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Original Article

Global Characterization of Fluorouracil-Induced Oral Mucositis: A Disproportionality Analysis and Signal Detection Study using Faers and Eudravigilance Databases

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Abstract:

Background: Oral mucositis (OM) is a debilitating dose-limiting toxicity of fluorouracil (5-FU) chemotherapy. Despite its clinical prevalence, large-scale real-world evidence characterizing its onset, demographic risk factors, and signal strength across global populations remains limited. This study aims to evaluate the safety profile of 5-FU-related OM using two major spontaneous reporting databases.

Methods: We conducted a retrospective pharmacovigilance analysis using the FDA Adverse Event Reporting System (FAERS) and EudraVigilance (EV) databases (2004–2025). Disproportionality was assessed using four algorithms: Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Information Component (IC), and Empirical Bayes Geometric Mean (EBGM). Time-to-onset (TTO) and subgroup analyses by age and sex were performed to identify clinical risk modifiers.

Results: In the FAERS database, 512 reports of 5-FU-related OM were identified, with peaks in 2013 and 2019. The majority of cases involved geriatric patients (≥65 years, 40.23%) and were classified as serious adverse events (95.51%). The median TTO was 13.50 days (IQR: 6.00–36.00), with 68.06% of events occurring within the first 30 days. Strong signals were detected for "Stomatitis" (ROR: 7.02) and "Hemorrhagic stomatitis" (ROR: 15.34). Parallel analysis in EudraVigilance (N = 1,107) corroborated these findings, highlighting significant associations for "Mucosal erosion" and "Aphthous ulcer" specifically in the elderly population.

Conclusion: Our findings confirm that 5-FU-induced oral mucosal toxicity is a high-severity event with a distinct early-onset pattern. Elderly patients represent the highest risk group. Proactive oral care and monitoring are critical during the first month of therapy, particularly around the second week post-administration.

Keywords: Fluorouracil; Oral mucositis; Pharmacovigilance; FAERS; EudraVigilance; Signal detection; Stomatitis.

Introduction

Fluorouracil (5-FU), a pyrimidine analog antimetabolite, remains a fundamental component of chemotherapy regimens for a broad spectrum

of malignancies, including gastrointestinal, breast, and head and neck cancers12. By inhibiting thymidylate synthase and incorporating fraudulent bases into RNA and DNA, 5-FU effectively disrupts the proliferation of malignant cells34. However, its cytotoxic mechanism is non-selective, frequently targeting rapidly dividing normal tissues, with the oral mucosa being one of the most vulnerable sites5.

Oral mucositis (OM) is a common and severe adverse effect of 5-FU therapy, characterized by erythema, edema, and painful ulcerative lesions67. Beyond the immediate physical distress, severe OM can lead to significant clinical complications, including malnutrition, systemic infections (particularly in neutropenic patients), and the necessity for opioid analgesia8. Furthermore, high-grade OM often compels clinicians to implement dose reductions or treatment interruptions, potentially compromising the overall survival and oncological outcomes of the patient9.

While the pathophysiology of 5-FU-induced mucosal damage, progressing from initial oxidative stress to the final ulcerative and healing phases, is well-documented in clinical models, real-world data regarding its onset and demographic distribution are often fragmented. Clinical trials typically operate under controlled conditions with specific inclusion criteria that may not fully represent the heterogeneity of the general patient population, particularly the geriatric cohort.

Large-scale pharmacovigilance databases, such as the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) and the European Medicines Agency's EudraVigilance (EV), provide a unique opportunity to explore drug-event associations in a "real-world" setting10. These platforms allow for the detection of rare but severe signals, the calculation of reporting trends over decades, and the identification of vulnerable subgroups across diverse geographical regions.This study utilizes both FAERS and EV databases (2004–2025) to provide a comprehensive evaluation of 5-FU-related oral mucosal toxicities. By employing multiple disproportionality algorithms and analyzing time-to-onset (TTO) patterns, we aim to refine the safety profile of 5-FU and provide evidence-based recommendations for clinical monitoring and prophylactic intervention.

2. Methods

2.1 Data Acquisition and Research Framework

This study utilized a retrospective pharmacovigilance design to systematically investigate the association between fluorouracil (5-FU) and oral mucositis (OM). Primary data were mined from the United States Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS), spanning the period from the first quarter of 2004 to the final quarter of 2025. To enhance the robustness and global applicability of our findings, we performed a secondary validation using the EudraVigilance (EV) database managed by the European Medicines Agency (EMA). Only reports where fluorouracil was identified as the "primary suspect" or "secondary suspect" drug were included for further processing.

2.2 Case Definition and Categorization

Oral mucosal toxicities were identified using Preferred Terms (PTs) within the Medical Dictionary for Regulatory Activities (MedDRA). Target events included, but were not limited to, "stomatitis," "stomatitis haemorrhagic," "mouth ulceration," and "mucosal erosion." Patient demographics and clinical characteristics—including age, sex, reporter qualification (e.g., pharmacist, physician), and clinical outcomes (e.g., serious vs. non-serious)—were extracted. For subgroup analysis, age was stratified into pediatric (<18 years), adult (18–64 years), and geriatric (≥65 years) cohorts.

2.3 Statistical Methodology

The analytical workflow was structured into three distinct phases to ensure a comprehensive safety evaluation.

2.3.1 Characterization of Baseline Data

Descriptive statistics were employed to summarize the reporting trends and demographic distribution. Qualitative data were expressed as absolute frequencies (N) and percentages (%). The time-to-onset (TTO), representing the interval from the initiation of 5-FU therapy to the clinical manifestation of OM, was analyzed and presented as median values with the interquartile range (IQR).

2.3.2 Signal Detection Algorithms

To quantify the strength of the association between 5-FU and OM, four distinct disproportionality algorithms were applied:Reporting Odds Ratio (ROR)11, Proportional Reporting Ratio (PRR)12, Information Component (IC)13,Empirical Bayes Geometric Mean (EBGM)15.

A statistically significant signal was defined based on the standard thresholds for these indices (e.g., the lower bound of the 95% CI for ROR > 1; PRR ≥ 2; IC025 > 0; EBGM05 > 2). This multi-algorithm approach was used to minimize potential false-positive signals and ensure the stability of the association.

2.3.3 Stratification and Comparative Analysis

Differential analysis was conducted to explore the impact of age and sex on the reporting patterns of OM. We utilized Fisher's exact test to compare the distribution of signals across different subgroups (e.g., geriatric vs. adult; fatal vs. non-fatal cases). To control for the potential inflation of type I error rates resulting from multiple comparisons, P-values were adjusted using the Benjamini-Hochberg False Discovery Rate (FDR) procedure. An adjusted two-sided P-value of less than 0.05 was considered to indicate statistical significance.

