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Original Article

Pembrolizumab-Associated Oral Mucositis: A Global Pharmacovigilance Analysis and External Validation Based on FAERS and EudraVigilance Databases

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Abstract:

Background: Pembrolizumab, a programmed cell death protein 1 (PD-1) inhibitor, has fundamentally altered the management of multiple malignancies; however, its immune-related adverse events (irAEs) can compromise treatment outcomes. Among these, oral mucositis (OM) is a clinically significant but often underestimated toxicity. This study aims to characterize the real-world safety signals, temporal dynamics, and risk factors of pembrolizumab-associated OM using global pharmacovigilance databases.

Methods: We performed a retrospective disproportionality analysis using data from the US FDA Adverse Event Reporting System (FAERS) (2014–2025) and the EudraVigilance (EV) database for external validation. Four statistical algorithms—Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Information Component (IC), and Empirical Bayes Geometric Mean (EBGM)—were utilized for signal detection. Time to onset (TTO), gender-based reporting preferences (log_2ROR), and clinical outcome associations were also systematically evaluated.

Results: A total of 679 and 816 OM reports were identified in FAERS and EV, respectively. The reporting frequency exhibited a steady upward trajectory, peaking in 2024. In FAERS, OM showed a distinct female predominance (57.58%) and was prevalent in elderly patients (≥65 years, 45.95%). Robust signals were confirmed for "Stomatitis" (ROR 3.78, 95% CI 3.48–4.10) and "Oral mucosa erosion" (ROR 5.06, 95% CI 3.09–8.28), with "Stomatitis haemorrhagic" exhibiting the highest signal intensity (ROR 6.29). The median TTO was 12.50 days (IQR: 4.00–35.00), with 71.74% of events occurring within the first 30 days. Subgroup analysis revealed a significant female susceptibility (EudraVigilance: log_2ROR = 0.502, FDR_P < 0.001), while age showed no significant difference after FDR correction. Correlation analysis associated stomatitis primarily with non-fatal clinical outcomes (P < 0.0001).

Conclusion: Pembrolizumab-associated OM is a high-risk, early-onset irAE that manifests predominantly within the first month of therapy. Female and elderly patients are particularly vulnerable, though the toxicity generally follows a non-lethal trajectory. Clinicians should prioritize proactive oral screening and early intervention during the initial 30-day "critical window" to mitigate the high burden of hospitalization and

optimize patient quality of life.
Keywords: Pembrolizumab; Oral mucositis; Pharmacovigilance; Immune-related adverse events (irAEs); FAERS; Sexual dimorphismIntroduction

Introduction

The therapeutic landscape of modern oncology has been fundamentally reshaped by the clinical translation of immune checkpoint inhibitors (ICIs), particularly those targeting the programmed cell death protein 1 (PD-1) pathway123. Pembrolizumab, a high-affinity humanized monoclonal antibody against PD-1, has demonstrated remarkable efficacy across a broad spectrum of malignancies, including melanoma, non-small cell lung cancer, and head and neck squamous cell carcinoma4. By rejuvenating exhausted T-cells and restoring anti-tumor surveillance5, pembrolizumab has significantly extended the overall survival of patients with advanced cancers. However, this immunological reinvigoration often comes at the expense of immune homeostasis, leading to a unique constellation of toxicities termed immune-related adverse events (irAEs).

Among the diverse spectrum of irAEs, mucosal toxicities, specifically oral mucositis (OM), emerge as a clinically significant but often underestimated complication. Unlike traditional chemotherapy-induced mucositis, which results from direct cytotoxic damage to the rapidly dividing basal epithelial cells, ICI-induced OM is driven by an aberrant T-cell-mediated inflammatory response within the oral microenvironment67. Clinically, this manifests as painful stomatitis, mucosal erosions, and ulcerations that can profoundly impair nutritional intake, compromise quality of life, and necessitate treatment interruptions or dose modifications. Despite its prevalence, OM is frequently overshadowed in literature by high-grade systemic toxicities such as pneumonitis or colitis, leading to a relative paucity of data regarding its real-world incidence and risk factors89.

Crucially, emerging evidence suggests that the susceptibility to irAEs may be influenced by host-specific biological determinants, with sexual dimorphism being a focal point of recent investigation. Preliminary studies have hinted that female patients may experience a higher frequency of certain irAEs, potentially due to differences in innate immune signaling and hormonal modulation of T-cell activity10. Furthermore, as pembrolizumab utilization expands into the elderly population, understanding the interplay between immunosenescence and mucosal vulnerability becomes imperative. To date, however, large-scale studies characterized by robust external validation that delineate the temporal dynamics and demographic predispositions of pembrolizumab-associated OM remain scarce.

To address these knowledge gaps, we conducted a comprehensive, global pharmacovigilance study using the US FDA Adverse Event Reporting System (FAERS) database, supplemented by external validation through the EudraVigilance (EV) system. By employing disproportionality analysis and multi-algorithm signal detection, this study aims to characterize the pathological spectrum, time-to-onset patterns, and high-risk subpopulations of pembrolizumab-induced OM. Our findings are intended to provide clinicians with an evidence-based framework for early recognition and risk stratification, ultimately optimizing the management of patients undergoing PD-1 blockade therapy.

2. Methods

2.1 Data Inception and Source Integration

In this study, a global retrospective pharmacovigilance analysis was performed to

characterize the risk of oral mucositis (OM) associated with the PD-1 inhibitor pembrolizumab. Primary data were harvested from the US FDA Adverse Event Reporting System (FAERS), spanning from the first quarter of 2014 through the final quarter of 2025. To cross-verify the reliability of our findings and mitigate geographical reporting bias, we utilized the EudraVigilance (EV) database as an independent external validation cohort, focusing on spontaneous reports where pembrolizumab was designated as the primary "suspect" medication.

2.2 Case Definition and MedDRA Mapping

Adverse events (AEs) were categorized using the Medical Dictionary for Regulatory Activities (MedDRA, version 27.0). The clinical spectrum of OM was defined by a cluster of Preferred Terms (PTs), including but not limited to Stomatitis, Oral mucosa erosion, Stomatitis haemorrhagic, and Aphthous ulcer. To ensure data cleanliness, a deduplication process was applied to remove overlapping reports based on key identifiers such as age, gender, event date, and reporting country.

2.3 Characterization of Clinical and Temporal Patterns

We systematically analyzed the clinical landscape of OM, focusing on demographic variables (sex, age), reporter qualification, and clinical outcomes. Time to Onset (TTO) was defined as the latency between the initiation of pembrolizumab therapy and the first manifestation of mucosal toxicity. TTO was expressed as the median with interquartile range (IQR). Given the non-normal distribution of the temporal data, the Wilcoxon rank-sum test was employed to evaluate TTO disparities between male and female cohorts.

2.4 Signal Detection Algorithms (Disproportionality Analysis)

To quantify the association strength between pembrolizumab and OM, four distinct disproportionality algorithms were utilized based on 2x2 contingency tables. This multi-algorithm approach included:Reporting Odds Ratio (ROR); Proportional Reporting Ratio (PRR); Information Component (IC) from the Bayesian Confidence Propagation Neural Network (BCPNN); Empirical Bayes Geometric Mean (EBGM) from the Multi-item Gamma Poisson Shrinker (MGPS)

A positive pharmacovigilance signal was identified only when consistent thresholds were met (e.g., ROR lower bound of 95% CI > 1; IC025 > 0; and EBGM05 > 2). This rigorous filtering ensured the exclusion of sporadic or incidental associations.

2.5 Differential Subgroup Analysis and Statistical Correlation

To pinpoint high-risk subpopulations, we conducted stratified analyses across gender and age dimensions. The reporting preference was quantified using the $\log_2$-transformed ROR ($\log_2$ROR). A positive $\log_2$ROR indicated a significantly higher reporting frequency in the target subgroup (e.g., females vs. males).Furthermore, association analyses between mucosal toxicities and clinical severity (Fatal vs. Non-fatal) were performed using Fisher's exact test. To account for the potential of type I errors inherent in multiple comparisons, all P-values underwent False Discovery Rate (FDR) correction. A two-sided adjusted P-value (FDR_P) < 0.05 was established as the threshold for statistical significance.

3. Result

3.1. Temporal Trends and Demographic Landscape of OM in FAERS

From 2014 to 2025, a total of 679 reports of pembrolizumab-associated oral mucositis (OM) were identified in the FAERS database. The annual reporting frequency exhibited a steady upward trajectory, reaching a peak of 168 cases in 2024 (Figure 1). Demographic analysis revealed a notable female predominance (57.58%; Figure 2)

and a high prevalence among elderly patients (aged ≥65 years, 45.95%; Figure 3). Reporting sources were primarily pharmacists (52.58%) and consumers (30.93%) (Figure 4). In terms of clinical severity, 78.94% of events were classified as serious (Figure 5), with critical outcomes including hospitalization (41.38%) and death (8.98%) (Figure 6). The median time to onset (TTO) was 12.50 days (IQR: 4.00–35.00 days), with 71.74% of events occurring within the first 30 days of treatment (Figures 7,8). Notably, no statistically significant difference in TTO was observed between male and female patients (Wilcoxon test, P=0.6985; Figure 9).

