaluation of irAEs, by examining a wide range of systemic toxicities including hepatitis, colitis, thyroiditis, dermatitis, and hematologic dyscrasias (e.g., anemia, thrombocytopenia, leukopenia). A key strength of our work lies in its inclusive design, which incorporates diverse racial groups and investigates the associations between various irAEs and demographic factors including BMI, age, and sex, thereby addressing notable gaps in the current understanding of these adverse events [9, 10]. By mapping such associations, the present effort seeks to supply risk stratification guidelines and personalize surveillance strategies in at-risk subgroups, to refine the safety profile of ICI in times of increasing clinical indications.

Materials and Methods

Study design and study population

A retrospective analysis was conducted on 244 patients aged > 18 who developed irAEs after receiving ≥ 1 dose of ICI, either PDL-1 or CTLA-4 inhibitor or combination regimen between 2019 and 2024 at an infusion center serving patients from three major oncology clinics in New Jersey, USA.

After retrospective evaluation of medical records, irAEs were defined and graded based on Common Toxicity Criteria for Adverse Events version 5.0 (CTCAE) [11]. Depending on BMI, patients were categorized as "underweight" (< 18.5 kg/m^2), "normal weight" (18.5 - 24.9 kg/m^2), "overweight" (25 - 29.9 kg/m^2), or "obese" (≥ 30 kg/m^2) as per World Health Organization (WHO) criteria [12]. To ensure clarity and simplicity in presenting our conclusions, we combined underweight and normal-weight patients into one category and overweight and obese patients into another. Patients either received pembrolizumab monotherapy (73%), nivolumab monotherapy (19%), or a combination regimen of ipilimumab and nivolumab (8%). Patients were categorized into three age groups: under 65 years, 65 to 79 years, and over 79 years. Among the total population, 58% were female, 84% were White, 13% Hispanic, 2% African American, and 1% Asian. Also, 23% of people aged < 65 years, 38% aged 65 - 79, and 39% aged > 80 years.

Ethical issues

The study protocol was approved by the institutional review board (IRB) with an IRB number 25-002. The need for informed consent was waived due to the observational and retrospective design of the study. The study was conducted according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association.

Statistical analyses

To examine the variability of irAEs with ranges in BMI, age, race, sex, and immunotherapy, we performed an exploratory data analysis (EDA). Contingency tables were generated, and results were expressed as numbers and percentages. Statistical analyses were performed using SPSS, version 27 (SPSS Inc., Chicago, IL, USA) and Stata, version 16. Univariate analysis of the contingency table results was conducted employing Pearson's Chi-square test. Additionally, to determine which factors contribute to distinct irAEs, we analyzed data using supervised learning with Firth's multivariable logistic regression and unsupervised learning employing two-step cluster analysis. In Firth's logistic regression analysis, the goodness of fit was determined by employing Pearson's Chi-squared goodness of fit. Odds ratios (ORs) and their 95% confidence intervals (95% CIs) were determined by exponentiation of the regression coefficient and its upper and lower CIs, respectively.

In our study, the unsupervised machine learning technique selected was the two-step cluster analysis. We used a two-step cluster analysis to categorize patients treated with ICIs based on our dataset. This scalable clustering algorithm, which supports categorical variables and automatically detects the optimal number of clusters, was chosen [13]. The log likelihood distance measure with variable independence and multinomial distributions was used. Cluster membership was determined automatically, using Bayesian information criterion (BIC) values to compare the fit of models of varying complexity. The BIC change ratios at each step were used to identify the optimal number of clusters. In the model, we included all irAE predictors (colitis, thyroiditis, pneumonitis, dermatitis, hepatitis, neutropenia, anemia, thrombocytopenia, pembrolizumab, nivolumab, ipilimumab and nivolumab, race, BMI, sex, and age) as categorical [13]. The silhouette measure of cohesion and separation was used to determine how well each case fits within its assigned cluster.

Results

The associations between irAEs and demographic or treatment variables were systematically evaluated across several toxicities.