3.Result

Descriptive Analysis of Fluorouracil-Related Oral Mucositis (FAERS)

A total of 512 adverse event (AE) reports of fluorouracil-related oral mucositis were identified in the FAERS database from 2004 to 2025. The annual reporting trend exhibited fluctuations, with prominent peaks observed in 2013 (N = 51) and 2019 (N = 57)(**Figure1**).

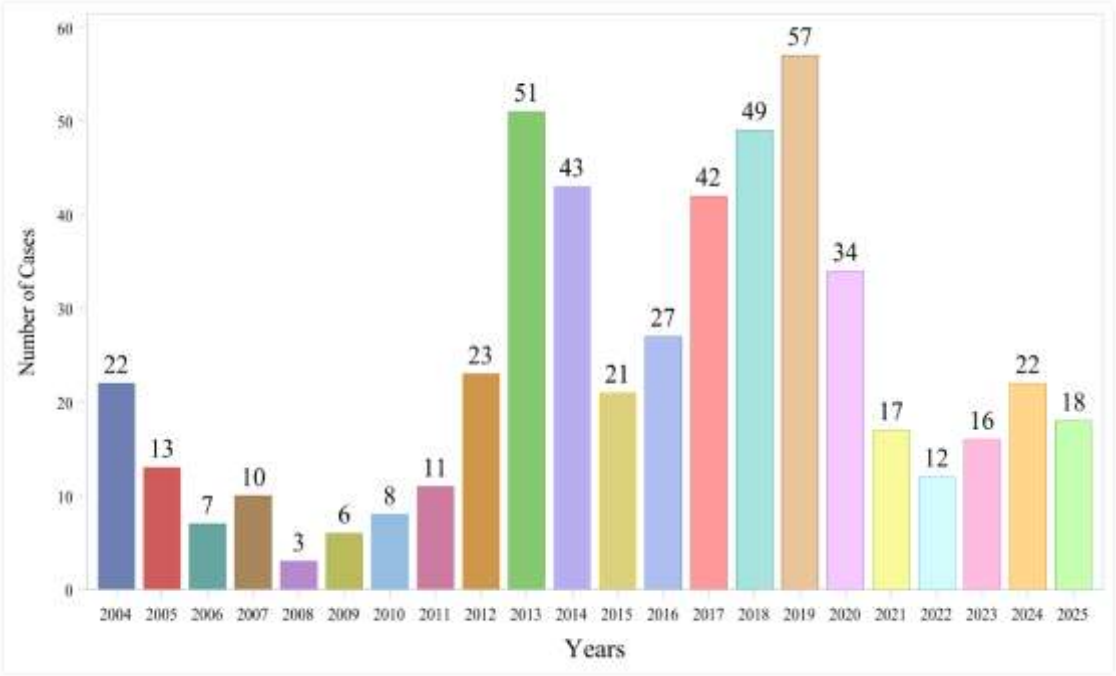


Figure1. Annual distribution of AE reports (FAERS)

Regarding demographic characteristics, these AEs were predominantly concentrated in middle-aged and elderly populations; elderly patients (≥65 **years) accounted for the highest proportion (40.23%), followed by the 45–64 age group (35.74%), while cases in patients under 18 years were extremely rare(Figure2).**

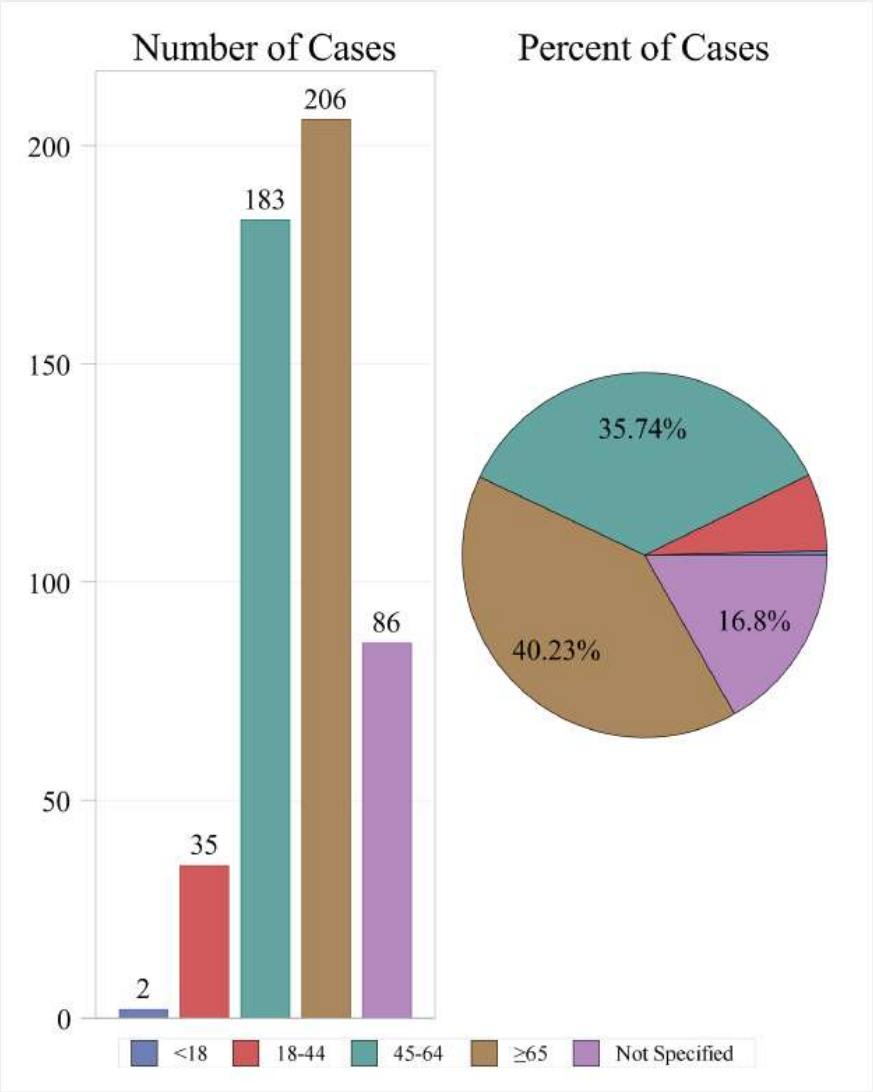


Figure2. Age distribution of AE reports (FAERS)

The primary reporting sources were pharmacists (37.7%), followed by other healthcare professionals (28.91%) and physicians (14.84%) (**Figure3**).