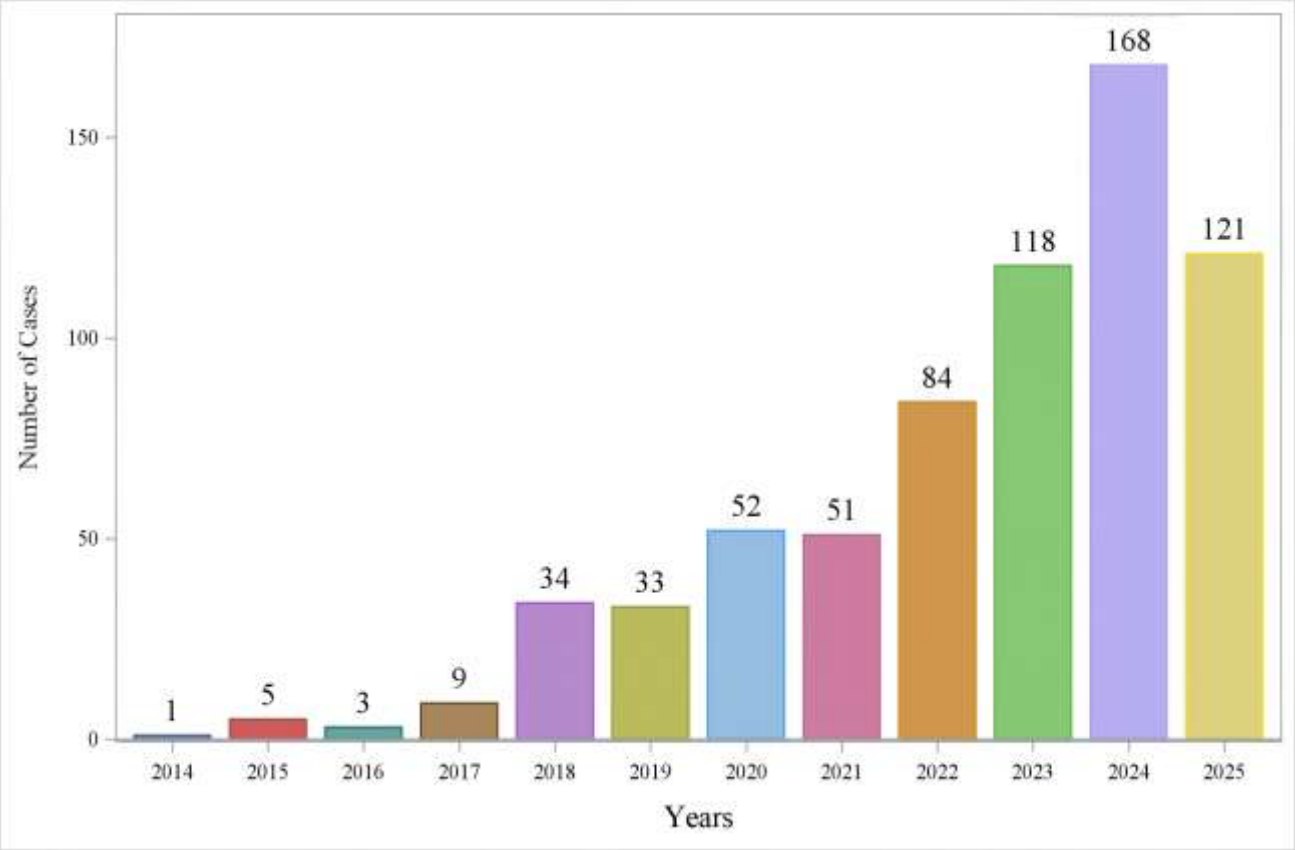


Figure1. Annual distribution of AE reports (FAERS)

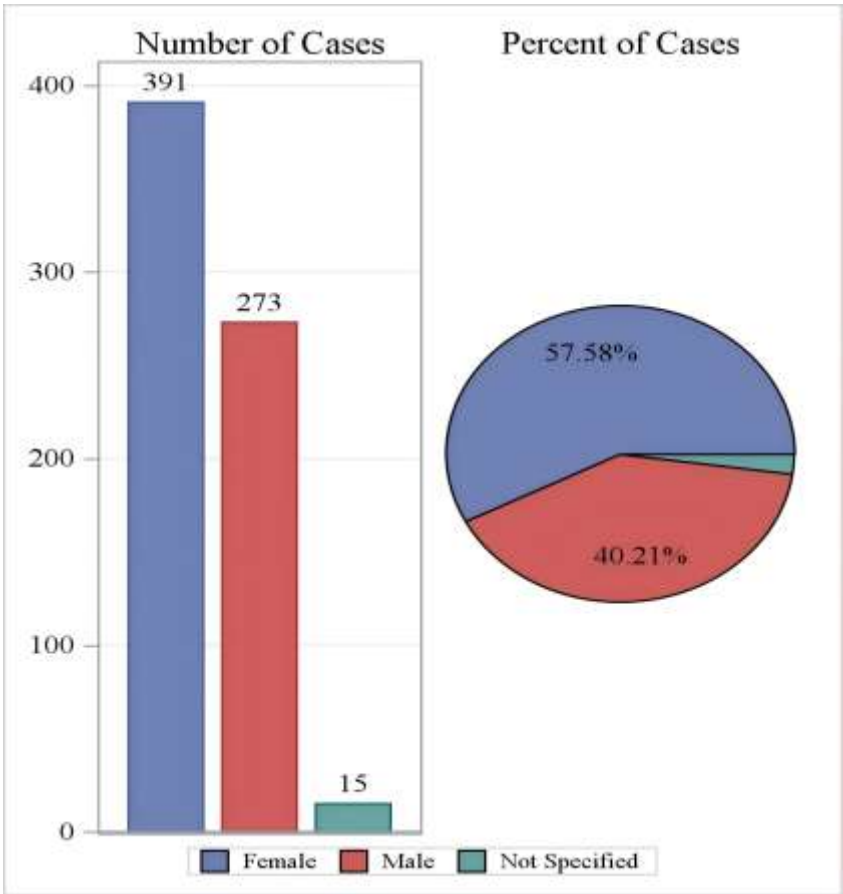


Figure2. Sex distribution of AE reports (FAERS)

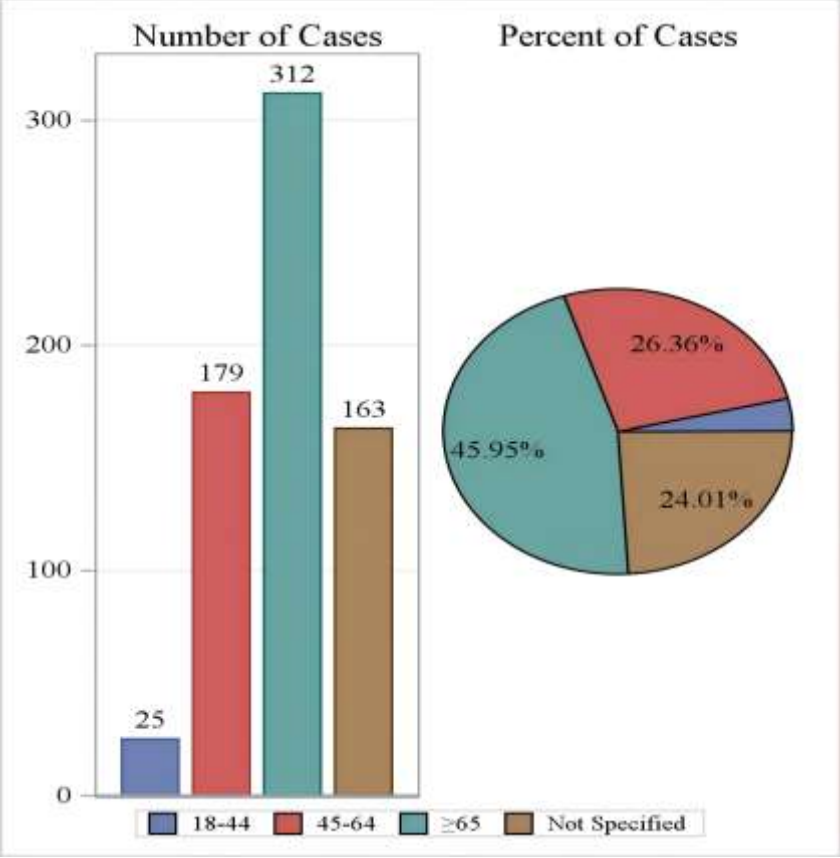


Figure3. Age distribution of AE reports (FAERS)

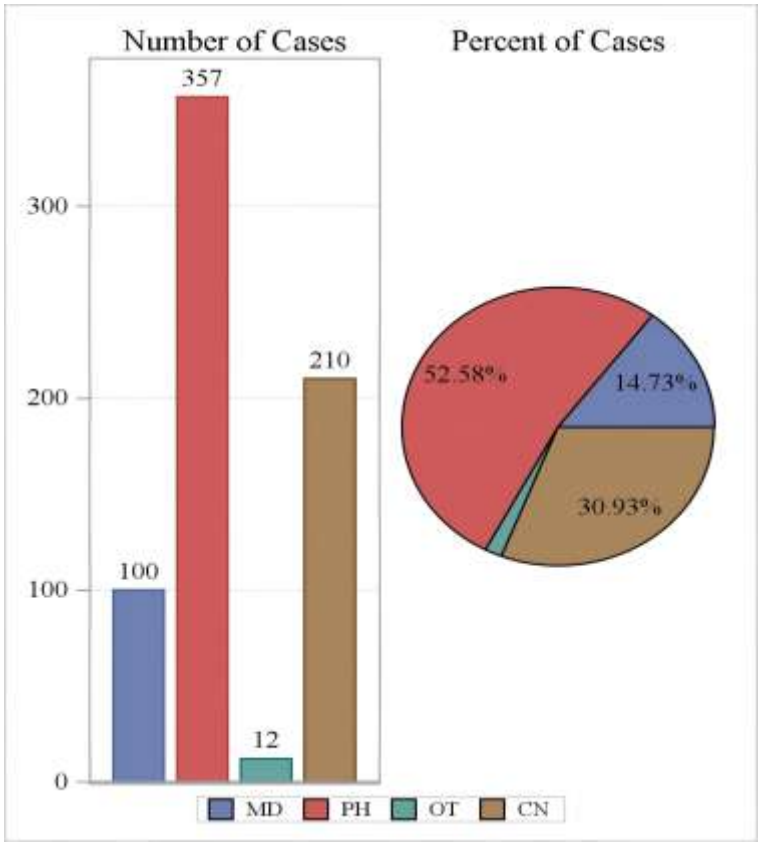


Figure4. Reporter distribution of AE reports (FAERS)