The results of the univariate analysis (Pearson Chi-square test) for all irAEs are summarized in Supplementary Material 1 (wjon.elmerpub.com).

A detailed system-wise breakdown of all irAEs is provided below.

Dermatitis

The results of univariate analysis showed that BMI had a sta-

tistically significant relationship with dermatitis (χ^2 = 16.97, df =3, P < 0.001), and BMI > 30 was associated with increased risk (OR = 5.36, 95% CI: 1.25, 22.9, P =0.02) on multivariate regression analysis. The Chi-square test showed a borderline significant relationship between race and dermatitis (χ^2 = 6.64, df =3, P = 0.08) but the multivariate logistic regression model revealed a more complex relationship when adjusting for confounders and found Hispanic race to be protective for dermatitis (OR = 0.22, 95% CI: 0.05, 0.86, P = 0.02). The analysis did not show any significant relationship between dermatitis and age or sex. The incidence rates of dermatitis were comparable between pembrolizumab and nivolumab-based therapies (79.5% vs. 81.0%) according to cluster analysis.

Hepatitis

Univariate analysis demonstrated statistically significant results, suggesting a potential association between race and hepatitis status (χ^2 = 8.18, df =3, P = 0.04). However, this association was not confirmed in multivariable logistic regression analysis after adjustment for confounders. Also, hepatitis was not significantly associated with sex, age, and BMI, or the type of immunotherapy regimen. Cluster analysis revealed a higher frequency of hepatitis in patients receiving pembrolizumab monotherapy compared to those treated with nivolumab alone or in combination with ipilimumab (67.6% vs. 63.8%).

Colitis

For colitis, neither the univariate analysis nor multivariable logistic regression analysis demonstrated significant associations with sex, race, BMI, or age. The cluster analysis revealed a higher incidence of colitis in the cluster which were primarily nivolumab recipients or ipilimumab and nivolumab combination recipients, as compared to the cluster that was primarily composed of pembrolizumab recipients (84.5% vs. 72.7%).

Thyroiditis

Neither univariate analysis nor multivariable logistic regression analysis revealed any significant associations between thyroiditis and sex, race, BMI, or age. The cluster analysis showed comparable thyroiditis trends between pembrolizumab and nivolumab-based regimens (64.8% vs. 65.5%), and the addition of ipilimumab did not significantly affect risk.

Pneumonitis

The Chi-square test indicated a statistically significant association between BMI and pneumonitis (χ^2 = 9.54, df = 3, P = 0.02), but multivariable logistic regression analysis did not indicate any significant association between the two after accounting for covariates. The cluster analysis revealed that pneumonitis was observed more frequently in the cluster where patients received nivolumab-based therapies, either alone or in combination with ipilimumab as compared to the cluster solely composed of pembrolizumab recipients (93.1% vs. 86.4%).

Anemia

For anemia, significant associations were observed with pembrolizumab monotherapy (χ^2 = 8.50, df = 1, P = 0.004) and nivolumab monotherapy (χ^2 = 5.59, df = 1, P = 0.018). The Chi-square indicated a borderline significant (χ^2 = 5.54, df = 2, P = 0.06) association between anemia and age and advancing age demonstrated an age-dependent protective relationship in those aged ≥ 80 years (OR = 0.48, 95% CI: 0.24, 0.95, P = 0.03) on multivariable logistic regression analysis. Although the Chi-square test did not show any significant association between race and anemia (P = 0.14), anemia was less frequently observed in people of Hispanic race (OR = 0.4, 95% CI: 0.18, 0.94, P = 0.03) on multivariate regression analysis. The cluster analysis revealed that the incidence of anemia was higher in the cluster composed of recipients of nivolumab monotherapy or nivolumab and ipilimumab combination therapy when compared to the cluster solely containing pembrolizumab recipients (75.9% vs. 53.4%).