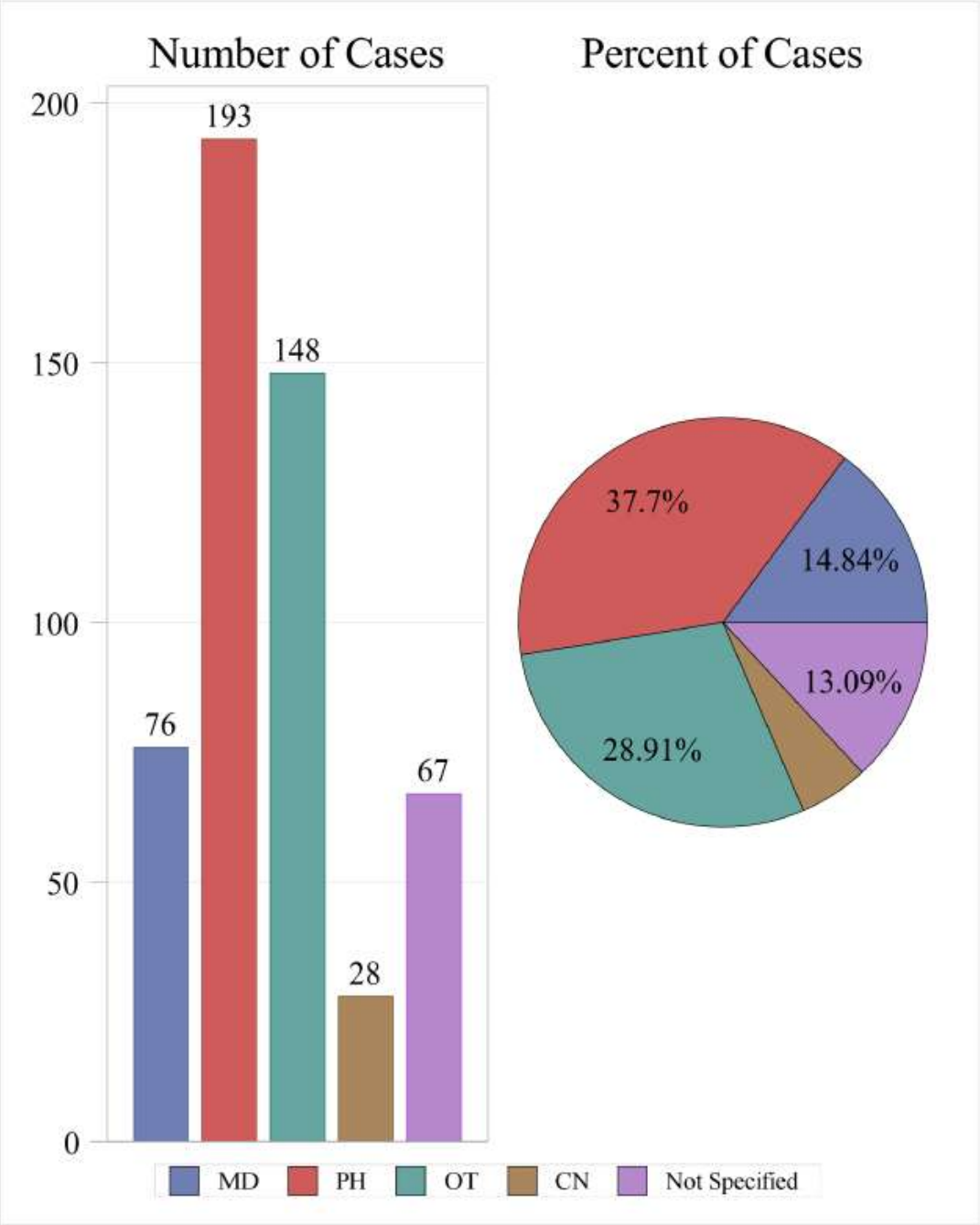


Figure3. Reporter distribution of AE reports (FAERS)

Severity assessment revealed that the vast majority of cases (95.51%) were classified as serious adverse events, indicating high clinical significance (**Figure4**).