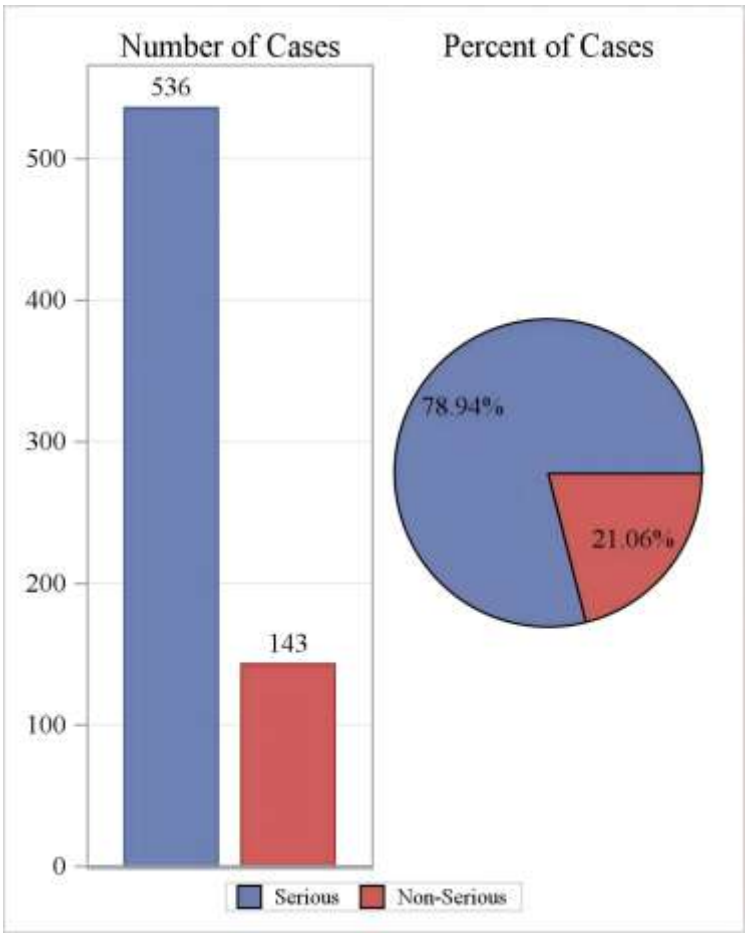


Figure5. Serious Report distribution of AE reports (FAERS)

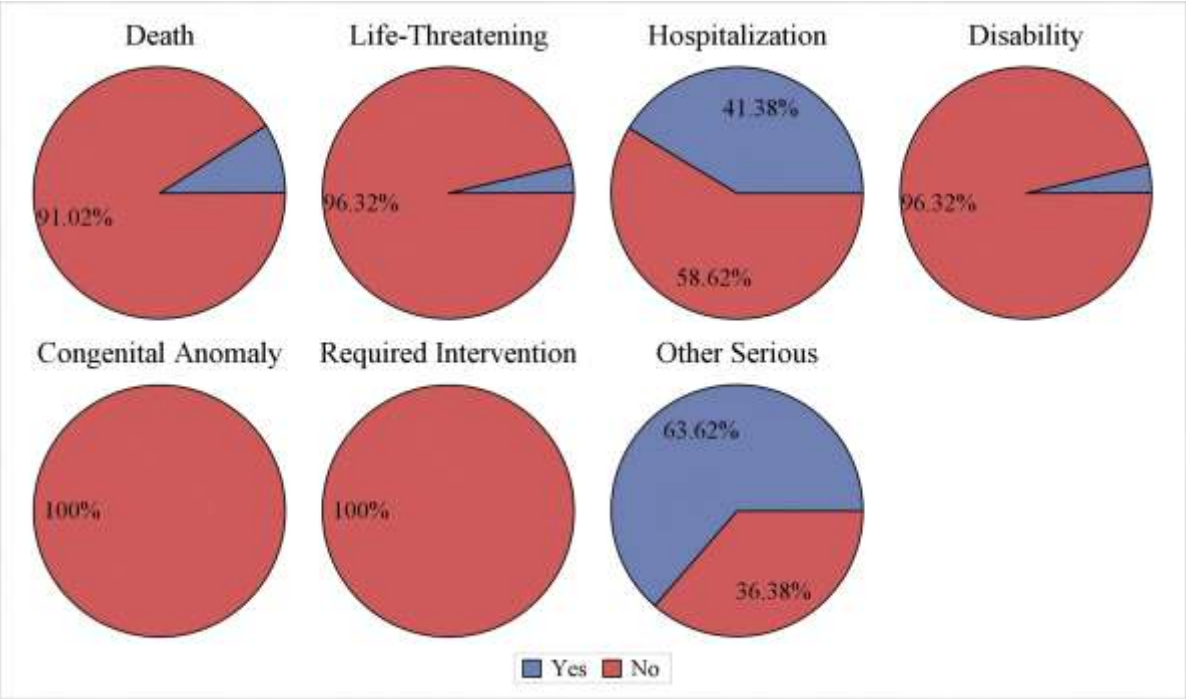


Figure6. Outcomes report distribution of AE reports (FAERS)

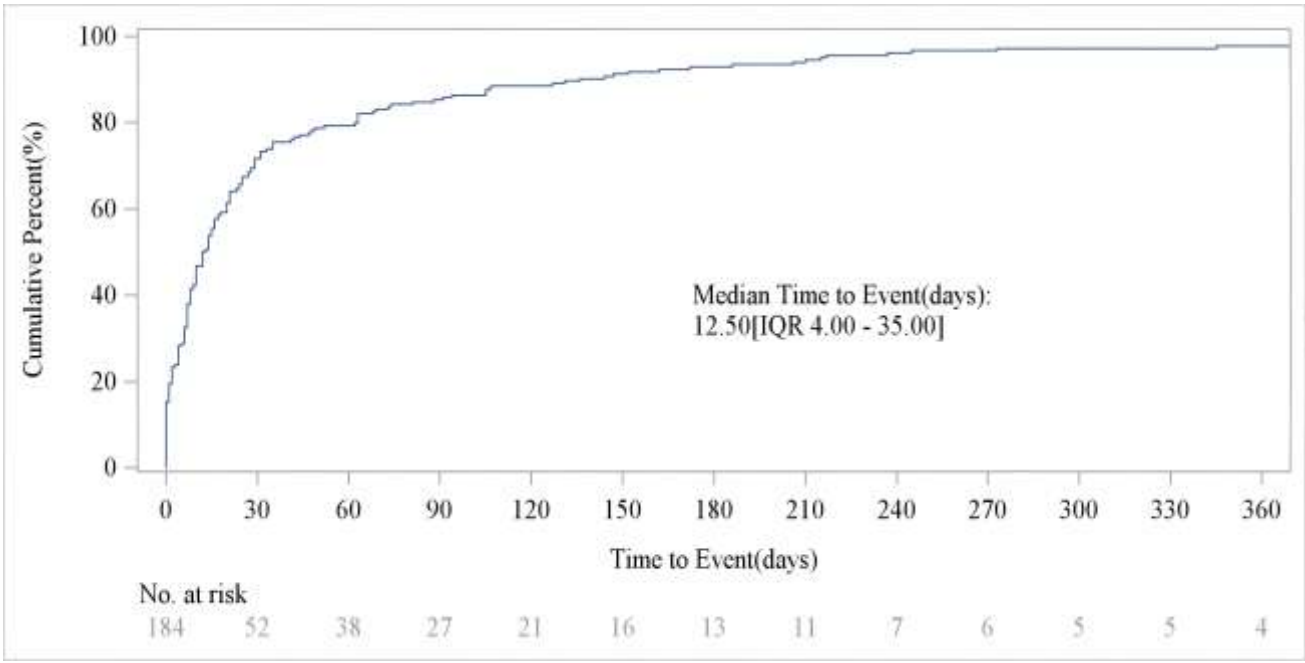


Figure7. Cumulative incidence of adverse events (FAERS)

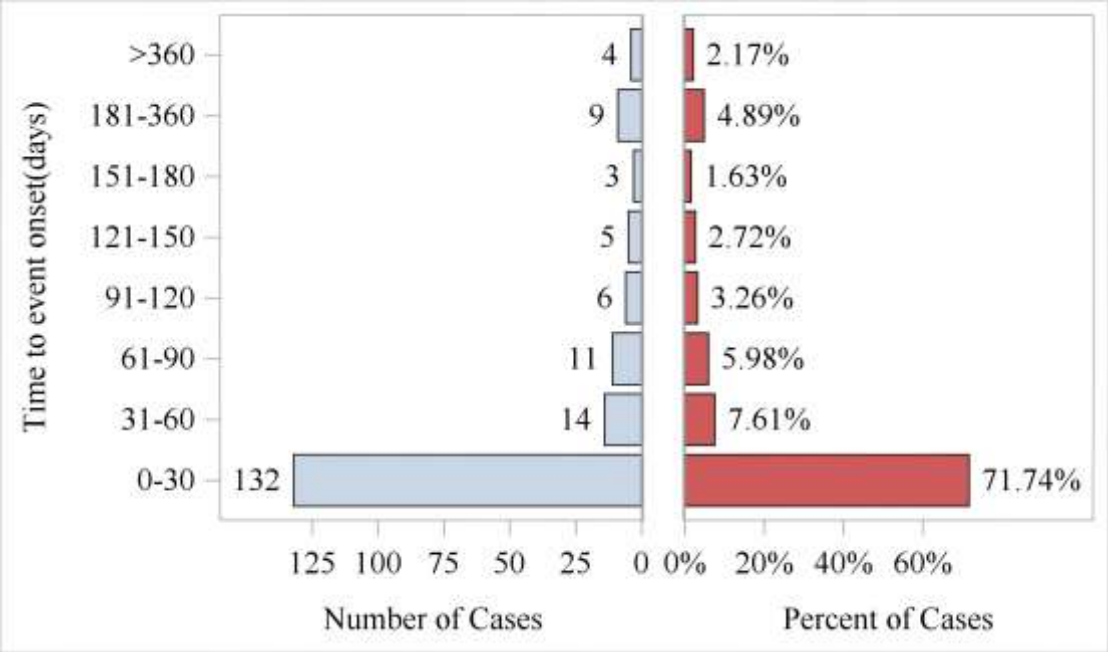


Figure8. Time to event report distribution of AE reports(FAERS)