Neutropenia

The univariate analysis revealed that neutropenia was significantly associated with sex (χ^2 = 5.47, df = 1, P = 0.019), race (χ^2 = 7.85, df = 3, P = 0.04), and age (χ^2 = 21.47, df = 2, P < 0.001). The multivariate logistic regression analysis showed that advancing age had a protective effect on neutropenia, with a significant reduction in risk in patients aged 65 - 79 (OR = 0.38, 95% CI: 0.19, 0.69, P = 0.007) and an even greater reduction in those over 80 years (OR = 0.18, 95% CI: 0.08, 0.39, P < 0.001). Additionally, African Americans were at higher risk (OR = 10.29, 95% CI: 1.36, 77.2, P = 0.02), while male sex appeared to be protective (OR = 0.51, 95% CI: 0.27, 0.95, P = 0.03). The cluster analysis revealed that patients had higher incidence rates of neutropenia in the cluster composed of nivolumab and ipilimumab recipients when compared to the cluster made of pembrolizumab recipients (81.0% vs. 70.5%).

Thrombocytopenia

The univariate analysis showed that thrombocytopenia correlated with age (χ^2 = 8.14, df = 2, P = 0.017), but no such correlation was found with sex, race, or BMI. The multivariate regression analysis revealed that patients aged 65 - 79 years had a lower risk of thrombocytopenia (OR = 0.41, 95% CI: 0.18, 0.94, P = 0.03). A similar protective effect against thrombocytopenia was observed in patients aged ≥ 80 years (OR = 0.36, 95% CI: 0.16, 0.82, P < 0.001). The cluster analysis showed that patients had higher incidence rates of thrombocytopenia in the cluster composed of nivolumab and ipilimumab recipients

Table 1. Summary of Significant Results of Multivariable Logistic Regression Analysis of Predictors for irAEs

irAEs	Demographic factors	Coefficient (β)	SE	OR	95% CI	Adjusted P-value
Dermatitis	BMI range > 30	1.8	0.64	5.36	1.25 - 22.9	0.024
	Hispanic Ethnicity	-1.5	0.69	0.22	0.057 - 0.86	0.029
Neutropenia	Age range 65 - 79	-0.88	0.37	0.38	0.19 - 0.69	0.007
	Age range > 79	-1.7	0.44	0.18	0.08 - 0.39	< 0.001
	African American Race	2.15	1.04	10.29	1.36 - 77.2	0.024
	Sex Male	-0.7	0.31	0.51	0.27 - 0.95	0.033
Anemia	Age range > 79	-0.64	0.35	0.48	0.24 - 0.95	0.034
	Hispanic ethnicity	-0.9	0.45	0.4	0.18 - 0.98	0.045
Thrombocytopenia	Age range 65 - 79	-0.91	0.44	0.41	0.18 - 0.94	0.036
	Age range > 79	-1.0	0.42	0.36	0.16 - 0.82	0.02

irAEs: immune-related adverse events; SE: standard error; OR: odds ratio; CI: confidence interval.

when compared to the cluster made of pembrolizumab recipients (89.7% vs. 85.2%).

The significant results of the multivariable regression analysis of all irAEs are summarized in Table 1. The adjusted P-values reflect the conditional association between each variable and the corresponding irAEs, controlling for other predictors in the model. A comprehensive multivariable logistic regression analysis for all irAEs is provided in the Supplementary Material 2 (wjon.elmerpub.com).

The cluster analysis revealed two distinct groups among 244 subjects where cluster 1 contained 75.2% (n = 176) of the subjects, and cluster 2 contained 24.8% (n = 58). The cluster assignment predictors showed the highest influence from pembrolizumab and nivolumab treatments and ipilimumab plus nivolumab combination therapy as well as anemia and age range and colitis and race and neutropenia and pneumonitis and sex and thrombocytopenia and hepatitis and dermatitis, and thyroiditis, and BMI range. Every patient in cluster 1 received pembrolizumab as their treatment. The patients in cluster 2 received nivolumab as their primary treatment, with 75.9% of patients taking the drug alone and 24.1% receiving ipilimumab and nivolumab combination therapy. The clusters showed different patterns regarding the occurrence of irAEs. The irAEs occurred at higher rates in cluster 2 than in cluster 1. The silhouette measure of cohesion and separation for this clustering solution was 0.3, indicating moderate separation between the identified clusters. The cluster analysis results are presented in Table 2.