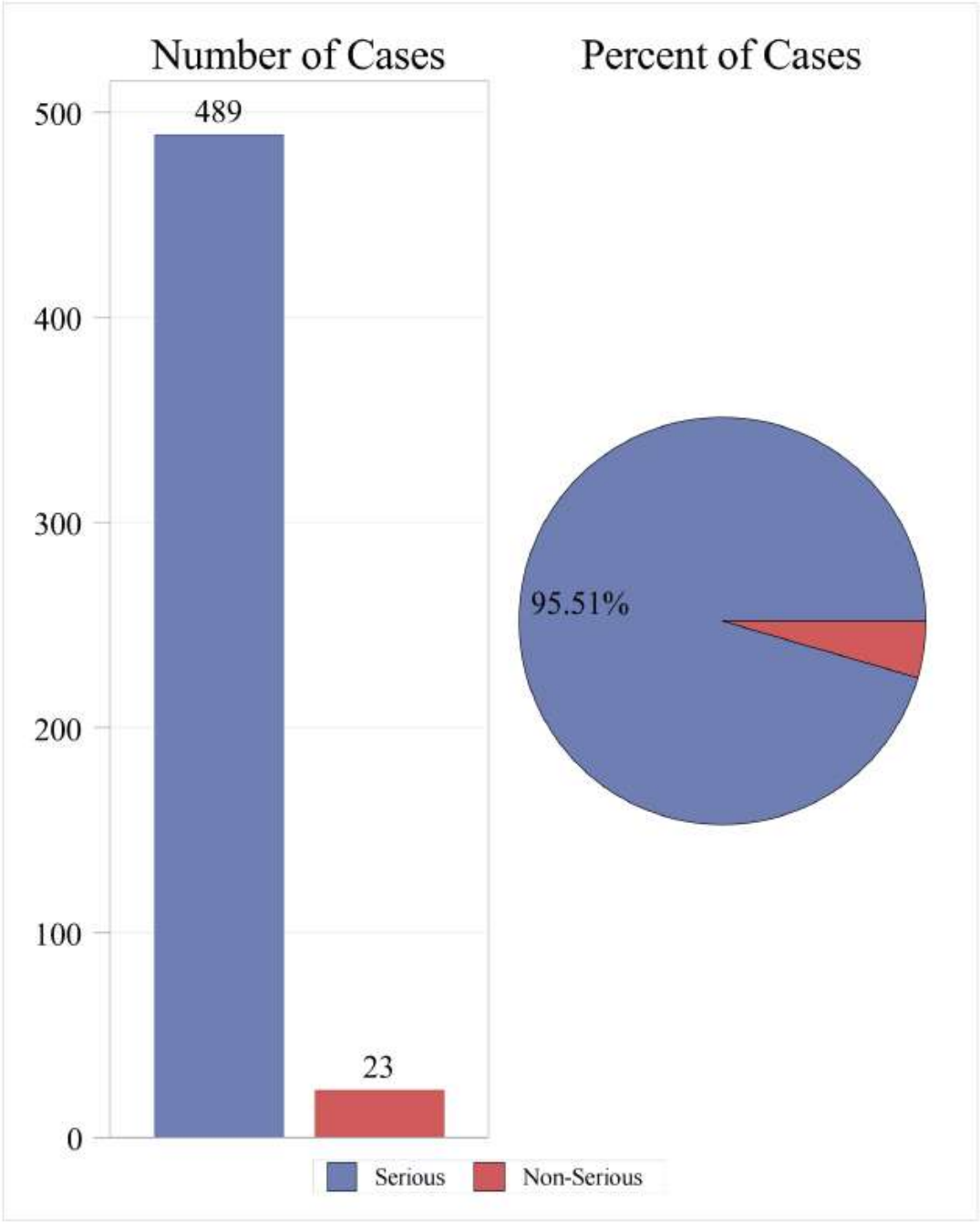


Figure4. Serious Report distribution of AE reports (FAERS)

Time-to-onset (TTO) analysis demonstrated a distinct early-onset pattern, with a median TTO of 13.50 days (IQR: 6.00–36.00) (**Figure5**).

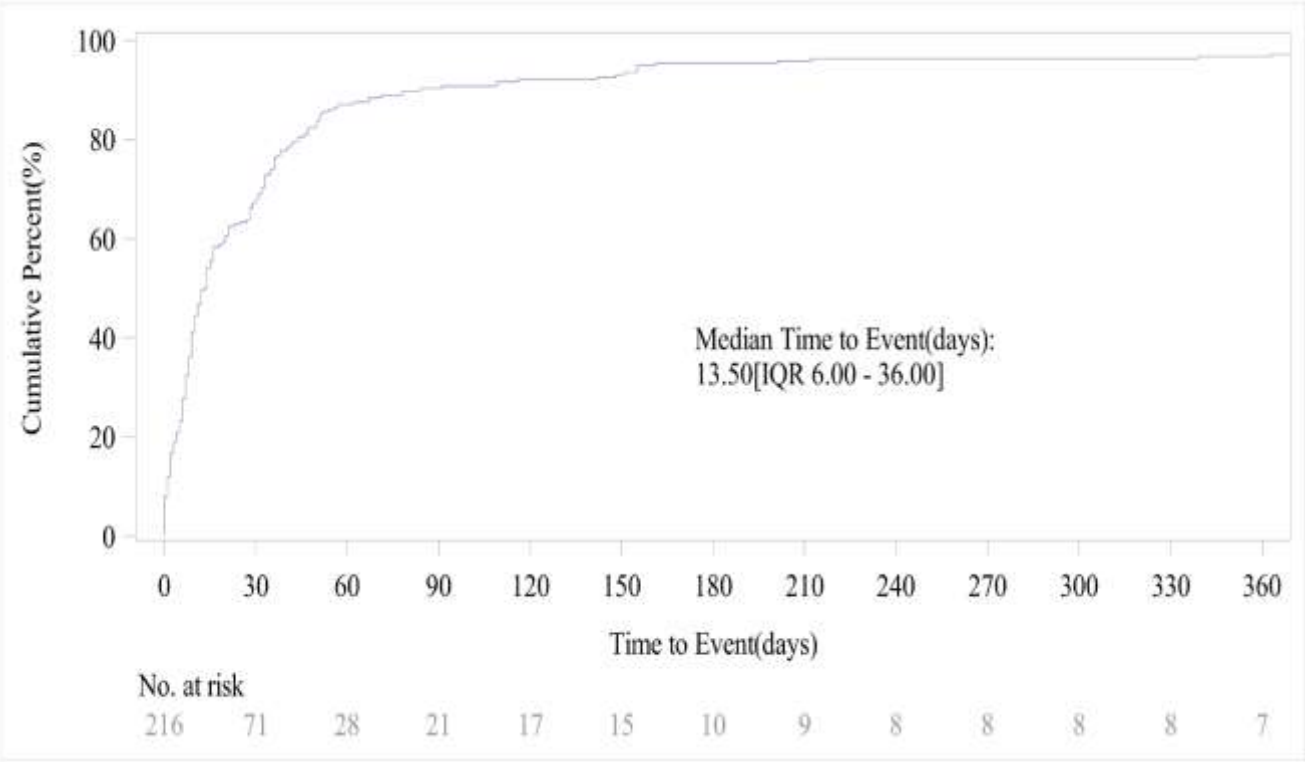


Figure5. Cumulative incidence of adverse events (Kaplan-Meier curve) (FAERS)

Notably, 68.06% of cases occurred within 30 days of drug administration, suggesting that fluorouracil exerts significant acute short-term toxicity on the oral mucosa (**Figure6**).