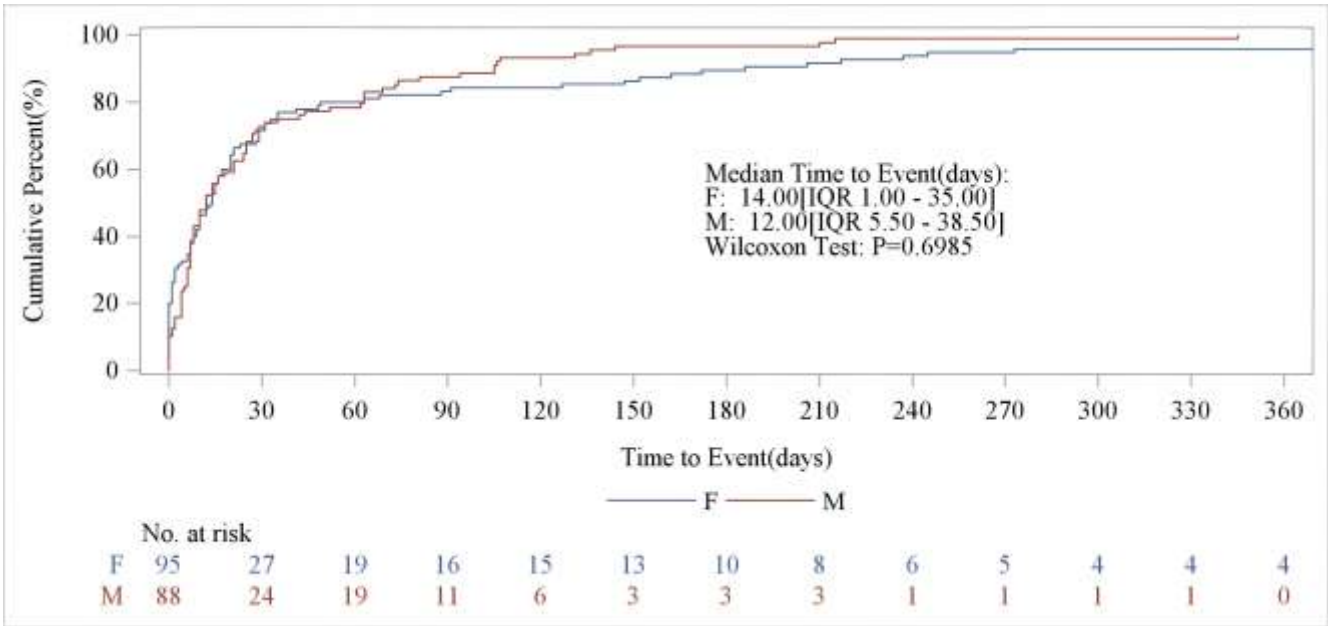


Figure9. Cumulative incidence of adverse events by sex (FAERS)

3.2. Disproportionality Analysis and Signal Characterization in FAERS

Comprehensive disproportionality analysis confirmed that pembrolizumab was significantly associated with several oral mucosal adverse events (AEs). Stomatitis was the most frequently reported Preferred Term (PT) (n=586, ROR 3.78, 95% CI 3.48–4.10), while Oral mucosa erosion exhibited a strong signal (ROR 5.06, 95% CI 3.09–8.28); both signals remained robust across all four algorithms (ROR, PRR, IC, and EBGM)(Table 1).

Table 1 Signal Detection Results Across MedDRA Hierarchical Levels (FAERS)

PT	ROR(95%	PRR(95%	IC(IC0	EBGM(EB	ROR	PRR	IC	EBG

	CI)	CI)	25)	GM05)	Signal	Signal	Signa l	M Signa l
Stomatitis	3.78(3.48, 4.10)	3.77(3.48, 4.09)	1.90(1. 78)	3.74(3.45)	Y	Y	Y	Y
Mouth ulceration	1.06(0.82, 1.37)	1.06(0.82, 1.37)	0.08(- 0.30)	1.06(0.82)	N	N	N	N
Oral mucosa erosion	5.06(3.09, 8.28)	5.05(3.09, 8.28)	2.32(1. 31)	5.00(3.05)	Y	Y	Y	Y
Aphthous ulcer	0.57(0.34, 0.95)	0.57(0.34, 0.95)	-0.81(- 1.49)	0.57(0.34)	N	N	N	N
Lip ulceration	1.99(0.89, 4.45)	1.99(0.89, 4.45)	0.99(- 0.29)	1.99(0.89)	N	N	N	N
Stomatitis necrotising	5.58(1.78, 17.46)	5.58(1.78, 17.46)	2.46(- 0.09)	5.51(1.76)	Y	Y	N	N
Lip erosion	1.52(0.49, 4.73)	1.52(0.49, 4.73)	0.60(- 1.02)	1.52(0.49)	N	N	N	N
Stomatitis haemorrhagic	6.29(1.55, 25.46)	6.29(1.55, 25.46)	2.63(- 0.51)	6.20(1.53)	N	N	N	N
Palatal ulcer	3.82(0.53, 27.42)	3.82(0.53, 27.42)	1.92(- 1.40)	3.79(0.53)	N	N	N	N

Subgroup analysis underscored the clinical stability of these associations, as the signal for Stomatitis remained significant regardless of gender, age, or report seriousness from 2018 through 2025. Interestingly, Stomatitis haemorrhagic showed the highest signal intensity (ROR 6.29) and was particularly prominent in the 18–44 age group (EBGM05 = 17.42)(Table 2-4).

Table 2 Signal Detection Results Across MedDRA Hierarchical Levels Stratified by Age (FAERS)

Subg roup	PT	ROR(95% CI)	PRR(95% CI)	IC(IC02 5)	EBGM(E BGM05)	ROR Signal	PRR Signal	IC Sign al	EBGM Signal
≥65	Stomatitis	3.34(2.96, 3.77)	3.33(2.96,3. 76)	1.72(1.5 3)	3.29(2.92)	Y	Y	Y	Y
45- 64	Stomatitis	3.57(3.05, 4.18)	3.56(3.04,4. 17)	1.82(1.5 6)	3.53(3.02)	Y	Y	Y	Y
NS	Stomatitis	3.90(3.29, 4.61)	3.89(3.29,4. 60)	1.95(1.6 7)	3.87(3.27)	Y	Y	Y	Y
NS	Mouth ulceration	1.98(1.31, 3.02)	1.98(1.30,3. 01)	0.99(0.3 2)	1.98(1.30)	Y	Y	Y	N
18- 44	Stomatitis	3.24(2.11, 4.97)	3.23(2.11,4. 96)	1.69(0.9 3)	3.23(2.10)	Y	Y	Y	Y
45- 64	Mouth ulceration	1.12(0.72, 1.76)	1.12(0.72,1. 76)	0.17(- 0.49)	1.12(0.72)	N	N	N	N
≥65	Mouth ulceration	0.65(0.40, 1.06)	0.65(0.40,1. 06)	-0.63(- 1.30)	0.65(0.40)	N	N	N	N
≥65	Oral mucosa erosion	6.14(3.36, 11.19)	6.13(3.36,1 1.19)	2.58(1.2 3)	5.96(3.27)	Y	Y	Y	Y
≥65	Aphthous ulcer	0.68(0.32, 1.43)	0.68(0.32,1. 43)	-0.55(- 1.52)	0.68(0.32)	N	N	N	N