Table 2. Cluster Profile Summary

Characteristics	Cluster 1 (n = 176, 75.2%)	Cluster 2 (n = 58, 24.8%)
Pembrolizumab	100.00%	0.00%
Nivolumab	0.00%	75.9%
Ipilimumab + nivolumab	0.00%	24.10%
Anemia	53.40%	75.9%
Age range (≥ 80)	38.10%	0.00%
Age range (65 - 79)	0.00%	44.80%
Colitis	72.70%	84.50%
Race (White)	84.10%	86.20%
Neutropenia	70.50%	81.00%
Pneumonitis	86.40%	93.10%
Sex (male)	59.70%	51.70%
Thrombocytopenia	85.20%	89.70%
Hepatitis	67.20%	63.80%
Dermatitis	79.50%	81.00%
Thyroiditis	64.80%	65.50%
BMI > 30	42.60%	46.60%

BMI: body mass index.

Discussion

Various studies in the last decade have described irAEs, but very few have highlighted their associations with BMI, age, and race, and, if present, have shown inconsistent results and have lacked detailed insight [14-16]. Our study unfolds one of the most extensive investigations of irAEs, analyzing various events across a diverse range of patient demographics, including age, race, and BMI.

Obesity was significantly linked to an increased risk of dermatitis, as demonstrated by both the Chi-square test and the multivariable logistic regression analysis, which aligns with previous research [17, 18]. This can be attributed to the adipocytes from visceral and subcutaneous fat secreting leptin, a pro-inflammatory adipokine that can stimulate the production of interleukin (IL)-1, IL-6, and tumor necrosis factor-α (TNF-α), further promoting T-cell proliferation and inhibiting regulatory T-cell proliferation [19]. Recent evidence suggests that visceral adipose tissue (VAT) itself expresses higher levels of PD-L1 receptors. This expression could help explain the correlation observed in our study between obesity and dermatitis with the use of immune checkpoint therapy [20, 21].

Moukarzel et al (2022) investigated whether inflammation in white adipose tissue (WAT) correlates with transcriptomic markers of immunotherapy response. Analysis revealed increased expression of eight immune-related genes in WAT inflammation, notably including CHIT1, which is a marker of macrophage activation. CHIT1 regulates various inflammatory mediators (e.g., IL-8, matrix metallopeptidase 9 (MMP9)), thereby enhancing the migration of immune cells such as T lymphocytes, potentially increasing susceptibility to ICI and more irAEs [22].

Advancing age demonstrated an age-dependent protective relationship in regards to the development of neutropenia and thrombocytopenia. A significantly reduced risk in patients aged 65 - 79 was observed with an even greater protection in those ≥ 80. Anemia also was observed to have an age-related protective effect but not observed until age ≥ 80 years. The decrease in incidence of these irAEs with age might be related in part to immunosenescence, which is the gradual deterioration of the immune system associated with aging [23]. Immunosenescence is characterized by the loss of naive T cells, diminished T-cell receptor diversity, and the accumulation of memory T cells that exhibit altered function and a decreased ability to mount effective responses to strong antigenic stimuli [24, 25]. A recent study observed that old aged patients had lower proportions of naive cytotoxic and helper T cells, B cells, and double negative T cells, but a higher proportion of natural killer cells. Additionally, aged patients exhibited diminished circulating cytokine responses after treatment, further underscoring the complex interplay between aging, immune responses, and the manifestation of toxicities with ICI therapy [26]. Also, it might reflect a more vigorous immune response to ICI therapy, potentially driven by a more intact and reactive immune system in young patients.

While the Chi-square test revealed a borderline significant association between dermatitis and race (P = 0.08), the regression model indicated a more nuanced relationship when controlling for confounders, concluding that Hispanic ethnicity is protective for dermatitis. These results align with prior studies depicting less incidence of cutaneous irAEs in patients of Hispanic ethnicity as compared to people of other ethnicities [27]. The genetic composition and higher melanin levels in Hispanics might have played a protective role by reducing ultraviolet (UV) damage and inflammation [28].