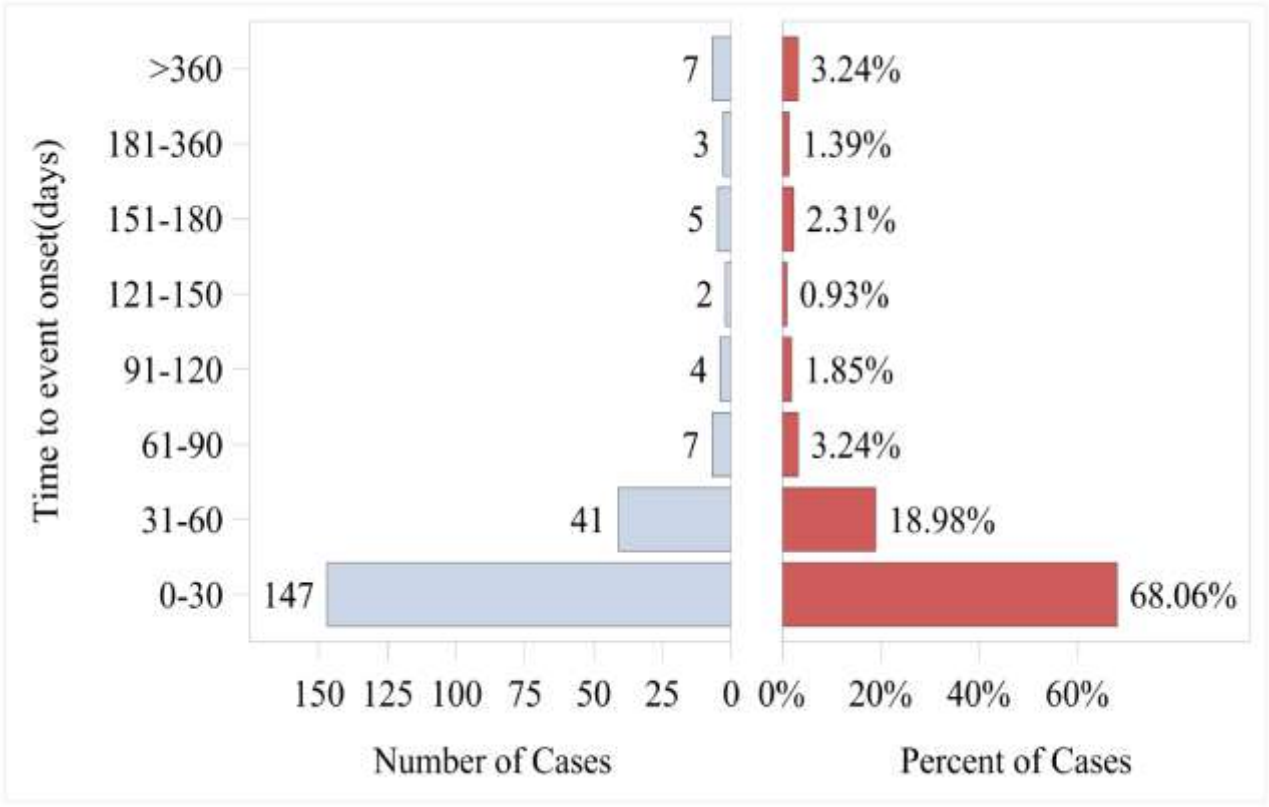


Figure6. Time to event report distribution of AE reports(FAERS)

Disproportionality Analysis and Signal Detection (FAERS)

In this study, multiple algorithms were employed for signal mining of fluorouracil-induced oral mucosal AEs. The analysis revealed that "stomatitis" was a strong positive signal across all detection models, with the highest reporting frequency (N = 446) and a Reporting Odds Ratio (ROR) of 7.02 (95% CI: 6.39–7.70). In contrast, "hemorrhagic stomatitis," despite fewer reported cases, exhibited the highest signal intensity (ROR = 15.34), suggesting a high risk of severe mucosal injury under specific conditions (**Figure7**).

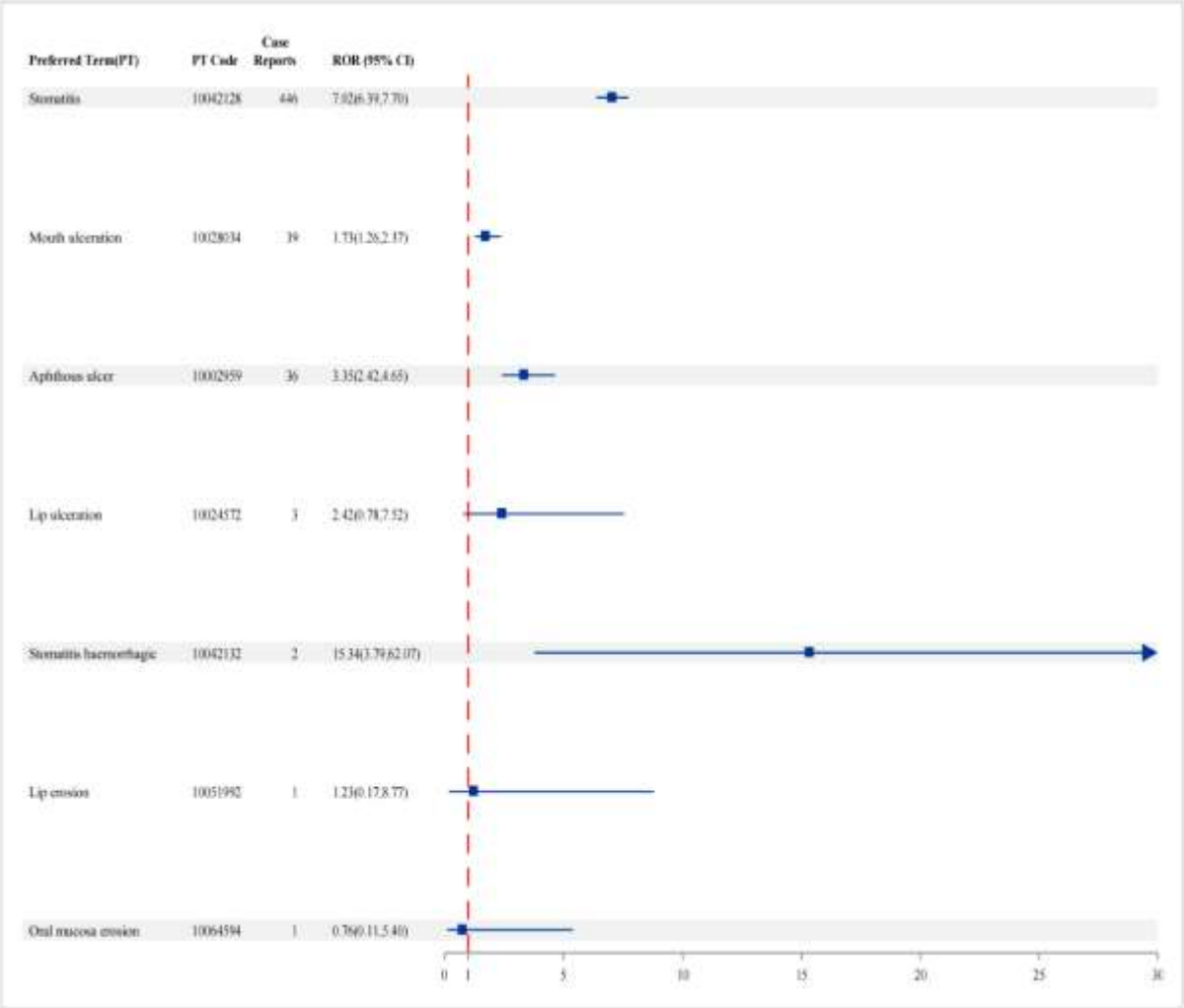


Figure7. Top 50 Preferred Terms (PTs) of Positive Signals Ranked by Frequency (Detected by ROR) (FAERS)

Additionally, "aphthous disease" and "mouth ulceration" showed significant statistical associations. Regarding specific clinical outcomes, "other statistically serious medical events" was the most frequently reported (62.3%), followed by hospitalization (41.02%) (**Figure8**).