NS	Aphthous ulcer	1.04(0.47, 2.32)	1.04(0.47,2.31)	0.06(-1.05)	1.04(0.47)	N	N	N	N
45-64	Oral mucosa erosion	3.57(1.14, 11.14)	3.57(1.14,11.14)	1.83(-0.34)	3.54(1.14)	Y	Y	N	N
≥65	Lip ulceration	1.29(0.32, 5.20)	1.29(0.32,5.20)	0.37(-1.44)	1.29(0.32)	N	N	N	N
45-64	Lip ulceration	2.22(0.55, 8.92)	2.22(0.55,8.92)	1.15(-1.02)	2.21(0.55)	N	N	N	N
≥65	Stomatitis necrotising	5.95(1.45, 24.34)	5.95(1.45,24.34)	2.53(-0.55)	5.79(1.41)	N	N	N	N
45-64	Lip erosion	4.50(1.12, 18.17)	4.50(1.12,18.17)	2.16(-0.64)	4.45(1.10)	N	N	N	N
NS	Oral mucosa erosion	5.94(1.47, 23.95)	5.94(1.47,23.95)	2.56(-0.52)	5.88(1.46)	N	N	N	N
18-44	Aphthous ulcer	0.65(0.09, 4.60)	0.65(0.09,4.60)	-0.63(-2.39)	0.65(0.09)	N	N	N	N
45-64	Aphthous ulcer	0.13(0.02, 0.90)	0.13(0.02,0.90)	-2.97(-4.19)	0.13(0.02)	N	N	N	N
NS	Lip ulceration	1.97(0.28, 14.03)	1.97(0.28,14.03)	0.97(-1.64)	1.97(0.28)	N	N	N	N
18-44	Lip ulceration	5.56(0.78, 39.69)	5.56(0.78,39.68)	2.47(-1.29)	5.54(0.78)	N	N	N	N
18-44	Mouth ulceration	0.32(0.05, 2.30)	0.32(0.05,2.30)	-1.63(-3.07)	0.32(0.05)	N	N	N	N
18-44	Stomatitis haemorrhagic	168.68(20.30,1401.29)	168.66(20.31,1400.82)	7.18(-1.29)	144.71(17.42)	N	N	N	Y
≥65	Stomatitis haemorrhagic	3.72(0.51, 26.94)	3.72(0.51,26.94)	1.87(-1.44)	3.66(0.51)	N	N	N	N
45-64	Stomatitis necrotising	6.85(0.94, 49.60)	6.85(0.94,49.59)	2.75(-1.28)	6.73(0.93)	N	N	N	N
≥65	Lip erosion	0.79(0.11, 5.63)	0.79(0.11,5.63)	-0.34(-2.23)	0.79(0.11)	N	N	N	N
45-64	Palatal ulcer	32.86(4.21,256.70)	32.86(4.21, 256.69)	4.91(-1.26)	29.96(3.84)	N	N	N	Y

Table 3 Signal Detection Results Across MedDRA Hierarchical Levels Stratified by Sex Type (FAERS)

Subgroup	PT	ROR(95% CI)	PRR(95% CI)	IC(IC025)	EBGM(EBGM05)	ROR Signal	PRR Signal	IC Signal	EBGM Signal
Female	Stomatitis	4.10(3.68, 4.56)	4.08(3.67, 4.54)	2.02(1.85)	4.05(3.64)	Y	Y	Y	Y
Male	Stomatitis	3.76(3.30, 4.28)	3.75(3.30, 4.27)	1.89(1.69)	3.71(3.26)	Y	Y	Y	Y
Female	Mouth ulceration	1.15(0.82, 1.61)	1.15(0.82, 1.61)	0.20(-0.29)	1.15(0.82)	N	N	N	N
Male	Mouth	1.10(0.73,	1.10(0.73,	0.14(-	1.10(0.73)	N	N	N	N

	ulceration	1.66)	1.66)	0.46)					
Not Specified	Stomatitis	2.41(1.42, 4.07)	2.40(1.42, 4.06)	1.26(0.39)	2.40(1.42)	Y	Y	Y	N
Female	Aphthous ulcer	0.66(0.35, 1.28)	0.66(0.35, 1.28)	-0.59(-1.45)	0.66(0.35)	N	N	N	N
Male	Oral mucosa erosion	5.25(2.71, 10.16)	5.25(2.71, 10.16)	2.37(0.94)	5.16(2.67)	Y	Y	Y	Y
Female	Oral mucosa erosion	4.88(2.32, 10.28)	4.88(2.32, 10.28)	2.27(0.68)	4.84(2.30)	Y	Y	Y	Y
Male	Aphthous ulcer	0.63(0.28, 1.40)	0.63(0.28, 1.40)	-0.67(-1.68)	0.63(0.28)	N	N	N	N
Female	Lip ulceration	1.87(0.60, 5.80)	1.87(0.60, 5.80)	0.90(-0.83)	1.86(0.60)	N	N	N	N
Male	Lip ulceration	2.41(0.77, 7.53)	2.41(0.77, 7.53)	1.26(-0.62)	2.40(0.77)	N	N	N	N
Male	Stomatitis necrotising	7.75(1.90, 31.66)	7.75(1.90, 31.66)	2.92(-0.46)	7.55(1.85)	N	N	N	N
Male	Lip erosion	1.98(0.49, 7.98)	1.98(0.49, 7.98)	0.98(-1.10)	1.98(0.49)	N	N	N	N
Not Specified	Mouth ulceration	0.45(0.06, 3.19)	0.45(0.06, 3.19)	-1.15(-2.73)	0.45(0.06)	N	N	N	N
Female	Stomatitis haemorrhagic	7.12(0.99, 51.39)	7.12(0.99, 51.39)	2.81(-1.27)	7.01(0.97)	N	N	N	N
Male	Stomatitis haemorrhagic	5.48(0.76, 39.71)	5.48(0.76, 39.71)	2.43(-1.33)	5.38(0.74)	N	N	N	N
Female	Stomatitis necrotising	3.62(0.51, 25.93)	3.62(0.51, 25.93)	1.85(-1.41)	3.60(0.50)	N	N	N	N
Female	Lip erosion	1.10(0.16, 7.86)	1.10(0.16, 7.86)	0.14(-1.98)	1.10(0.16)	N	N	N	N
Male	Palatal ulcer	10.95(1.48,81.11)	10.95(1.48,81.11)	3.40(-1.26)	10.54(1.42)	N	N	N	N

Table 4 Signal Detection Results Across MedDRA Hierarchical Levels Stratified by Serious Reports. (FAERS)

Subgroup	PT	ROR(95% CI)	PRR(95% CI)	IC(IC025)	EBGM(EBGM05)	ROR Signal	PRR Signal	IC Signal	EBGM Signal
Serious	Stomatitis	3.51(3.20, 3.85)	3.51(3.20, 3.84)	1.80(1.65)	3.47(3.17)	Y	Y	Y	Y
Non-Serious	Stomatitis	5.91(4.97, 7.02)	5.88(4.95, 6.98)	2.55(2.24)	5.85(4.92)	Y	Y	Y	Y
Serious	Mouth ulceration	0.93(0.70, 1.23)	0.93(0.70, 1.23)	-0.10(-0.51)	0.93(0.70)	N	N	N	N
Serious	Aphthous	0.57(0.34,	0.57(0.34,	-0.81(-	0.57(0.34)	N	N	N	N

	ulcer	0.96)	0.96)	1.52)					
Serious	Oral mucosa erosion	3.55(2.09, 6.01)	3.55(2.09, 6.01)	1.81(0.84)	3.52(2.08)	Y	Y	Y	Y
Non-Serious	Mouth ulceration	1.58(0.82, 3.04)	1.58(0.82, 3.04)	0.66(-0.34)	1.58(0.82)	N	N	N	N
Serious	Lip ulceration	1.25(0.47, 3.34)	1.25(0.47, 3.34)	0.32(-1.04)	1.25(0.47)	N	N	N	N
Serious	Stomatitis necrotising	4.39(1.40, 13.72)	4.39(1.40, 13.72)	2.12(-0.22)	4.33(1.39)	Y	Y	N	N
Serious	Lip erosion	1.20(0.39, 3.73)	1.20(0.39, 3.73)	0.26(-1.26)	1.20(0.39)	N	N	N	N
Non-Serious	Lip ulceration	9.47(2.35, 38.17)	9.47(2.35, 38.16)	3.23(-0.37)	9.38(2.33)	N	N	N	Y
Serious	Stomatitis haemorrhagic	5.19(1.28, 21.03)	5.19(1.28, 21.03)	2.35(-0.58)	5.12(1.26)	N	N	N	N
Non-Serious	Oral mucosa erosion	59.45(14.18,249.17)	59.45(14.19,249.12)	5.80(-0.21)	55.68(13.28)	N	N	N	Y
Non-Serious	Aphthous ulcer	0.35(0.05, 2.45)	0.35(0.05, 2.45)	-1.53(-3.00)	0.35(0.05)	N	N	N	N
Serious	Palatal ulcer	3.12(0.43, 22.40)	3.12(0.43, 22.40)	1.63(-1.47)	3.10(0.43)	N	N	N	N

Conversely, terms such as Aphthous ulcer failed to meet the signal detection threshold (Figure 10), suggesting a specific pathological spectrum of pembrolizumab-induced mucosal toxicity rather than general ulceration.