Hispanic ethnicity was also associated with a reduction in anemia risk. Previous studies have also reported lower incidence of hematological irAEs in people of Hispanic ethnicity as compared to people of other ethnicities, suggesting a relatively blunted immune response in people of this ethnicity [29]. Of note, African Americans receiving immunotherapy demonstrated a substantially increased risk for developing neutropenia. This may be attributed to the baseline benign ethnic neutropenia, associated with Duffy-null antigen neutrophil count seen in African Americans, along with a higher prevalence of "exhausted, non-functional T-cells" that become reactivated through T cell-targeting immunotherapy [30]. While the mechanisms underlying these racial disparities are not fully understood, a confluence of factors, including differential access to healthcare, variations in dietary patterns, environmental exposure, and potential genetic predispositions, might have played a role. Also, differences in tumor biology, expression of PDL-1, CTLA-4 receptors, and treatment response across different racial groups could also influence irAE development.

Conclusion

A key strength of our study is its comprehensive assessment of irAEs, examining multiple irAEs in relation to a wide range of variables; unlike prior studies that focused on isolated factors (e.g., BMI or race) or limited irAEs, our analysis provides a broader exploration of potential correlations [17, 19, 27]. Also, our study compared the irAEs between pembrolizumab, nivolumab, and ipilimumab in contrast to previous studies which were limited to single immunotherapy agents [18]. Our study included participants from a wider range of racial backgrounds as compared to many previous studies, which focused on the Caucasian population only. Despite including patients from all races, the White race constituted the majority of our study population, followed by Hispanics, reflecting the demographics of the region.

The study demonstrates that hematologic irAEs are strongly correlated with demographic characteristics. Advancing age showed a protective effect on anemia, leukopenia, and thrombocytopenia. Hispanic race was associated with reduced risk of anemia and dermatitis. However, higher incidence of neutropenia was observed in African Americans and females, along with higher rates of dermatitis in obese patients.

The study comes with its own limitations. Although we had a diverse cohort of patients, the racial distribution was quite skewed (84% Whites), so conclusions on race-based associations should be explored in prospective studies with a larger cohort of patients. The modest silhouette value in the cluster analysis reflects limited cluster separation which suggests that the groupings should be interpreted with caution. Al-

together, the findings from our study can serve as a foundation for future research involving larger, more diverse cohorts that account for socioeconomic, environmental, and genetic factors to help further explore the complex relationships between age, sex, race, BMI, and irAEs in patients receiving ICI therapy. This study can also guide providers to communicate the benefit and risk profile of ICI therapy effectively and to identify populations who may be at higher risk of irAE development.

Supplementary Material

Suppl 1. Summary of Results of Univariate Analysis of irAEs.

Suppl 2. Multivariable logistic regression analysis for all irAEs.

Acknowledgments

We appreciate the support of the Research Department at Rutgers Health/Community Medical Center.

Financial Disclosure

The authors have no relevant financial interests to disclose.

Conflict of Interest

The authors have no conflict of interest to declare that are relevant to the content of this article.

Informed Consent

Informed consent was waived by the institution due to the retrospective nature of the study design.

Author Contributions

SS and JI drafted the manuscript. SS and TP designed the study, and, together with the assistance of MD and SS, conducted data collection and statistical analysis. JI contributed to the statistical analyses, including logistic regression and cluster analysis. AK thoroughly reviewed the manuscript for accuracy and eliminated redundancy. HS and AK also made significant contributions to the discussion section, emphasizing the important gaps addressed by our study and its limitations. HS and AG assisted with editing and the overall design of the manuscript and tables, as well as citing relevant literature.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

BIC: Bayesian information criterion; BMI: body mass index; CD: cluster of differentiation; CIs: confidence intervals; CTCAE: Common Toxicity Criteria for Adverse Events; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; GI: gastrointestinal; ICIs: immune checkpoint inhibitors; irAEs: immune-related adverse events; IRB: institutional review board; ORs: odds ratios; P: P-value; PD-L1: programmed death ligand 1; SHP2: Src homology 2 domain-containing protein tyrosine phosphatase 2; SPSS: Statistical package for Social Sciences; TCR: T-cell receptor; TNF-α: tumor necrosis factor-α; UV: ultraviolet; VAT: visceral adipose tissue; WHO: World Health Organization