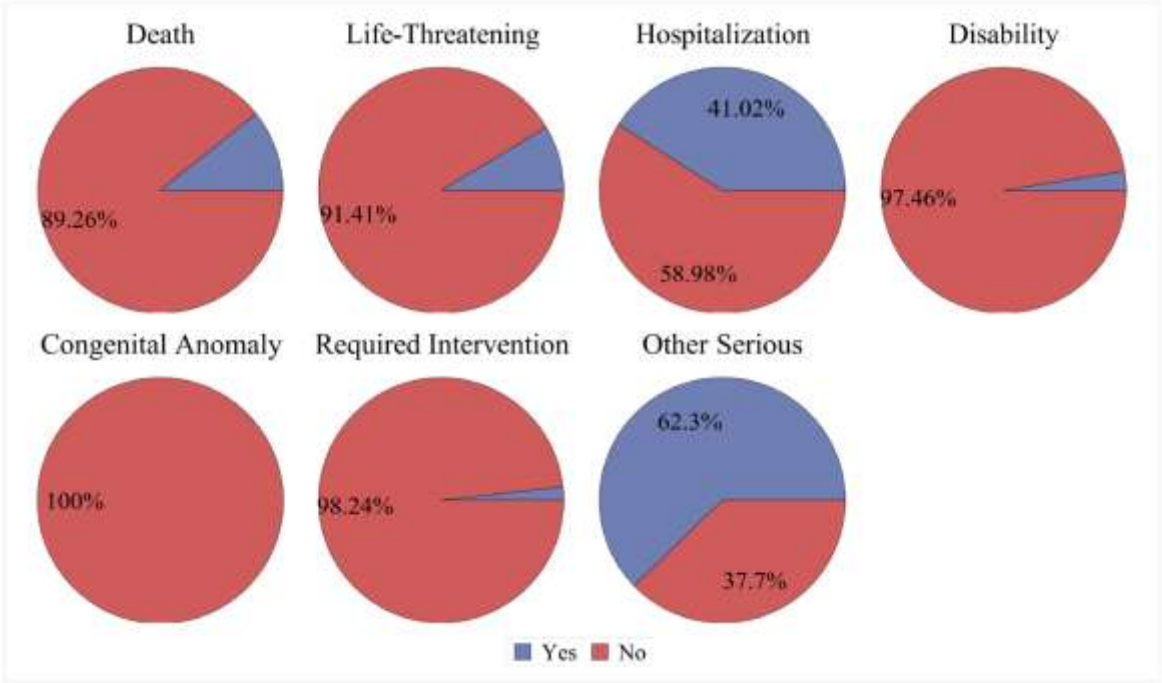


Figure 8. Outcomes report distribution of AE reports(FAERS)

These results confirm a robust and statistically significant association between fluorouracil and oral mucosal injury, regardless of the statistical method applied.

Subgroup Stratification and Differential Analysis (FAERS)

Multidimensional stratification and differential testing further elucidated the specific characteristics of fluorouracil-induced oral injury. Age-stratified analysis indicated that the signal remained positive across all age groups **(Table1)**.

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

PT	ROR(95% CI)	PRR(95% CI)	IC(IC025)	EBGM(EBGM05)	ROR Signal	PRR Signal	IC Signal	EBGM Signal
Stomatitis	6.65(5.73,7.71)	6.61(5.70,7.65)	2.71(2.45)	6.54(5.64)	Y	Y	Y	Y
Stomatitis	6.44(5.50,7.54)	6.40(5.47,7.49)	2.66(2.39)	6.34(5.42)	Y	Y	Y	Y
Stomatitis	6.46(5.17,8.06)	6.43(5.16,8.01)	2.68(2.26)	6.40(5.13)	Y	Y	Y	Y
Stomatitis	8.00(5.58,11.47)	7.96(5.57,11.38)	2.99(2.17)	7.93(5.53)	Y	Y	Y	Y
Aphthous ulcer	5.65(3.60,8.88)	5.65(3.60,8.87)	2.49(1.54)	5.60(3.56)	Y	Y	Y	Y
Aphthous ulcer	3.40(2.05,5.65)	3.40(2.05,5.65)	1.76(0.83)	3.39(2.04)	Y	Y	Y	Y
Mouth ulceration	1.36(0.79,2.35)	1.36(0.79,2.35)	0.45(-0.36)	1.36(0.79)	N	N	N	N
Mouth ulceration	1.35(0.75,2.44)	1.35(0.75,2.44)	0.43(-0.44)	1.35(0.75)	N	N	N	N

Mouth ulceration	2.07(1.03,4.14)	2.07(1.03,4.14)	1.05(-0.08)	2.07(1.03)	Y	Y	N	N
Mouth ulceration	3.35(1.50,7.46)	3.35(1.50,7.45)	1.74(0.23)	3.34(1.50)	Y	Y	Y	N
Lip ulceration	5.93(1.90,18.49)	5.93(1.90,18.49)	2.56(-0.05)	5.88(1.89)	Y	Y	N	N
Aphthous ulcer	1.11(0.16,7.91)	1.11(0.16,7.91)	0.16(-1.97)	1.11(0.16)	N	N	N	N
Aphthous ulcer	0.50(0.07,3.53)	0.50(0.07,3.53)	-1.01(-2.63)	0.50(0.07)	N	N	N	N
Mouth ulceration	4.28(0.60,30.44)	4.27(0.60,30.32)	2.09(-1.35)	4.27(0.60)	N	N	N	N
Stomatitis	1.78(0.25,12.63)	1.77(0.25,12.59)	0.83(-1.69)	1.77(0.25)	N	N	N	N
Stomatitis haemorrhagic	18.81(2.57,137.77)	18.81(2.57,137.75)	4.19(-1.18)	18.25(2.49)	N	N	N	Y
Stomatitis haemorrhagic	11.31(1.56,81.94)	11.31(1.56,81.93)	3.47(-1.21)	11.10(1.53)	N	N	N	N
Lip erosion	12.49(1.74,89.39)	12.48(1.74,89.37)	3.63(-1.17)	12.39(1.73)	N	N	N	N
Oral mucosa erosion	6.43(0.90,45.81)	6.43(0.90,45.78)	2.68(-1.26)	6.41(0.90)	N	N	N	N

Sex-stratified analysis showed no significant difference in median TTO between females (14.00 days) and males (11.00 days) (P = 0.9251)**(Figure9)**, suggesting that biological sex is not a key factor affecting the timing of onset. Notably, severity stratification confirmed clear signal detection within the "serious report" group, consistent with the high clinical severity rate **(Table2)**.