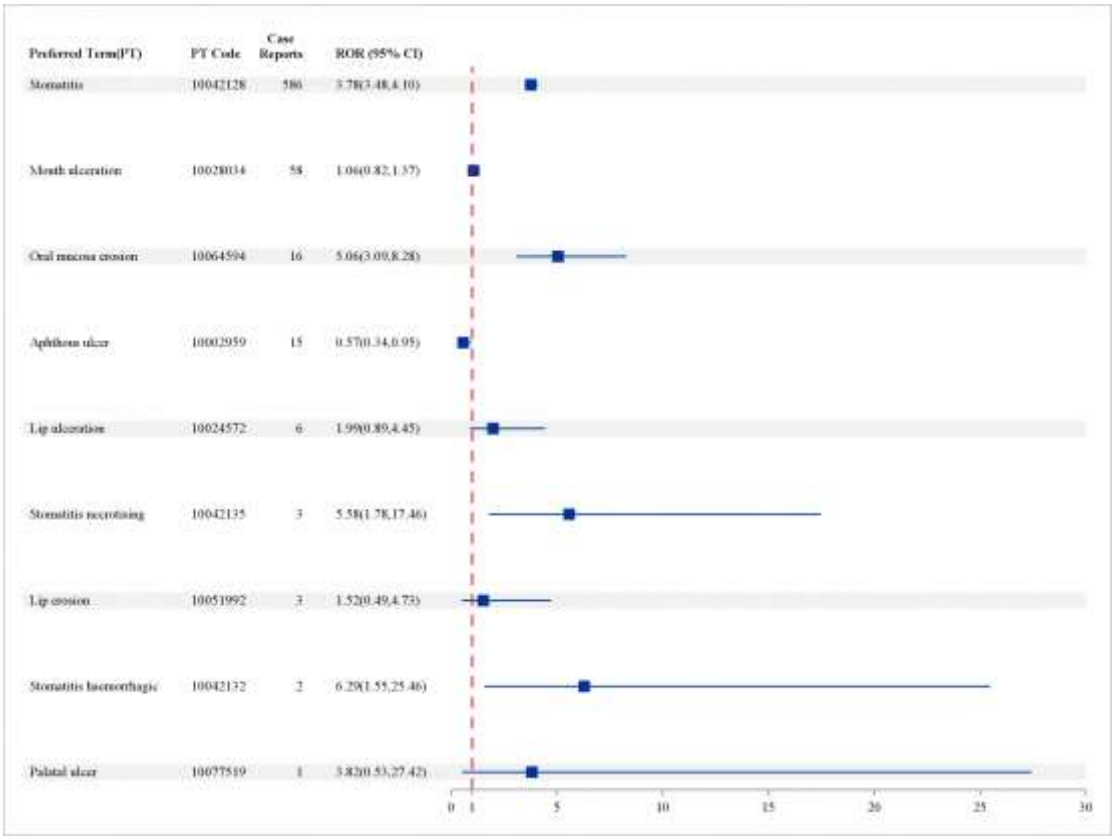
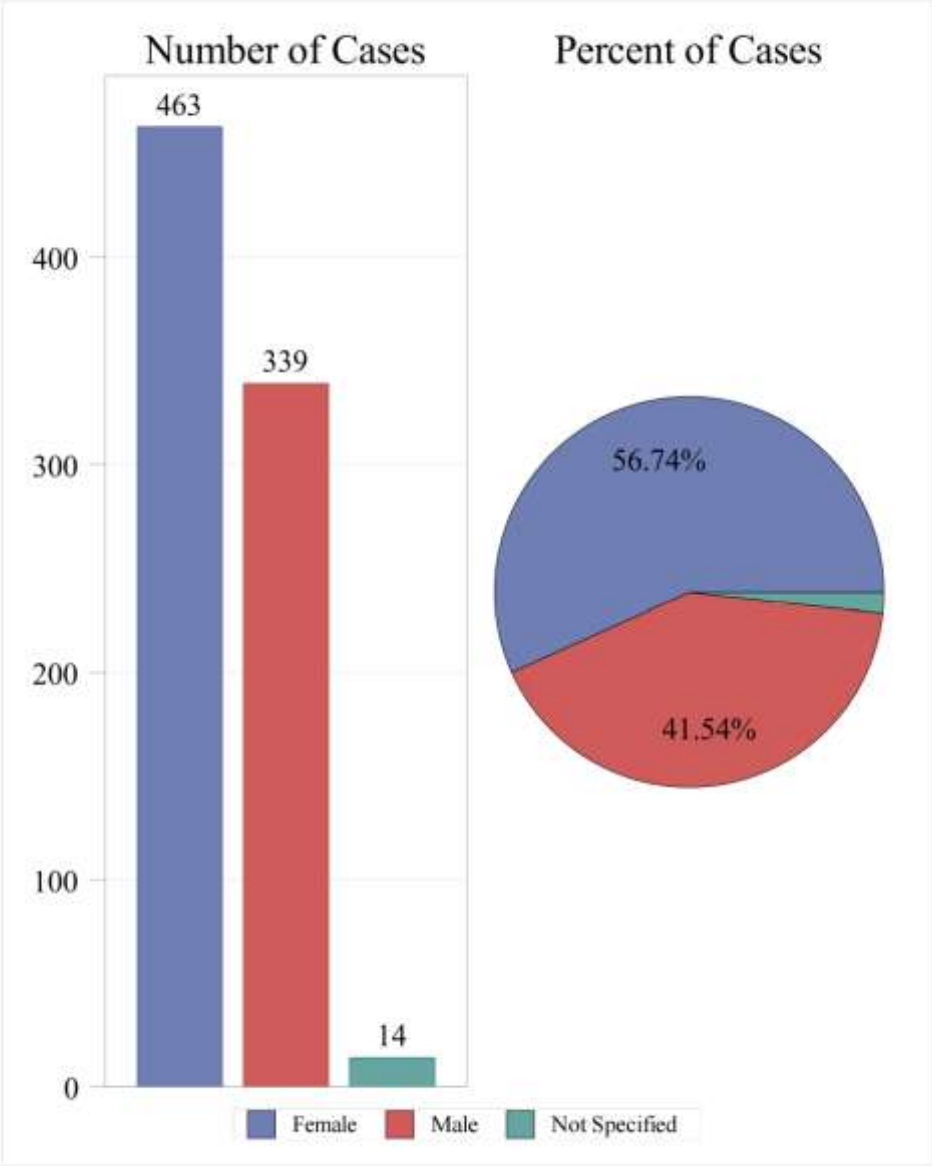


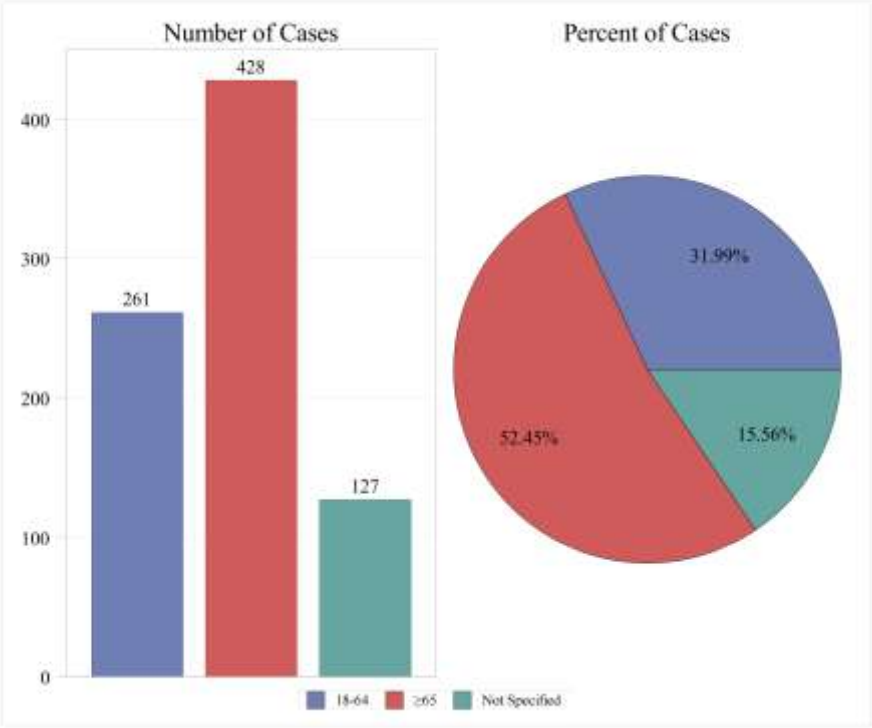
Figure10. The top 50 frequent of PTs(FAERS)

3.3. External Validation of Demographic and Safety Signals in EudraVigilance

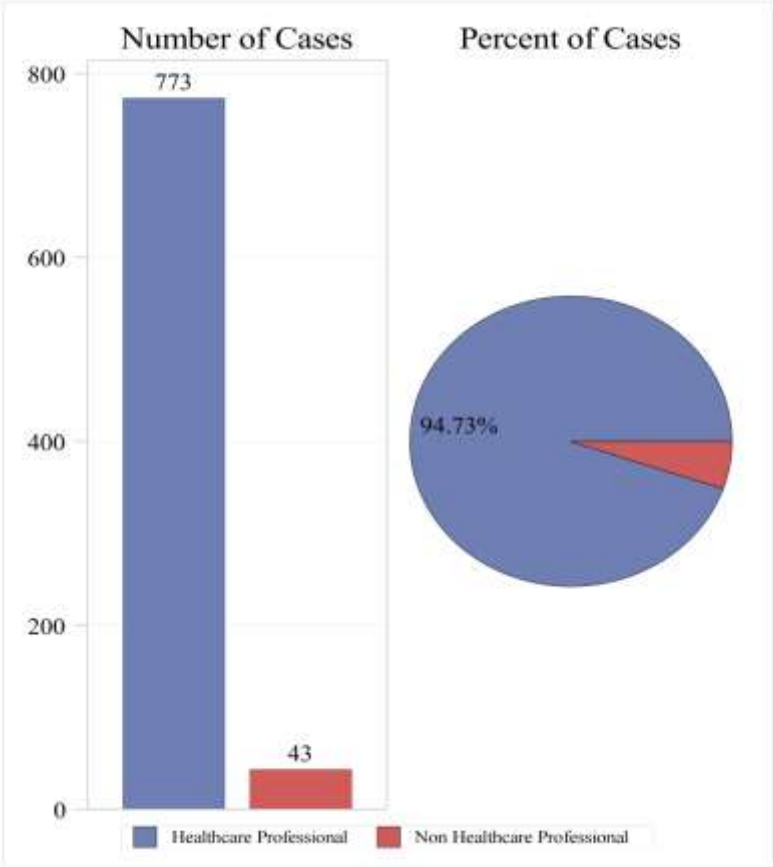
To ensure the robustness of our findings, an external validation was conducted using the EudraVigilance database (n = 816). Consistent with the FAERS findings, a higher proportion of reports involved females (56.74%) (Figure S1), and the elderly population (52.45%) (Figure S2), with the majority of cases (94.73%) , reported by healthcare professionals (Figure S3).