References

1. Fundamental mechanisms of immune checkpoint blockade therapy. Cancer Discovery. American Association for Cancer Research. (n.d.). Retrieved July 17, 2025, from https://aacrjournals.org/cancerdiscovery/article/8/9/1069/10253/Fundamental-Mechanisms-of-Immune-Checkpoint.
2. Buchbinder EI, Desai A. CTLA-4 and PD-1 pathways: similarities, differences, and implications of their inhibition. Am J Clin Oncol. 2016;39(1):98-106. doi pubmed
3. Martins F, Sofiya L, Sykiotis GP, Lamine F, Maillard M, Fraga M, Shabafrouz K, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat Rev Clin Oncol. 2019;16(9):563-580. doi pubmed
4. Immunotherapy for Cancer - NCI (nciglobal,ncienterprise). 2015. [cgvArticle]. https://www.cancer.gov/about-cancer/treatment/types/immunotherapy.
5. Mallio CA, Bernetti C, Cea L, Buoso A, Stiffi M, Vertulli D, Greco F, et al. Adverse effects of immune-checkpoint inhibitors: a comprehensive imaging-oriented review. Curr Oncol. 2023;30(5):4700-4723. doi pubmed
6. Yao L, Jia G, Lu L, Bao Y, Ma W. Factors affecting tumor responders and predictive biomarkers of toxicities in cancer patients treated with immune checkpoint inhibitors. Int Immunopharmacol. 2020;85:106628. doi pubmed
7. Ramos-Casals M, Brahmer JR, Callahan MK, Flores-Chavez A, Keegan N, Khamashta MA, Lambotte O, et al. Immune-related adverse events of checkpoint inhibitors. Nat Rev Dis Primers. 2020;6(1):38. doi pubmed
8. Tran JM. Immune-related adverse events linked to immune checkpoint inhibitors: retrospective analysis of a single-center veteran population. 2021. https://jhoponline.com/issue-archive/2021-issues/june-2021-vol-11-no-3/18934-immune-related-adverse-events-linked-to-immune-checkpoint-inhibitors-retrospective-analysis-of-a-single-center-veteran-population.
9. Zhang D, Shah NJ, Cook M, Blackburn M, Serzan MT, Advani S, Potosky AL, et al. Association between body mass index and immune-related adverse events (irAEs) among advanced-stage cancer patients receiving immune checkpoint inhibitors: a pan-cancer analysis. Cancers