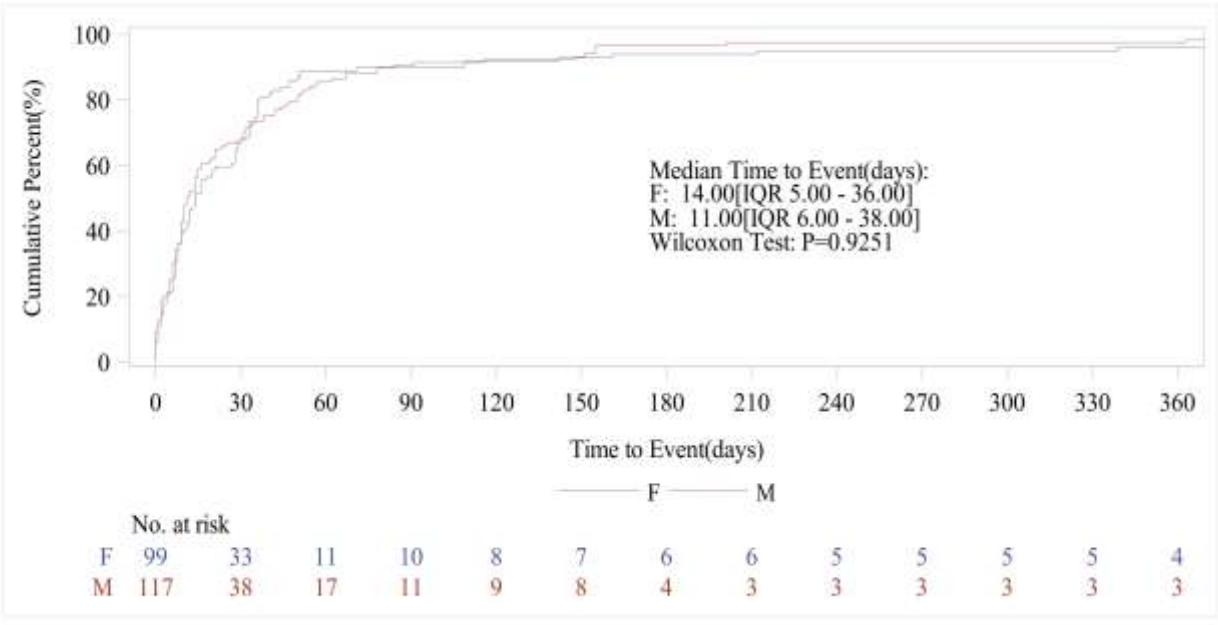


Figure9. Cumulative incidence of adverse events by sex (FAERS)

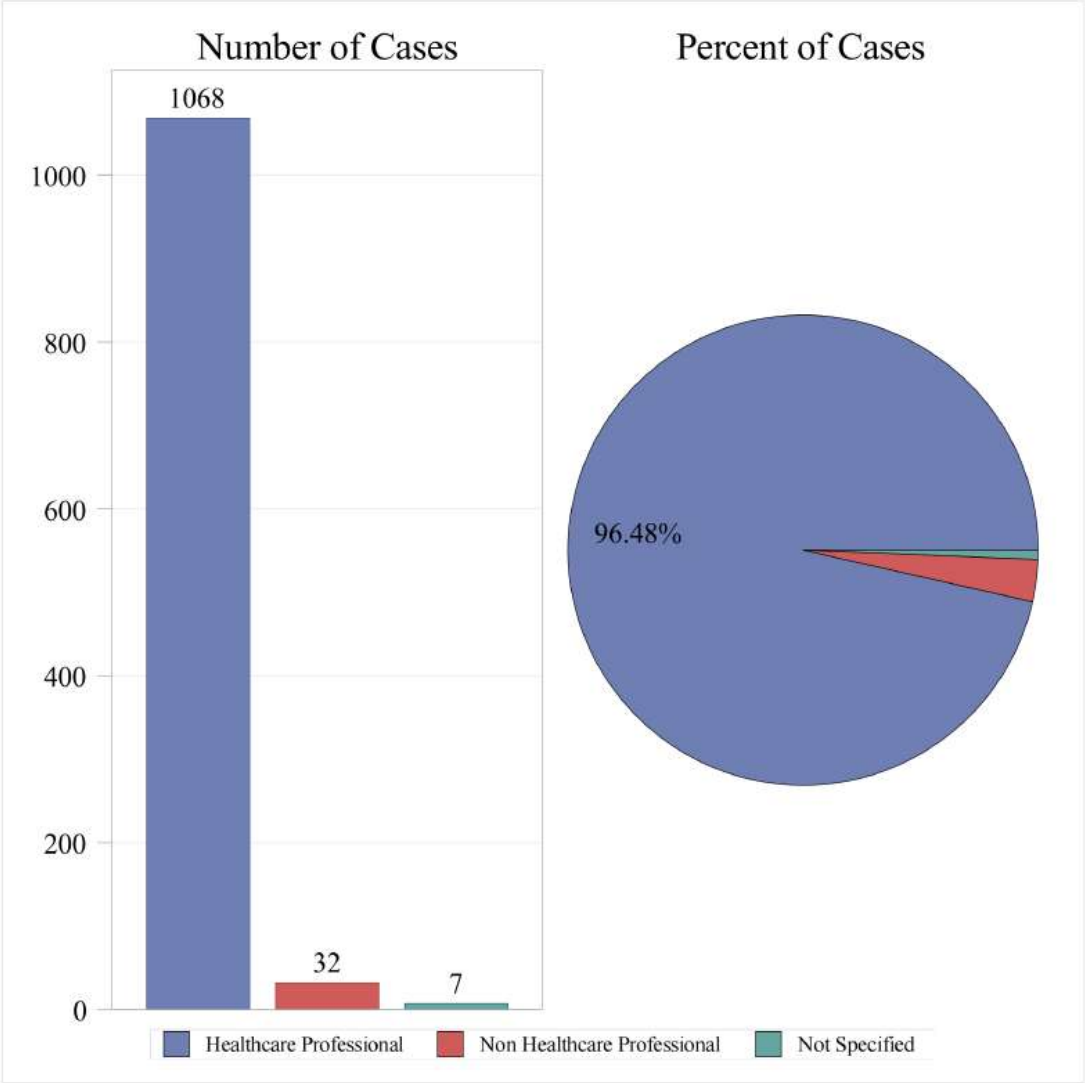
Table 2 Signal detection results across MedDRA hierarchies stratified by report seriousness. (FAERS)