FigureS1. Sex distribution of AE reports(EV)



FigureS2. Age distribution of AE reports(EV)



FigureS3. Reporter distribution of AE reports(EV)

Signal detection in EudraVigilance corroborated the primary analysis: Stomatitis (ROR 3.47, 95% CI: 3.22–3.74) and Oral mucosa erosion (ROR 2.35, 95% CI: 1.56–3.54) emerged as the most consistent and robust signals. While Palatal ulcer and Stomatitis haemorrhagic exhibited high RORs (4.47 and 4.15, respectively), they did not consistently meet the detection thresholds across all four statistical methods. Furthermore, validation confirmed that Mouth ulceration and Aphthous ulcer lacked statistically significant disproportionality, with 95% CI lower limits falling below 1.0(Table S1).

Table S1 Signal Detection Results Across MedDRA Hierarchical Levels(EV)

PT	ROR(95% CI)	PRR(95% CI)	IC(IC025)	EBGM(EBGM05)	ROR Signal	PRR Signal	IC Signal	EBGM Signal
Stomatitis	3.47(3.22, 3.74)	3.46(3.21, 3.73)	1.78(1.66)	3.43(3.18)	Y	Y	Y	Y
Mouth ulceration	0.86(0.67, 1.10)	0.86(0.67, 1.10)	-0.22(-0.58)	0.86(0.67)	N	N	N	N
Aphthous ulcer	0.58(0.40, 0.83)	0.58(0.40, 0.83)	-0.79(-1.31)	0.58(0.40)	N	N	N	N
Oral mucosa erosion	2.35(1.56, 3.54)	2.35(1.56, 3.54)	1.23(0.55)	2.34(1.55)	Y	Y	Y	N
Lip ulceration	1.40(0.67, 2.94)	1.40(0.67, 2.94)	0.48(-0.61)	1.40(0.67)	N	N	N	N
Lip erosion	1.13(0.54, 2.37)	1.13(0.54, 2.37)	0.18(-0.87)	1.13(0.54)	N	N	N	N
Stomatitis necrotising	2.77(0.89, 8.64)	2.77(0.89, 8.64)	1.46(-0.52)	2.75(0.88)	N	N	N	N
Stomatitis haemorrhagic	4.15(1.03, 16.78)	4.15(1.03, 16.78)	2.04(-0.68)	4.10(1.01)	N	N	N	N
Palatal ulcer	4.47(1.11, 18.10)	4.47(1.11, 18.10)	2.14(-0.64)	4.41(1.09)	N	N	N	N

3.4. Subgroup Vulnerability and Clinical Outcome Associations

Subgroup analyses based on gender and age were performed to identify high-risk populations. In both databases, a significant gender-based disparity was observed for Stomatitis, with female patients exhibiting a higher reporting preference than males (EudraVigilance: $\log_2$ROR = 0.502, FDR_P < 0.001; FAERS: $\log_2$ROR = 0.53, FDR = 0.0015) (Table 5,S2).

Table 5 Analysis of Sex-related Differences (Group1: Female; Group2: Male) (FAERS)

PT	P value	FDR_Pvalue
Stomatitis	<.0001	0.001464541
Mouth ulceration	0.1636	0.968121758
Oral mucosa erosion	0.5933	1
Aphthous ulcer	0.4582	0.968121758
Lip ulceration	1.0000	1
Stomatitis necrotising	0.9883	1
Lip erosion	0.9883	1
Stomatitis haemorrhagic	1.0000	1
Palatal ulcer	0.4958	0.968121758

Table S2 Analysis of Sex-related Differences (Group1: Female; Group2: Male) (EV)

PT	P value	FDR_Pvalue
Stomatitis	<.0001	0.000669765
Mouth ulceration	0.3052	1
Aphthous ulcer	0.4460	1
Oral mucosa erosion	0.5279	1
Lip ulceration	1.0000	1
Lip erosion	0.4515	1
Stomatitis necrotising	1.0000	1
Stomatitis haemorrhagic	1.0000	1
Palatal ulcer	0.5000	1

In contrast, age-based analysis revealed no statistically significant differences between patients aged <65 and ≥65 years after False Discovery Rate (FDR) correction FDR_P > 0.05), indicating that age may not be a primary determinant for these toxicities (Table 6).

Table 6 Analysis of Age-related Differences (Group 1: < 65 years; Group 2: ≥ 65 years) (FAERS)

PT	P value	FDR_Pvalue
Stomatitis	0.3957	0.996467495
Mouth ulceration	0.0794	0.996467495
Oral mucosa erosion	0.1334	0.996467495
Aphthous ulcer	0.4144	0.996467495
Lip ulceration	0.6882	1
Stomatitis necrotising	1.0000	1
Lip erosion	0.7559	1
Stomatitis haemorrhagic	1.0000	1
Palatal ulcer	0.4117	0.996467495

Notably, association analysis with clinical outcomes demonstrated that Stomatitis was significantly correlated with non-fatal cases ($P < 0.0001$, $\log_2ROR = -1.41$) (Table 7), suggesting that while pembrolizumab-induced stomatitis is more frequent in women, it generally follows a non-lethal clinical trajectory.

Table 7 Analysis of Differences Based on Fatal Outcomes (Group 1: Fatal; Group 2: Non-Fatal) (FAERS)

PT	P value	FDR_Pvalue
Stomatitis	<.0001	2.58123E-10
Mouth ulceration	0.0090	0.149404034
Oral mucosa erosion	0.6090	1
Aphthous ulcer	0.6922	1
Lip ulceration	0.4514	1
Stomatitis necrotising	1.0000	1
Lip erosion	0.5035	1
Stomatitis haemorrhagic	1.0000	1
Palatal ulcer	1.0000	1

4. Discussion

The clinical integration of pembrolizumab, a programmed cell death protein 1 (PD-1) inhibitor, has revolutionized the treatment landscape of

various malignancies. However, its immune-related adverse events (irAEs) pose significant challenges to patient quality of life and treatment continuity11. This study provides a comprehensive pharmacovigilance analysis of pembrolizumab-associated oral mucositis (OM) using the FAERS and EudraVigilance databases. Our findings reveal a consistent upward trend in reporting, a distinct female predominance, and a specific pathological spectrum that differentiates pembrolizumab-induced mucosal toxicity from general oral ulceration12.

The steady increase in OM reports from 2014 to 2025 aligns with the expanding indications for pembrolizumab. However, the peak in 2024 likely reflects not only increased drug utilization but also improved clinician awareness of dermatologic and mucosal irAEs13. Interestingly, while 78.94% of cases were classified as "serious," this may represent a reporting bias inherent in spontaneous reporting systems (SRSs), where mild (Grade 1-2) mucositis often goes unreported14. The median TTO of 12.5 days suggests that OM is an early-onset irAE, appearing significantly sooner than other systemic irAEs such as pneumonitis or colitis, which typically manifest after 2-3 months of therapy. This early window suggests a direct inflammatory response in the oral epithelium following the initial disruption of immune tolerance15.

One of the most striking findings in our analysis is the significant female predominance (log2ROR = 0.53 in FAERS) for stomatitis. This gender disparity in irAEs is increasingly recognized but poorly understood16. Immunologically, females often mount more robust innate and adaptive immune responses than males, partly due to the stimulatory effects of estrogen on TLR pathways and the presence of immune-related genes on the X chromosome (e.g., TLR7, FOXP3)17. Our data suggests that the female oral mucosa may be more sensitive to the "unleashed" T-cell activity induced by PD-1 blockade. Despite this higher frequency, the association of stomatitis with non-fatal outcomes suggests that while females are more susceptible, the severity is often manageable through dose interruptions or topical corticosteroids18.

Our disproportionality analysis identified "Stomatitis" and "Oral mucosa erosion" as robust signals, whereas "Aphthous ulcer" failed to reach significance. This distinction is clinically vital. Unlike idiopathic aphthous ulcers, pembrolizumab-induced OM represents a T-cell mediated attack on basal keratinocytes, mimicking the histology of lichenoid mucositis. The high signal intensity of "Stomatitis haemorrhagic" (ROR 6.29) particularly in younger cohorts (18-44 years) is a novel observation. This could be attributed to a more vigorous immune microenvironment in younger patients or potential synergistic toxicity with other concurrent treatments like radiotherapy or cytotoxic chemotherapy, which are frequently used in younger patients with aggressive disease19.

The lack of significant difference in TTO between genders (P=0.6985) indicates that the biological clock of immune activation is independent of sex, even if the magnitude of the response differs. For clinicians, the concentration of events within the first 30 days necessitates proactive oral screening during the first two cycles of pembrolizumab20. Given that 41.38% of reported cases led to hospitalization, early intervention with topical dexamethasone or high-potency steroid rinses is essential to prevent secondary infections and nutritional compromise, which are the primary drivers of hospitalization in OM patients20.

5. Limitations

Despite the robustness of the dual-database validation, several limitations inherent to spontaneous reporting systems (SRSs) must be acknowledged. First, the FAERS and EudraVigilance databases are subject to under-

reporting and reporting bias, particularly for mild (Grade 1-2) toxicities, which may lead to an overestimation of clinical severity. Second, as a retrospective analysis of spontaneous reports, we lack granular clinical details, such as PD-L1 expression levels, specific pembrolizumab dosages, tumor staging, and the use of concomitant medications that might influence mucosal health. Third, while disproportionality analysis indicates a strong statistical association, it cannot definitively establish a causal relationship or calculate absolute incidence rates. Finally, although we observed a striking gender disparity, the underlying biological mechanisms—potentially involving hormonal modulation or X-linked immune gene expression—remain speculative and necessitate further investigation through prospective translational studies.

6. Conclusion

In conclusion, this large-scale, dual-database pharmacovigilance study provides robust evidence for the association between pembrolizumab and oral mucositis (OM), characterized by a distinct pathological spectrum of erosive and hemorrhagic stomatitis. Our findings highlight a significant female predominance and an early-onset temporal pattern (median TTO: 12.5 days), with the majority of events manifesting within the first month of therapy. These results suggest that female and elderly patients may represent high-risk subpopulations requiring intensive oral health surveillance. For clinicians, the first 30 days of pembrolizumab treatment constitute a critical window for proactive screening; early intervention with topical corticosteroids could potentially mitigate the high hospitalization rates associated with this irAE, thereby optimizing patient quality of life and treatment adherence.