(Basel). 2021;13(23):6109. doi pubmed
10. Long-term side effects of immune checkpoint inhibitors-NCI (nciglobal, ncienterprise). 2021. [cgvBlogPost]. https://www.cancer.gov/news-events/cancer-currents-blog/2021/immune-checkpoint-inhibitors-melanoma-long-term-side-effects.
11. CTEP Trial Development and Conduct-NCI (nciglobal,ncienterprise). 2025. [cgvArticle]. https://dctd.cancer.gov/research/ctep-trials/trial-development.
12. Everyday actions for better health - WHO recommendations. n.d.). Retrieved July 18, 2025, from https://www.who.int/europe/news-room/fact-sheets/item/everyday-actions-for-better-health-who-recommendations.
13. Benassi M, Garofalo S, Ambrosini F, Sant'Angelo RP, Raggini R, De Paoli G, Ravani C, et al. Using two-step cluster analysis and latent class cluster analysis to classify the cognitive heterogeneity of cross-diagnostic psychiatric inpatients. Front Psychol. 2020;11:1085. doi pubmed
14. Are immune-related adverse events associated with the efficacy of immune checkpoint inhibitors in patients with cancer? A systematic review and meta-analysis. BMC Medicine. Retrieved July 18, 2025, from https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-020-01549-2.
15. Peravali M, Gomes-Lima C, Tefera E, Baker M, Sherchan M, Farid S, Burman K, et al. Racial disparities in immune-related adverse events of immune checkpoint inhibitors and association with survival based on clinical and biochemical responses. World J Clin Oncol. 2021;12(2):103-114. doi pubmed
16. You Y, Jiang C, Peng K, He W, Wang L, Jin Y, Xia L. The predictive value of body mass index on prognosis and adverse events of cancers treated with immunotherapy: a systematic review and meta-analysis. Cancer Immunol Immunother. 2021;70(8):2323-2335. doi pubmed
17. Cortellini A, Bersanelli M, Buti S, Cannita K, Santini D, Perrone F, Giusti R, et al. A multicenter study of body mass index in cancer patients treated with anti-PD-1/PD-L1 immune checkpoint inhibitors: when overweight becomes favorable. J Immunother Cancer. 2019;7(1):57. doi pubmed
18. Eun Y, Kim IY, Sun JM, Lee J, Cha HS, Koh EM, Kim H, et al. Risk factors for immune-related adverse events associated with anti-PD-1 pembrolizumab. Sci Rep. 2019;9(1):14039. doi pubmed
19. Immunotherapy-related hematological adverse events: incidence and outcomes. Blood. American Society of Hematology. (n.d.). Retrieved July 18, 2025, from https://ashpublications.org/blood/article/142/Supplement%201/2368/499217/Immunotherapy-Related-Hematological-Adverse-Events.
20. JCI - Unhealthy visceral fat is associated with improved efficacy of immunotherapy in endometrial cancer. n.d.). Retrieved July 18, 2025, from https://www.jci.org/articles/view/183675.
21. Gomez-Banoy N, Ortiz EJ, Jiang CS, Dagher C, Sevilla C, Girshman J, Pagano AM, et al. Body mass index and adiposity influence responses to immune checkpoint inhibition in endometrial cancer. J Clin Invest. 2024;134(17). doi pubmed
22. Moukarzel LA, Ferrando L, Stylianou A, Lobaugh S, Wu M, Nobre SP, Iasonos A, et al. Impact of obesity and white adipose tissue inflammation on the omental microenvironment in endometrial cancer. Cancer. 2022;128(18):3297-3309. doi pubmed
23. Nikolich-Zugich J. The twilight of immunity: emerging concepts in aging of the immune system. Nat Immunol. 2018;19(1):10-19. doi pubmed
24. Fulop T, Larbi A, Witkowski JM, McElhaney J, Loeb M, Mitnitski A, Pawelec G. Aging, frailty and age-related diseases. Biogerontology. 2010;11(5):547-563. doi pubmed
25. Goronzy JJ, Weyand CM. Understanding immunosenescence to improve responses to vaccines. Nat Immunol. 2013;14(5):428-436. doi pubmed
26. Kao C, Charmsaz S, Tsai HL, Aziz K, Shu DH, Munjal K, Griffin E, et al. Age-related divergence of circulating immune responses in patients with solid tumors treated with immune checkpoint inhibitors. Nat Commun. 2025;16(1):3531. doi pubmed
27. Yale K, Roux J, Shiu J. A cross-sectional study of cutaneous immune-related adverse effects in Hispanic patients after immune checkpoint inhibitor use for cancer therapy. J Am Acad Dermatol. 2025;92(1):168-170. doi pubmed
28. Yale K, Shiu J. 51327 Racial and ethnic disparities in immune checkpoint inhibitor-induced cutaneous immune-related adverse effects. Journal of the American Academy of Dermatology. 2024;91(3):AB76. doi
29. Impact of race/ethnicity on the relationship between visceral fat and inflammatory biomarkers. Carroll-2009-Obesity-Wiley Online Library. Retrieved July 18, 2025, from https://onlinelibrary.wiley.com/doi/10.1038/oby.2008.657.
30. Atallah-Yunes SA, Ready A, Newburger PE. Benign ethnic neutropenia. Blood Rev. 2019;37:100586. doi pubmed