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Authors' Contributions: Ung Rattanaricky and IV NORA collected, analyzed, and interpreted the data, wrote the manuscript. Yuan Liang and Pengkhun Nov designed, revised, and supervised the study. All authors had reviewed and approved the final manuscript.

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References

1. Xu Y, Liu Y, Han H, He Z, Cao W. The predictive value of the neutrophil/eosinophil ratio in cancer patients undergoing immune checkpoint inhibition: a meta-analysis and a validation cohort in hepatocellular carcinoma. Front Immunol. 2025 Jul 21;16:1633034. doi: 10.3389/fimmu.2025.1633034. PMID:40761780; PMCID: PMC12318750.
2. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, Powderly JD, Carvajal RD, Sosman JA, Atkins MB, Leming PD, Spigel DR, Antonia SJ, Horn L, Drake CG, Pardoll DM, Chen L, Sharfman WH, Anders RA, Taube JM, McMiller TL, Xu H, Korman AJ, Jure-Kunkel M, Agrawal S, McDonald D, Kollia GD, Gupta A, Wigginton JM, Sznol M. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012 Jun 28;366(26):2443-54. doi: 10.1056/NEJMoa1200690. Epub 2012 Jun 2. PMID: 22658127; PMCID: PMC3 54 4539.
3. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, Daud A, Carlino MS,

McNeil C, Lotem M, Larkin J, Lorigan P, Neyns B, Blank CU, Hamid O, Mateus C, Shapira-Frommer R, Kosh M, Zhou H, Ibrahim N, Ebbinghaus S, Ribas A; KEYNOTE-006 investigators. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med. 2015 Jun 25;372 (26):2521-32. doi: 10.1056/NEJMoa1503093. Epub 2015 Apr 19. PMID: 25891173.

4. Wang CQ, Choy FC, Sanny A, Murakami T, Tan AH, Lam KP. An Inhibitory Role for Human CD96 Endodomain in T Cell Anti-Tumor Responses. Cells. 2023 Jan 13;12(2): 309. doi: 10.3390/cells12020309. PMID: 36672244; PMCID: PMC9856660.
5. Deng S, Yang Q, Shu X, Lang J, Lu S. The Relative Risk of Immune-Related Liver Dysfunction of PD-1/PD-L1 Inhibitors Versus Chemotherapy in Solid Tumors: A Meta-Analysis of Randomized Controlled Trials. Front Pharmacol. 2019 Sep 23;10:1063. doi: 10.3389/fphar.2019.01063. PMID: 31607917; PMCID: PMC6767975.
6. Basile D, Di Nardo P, Corvaja C, Garattini SK, Pelizzari G, Lisanti C, Bortot L, Da Ros L, Bartoletti M, Borghi M, Gerratana L, Lombardi D, Puglisi F. Mucosal Injury during Anti-Cancer Treatment: From Pathobiology to Bedside. Cancers (Basel). 2019 Jun 20;11(6): 857. doi:10.3390/cancers11060857. PMID: 31226812; PMCID: PMC6627284.
7. Jacob JS, Dutra BE, Garcia-Rodriguez V, Panneerselvam K, Abraham FO, Zou F, Ma W, Grivas P, Thompson JA, Altan M, Oliva ICG, Zhang HC, Thomas AS, Wang Y. Clinical Characteristics and Outcomes of Oral Mucositis Associated With Immune Checkpoint Inhibitors in Patients With Cancer. J Natl Compr Canc Netw. 2021 Aug 4;19(12):1415-1424. doi: 10.6004/jnccn.2020.7697. PMID: 34348238.
8. Vigarios E, Epstein JB, Sibaud V. Oral mucosal changes induced by anticancer targeted therapies and immune checkpoint inhibitors. Support Care Cancer. 2017 May; 25(5):1713-1739. doi: 10.1007/s00520-017-3629-4. Epub 2017 Feb 22. PMID: 28224235.
9. Elad S, Cheng KKF, Lalla RV, Yarom N, Hong C, Logan RM, Bowen J, Gibson R, Saunders DP, Zadik Y, Ariyawardana A, Correa ME, Ranna V, Bossi P; Mucositis Guidelines Leadership Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO). MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer. 2020 Oct 1;126(19):4423-4431. doi: 10.1002/cncr.33100. Epub 2020 Jul 28. Erratum in: Cancer. 2021 Oct 1;127 (19): 3700. doi: 10.1002/cncr.33549. PMID: 32786044; PMCID: PMC7540329.
10. Canzian J, Conforti F, Jacobs F, Benvenuti C, Gaudio M, Gerosa R, De Sanctis R, Zambelli A. Sex-Related Differences in Immunotherapy Toxicities: Insights into Dimorphic Responses. Cancers (Basel). 2025 Mar 21;17 (7):1054. doi: 10.3390/cancers17071054. PMID: 40227458; PMCID: PMC11987764.
11. Song J, Xu B, Yu L, Fu H, Wang B, Zhou M, Hu Y, Xia Y. Bimodal onset and pan-cancer uniformity of immune-mediated liver injury: a retrospective cohort study. Front Immunol. 2025 Jul 2;16:1612287. doi: 10.3389/fimmu.2025.1612287. PMID: 40672949; PMCID: PMC12263589.
12. Vilar CJF, Ribeiro SB, de Araújo AA, Guerra GCB, de Araújo Júnior RF, Brito GAC, Leitão RFC, Pontes DL, Gasparotto LHDS, Oliveira MMB, Viana AD, de Medeiros WMTQ, Bezerra BGP, de Medeiros CACX. Effect of Gold Nanoparticle on 5-Fluorouracil-Induced Experimental Oral Mucositis in Hamsters. Pharmaceutics. 2020 Mar 27;12(4):304. doi:10.3390/pharmaceutics12040304. PMID: 32230975; PMCID: PMC7238277.
13. McCotter OZ, Benedict K, Engelthaler DM,

Komatsu K, Lucas KD, Mohle-Boetani JC, Oltean H, Vugia D, Chiller TM, Sondermeyer Cooksey GL, Nguyen A, Roe CC, Wheeler C, Sunenshine R. Update on the Epidemiology of coccidioidomycosis in the United States. Med Mycol. 2019 Feb 1;57(Supplement_1):S30-S40. doi: 10.1093/mmy/myy095. PMID: 30690599; PMCID: PMC6823633.

14. Gonzalez-Hernandez G, Krallinger M, Muñoz M, Rodriguez-Esteban R, Uzuner Ö, Hirschman L. Challenges and opportunities for mining adverse drug reactions: perspectives from pharma, regulatory agencies, healthcare providers and consumers. Database (Oxford). 2022 Sep 2;2022:baac071. doi: 10.1093/database/baac071. PMID: 36050787; PMCID: PMC9436770.
15. Ma Y, Ma X, Wang J, Wu S, Wang J, Cao B. Absolute eosinophil count may be an optimal peripheral blood marker to identify the risk of immune-related adverse events in advanced malignant tumors treated with PD-1/PD-L1 inhibitors: a retrospective analysis. World J Surg Oncol. 2022 Jul 28;20(1):242. doi: 10.1186/s12957-022-02695-y. PMID: 35897018; PMCID: PMC9331074.
16. O'Connell TJ, Dadafarin S, Jones M, Rodríguez T, Gupta A, Shin E, Moscatello A, Iacob C, Islam H, Tiwari RK, Geliebter J. Androgen Activity Is Associated With PD-L1 Downregulation in Thyroid Cancer. Front Cell Dev Biol. 2021 Aug 6;9:663130. doi: 10.3389/fcell.2021.663130. PMID: 34422798; PMCID: PMC8377372.
17. Hammad MO, Alseoudy MM. The sex-related discrepancy in laboratory parameters of severe COVID-19 patients with diabetes: A retrospective cohort study. Prim Care Diabetes. 2021 Aug;15(4):713-718. doi: 10.1016/j.pcd.2021.05.002. Epub 2021 May 12. PMID: 34006475; PMCID: PMC8114673.
18. Ishida Y. PD-1: Its Discovery, Involvement in Cancer Immunotherapy, and Beyond. Cells. 2020 Jun 1;9(6):1376. doi:10.3390/cells9061376. PMID: 32492969; PMCID: PMC7349669.
19. Short NJ, Kantarjian H. Choosing between intensive and less intensive front-line treatment approaches for older patients with newly diagnosed acute myeloid leukaemia. Lancet Haematol. 2022 Jul;9(7):e535-e545. doi: 10.1016/S2352-3026(22)00167-3. PMID: 35772432.
20. Carlone S, Minenna M, Morlino P, Mosca L, Pasqua F, Pela R, Schino P, Tubaldi A, Tupputi E, De Benedetto F; Buccalin Trial Group. Clinical efficacy and tolerability of an immune-stimulant(*) constituted by inactivated bacterial bodies in the prophylaxis of infectious episodes of airways: a double blind, placebo-controlled, randomized, multicentre study. Multidiscip Respir Med. 2014 Nov 19;9(1):58. doi: 10.1186/2049-6958-9-58. PMID: 25699178; PMCID: PMC4334598.
21. Wang WY, Shenoy VS, Fong CT, Walters AM, Sekhar L, Curatolo M, Vavilala MS, Lele AV. The Prevalence and Factors Associated with the Prescription of Opioids for Head/Neck Pain after Elective Craniotomy for Tumor Resection/Vascular Repair: A Retrospective Cohort Study. Medicina (Kaunas). 2022 Dec 23;59(1):28. doi: 10.3390/medicina59010028. PMID: 36676652; PMCID: PMC9864119.