PT	ROR(95% CI)	PRR(95% CI)	IC(IC025)	EBGM(EBGM05)	ROR Signal	PRR Signal	IC Signal	EBGM Signal
Stomatitis	7.58(6.89,8.34)	7.54(6.85,8.29)	2.90(2.74)	7.46(6.78)	Y	Y	Y	Y
Aphthous ulcer	3.37(2.43,4.67)	3.37(2.43,4.67)	1.75(1.18)	3.35(2.42)	Y	Y	Y	Y
Mouth ulceration	1.57(1.13,2.18)	1.57(1.13,2.17)	0.65(0.15)	1.57(1.13)	Y	Y	Y	N
Stomatitis	3.55(2.26,5.57)	3.54(2.26,5.54)	1.82(1.00)	3.54(2.25)	Y	Y	Y	Y
Lip ulceration	2.15(0.69,6.68)	2.15(0.69,6.68)	1.10(-0.71)	2.15(0.69)	N	N	N	N
Mouth ulceration	2.20(0.71,6.82)	2.20(0.71,6.81)	1.13(-0.69)	2.20(0.71)	N	N	N	N
Stomatitis haemorrhagic	11.90(2.94,48.21)	11.90(2.94,48.21)	3.55(-0.33)	11.70(2.89)	N	N	N	Y
Lip erosion	719.45(84.04,6159.34)	719.31(84.05,6156.04)	9.23(-1.32)	599.59(70.04)	N	N	N	Y
Oral mucosa erosion	0.57(0.08,4.08)	0.57(0.08,4.08)	-0.80(-2.50)	0.57(0.08)	N	N	N	N

Longitudinal analysis from 2004 to 2025 demonstrated that despite fluctuations in sample size, this safety signal persisted over the years, confirming the ubiquity and persistence of the risk.

Validation Analysis Based on the EudraVigilance Database

To verify the robustness and generalizability of the FAERS findings, a parallel analysis was conducted using the EudraVigilance database, identifying 1,107 reports that largely corroborated the primary findings. Consistent with FAERS, EudraVigilance data showed a high level of clinical validation, with 96.48% of reports originating from healthcare professionals **(FigureS1)**.



FigureS1. Reporter distribution of AE reports(EV)

Demographic dominance was similarly observed in elderly (≥65 years, 45.62%) and adult patients (18–64 years, 43.09%), while pediatric cases accounted for only 0.45% **(FigureS2)**.

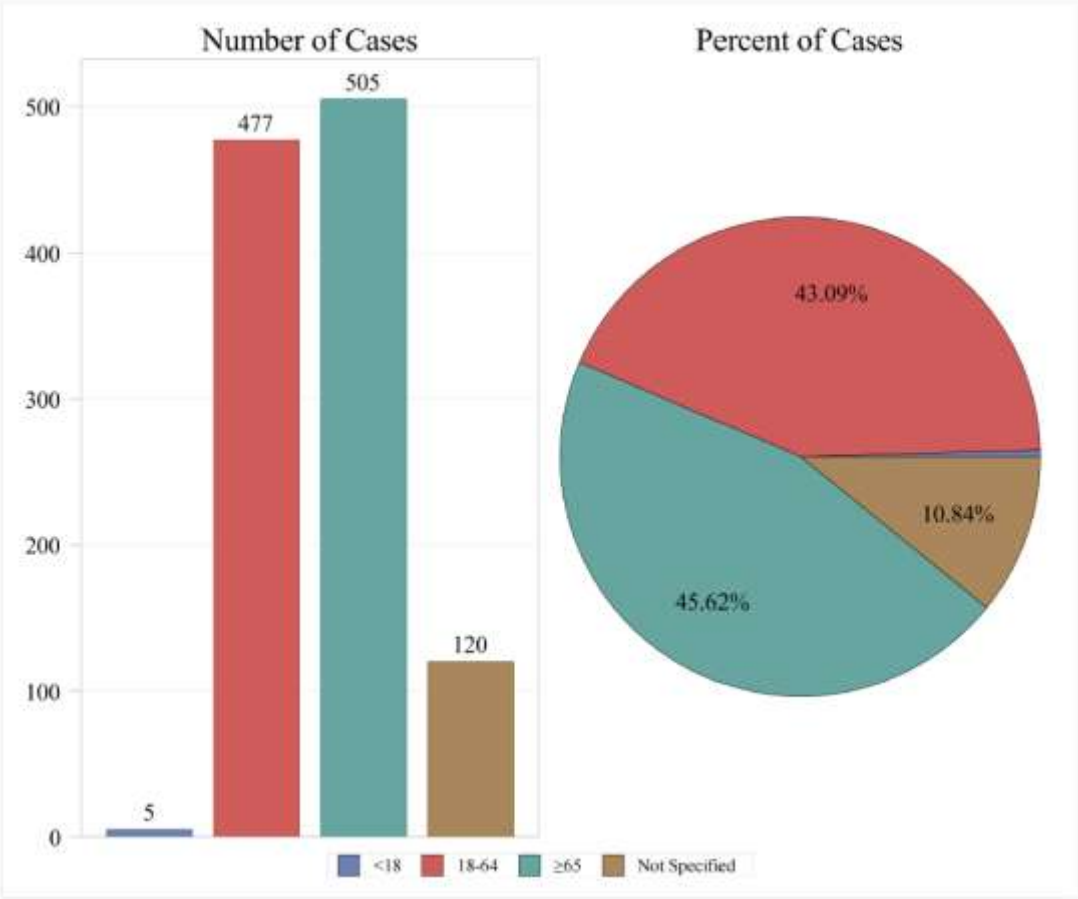


Figure S2. Age distribution of AE reports(EV)

Signal detection across multiple algorithms confirmed the strong association between the drug and oral mucosal damage, reproducing significant signals for "stomatitis" (N = 947, ROR = 9.14) and "mouth ulceration" (ROR = 2.36) **(TableS1)**.

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	9.14(8.57,9.75)	9.06(8.50,9.66)	3.16(3.05)	8.92(8.36)	Y	Y	Y	Y
Mouth ulceration	2.36(1.92,2.90)	2.36(1.92,2.90)	1.23(0.91)	2.35(1.91)	Y	Y	Y	N
Aphthous ulcer	2.87(2.28,3.62)	2.87(2.28,3.62)	1.52(1.14)	2.86(2.27)	Y	Y	Y	Y
Oral mucosa erosion	1.35(0.65,2.84)	1.35(0.65,2.84)	0.44(-0.65)	1.35(0.64)	N	N	N	N
Stomatitis haemorrhagic	11.96(3.81, 37.60)	11.96(3.81, 37.59)	3.55(0.20)	11.70(3.72)	Y	Y	Y	Y
Lip ulceration	1.14(0.37,3.54)	1.14(0.37,3.54)	0.19(-1.31)	1.14(0.37)	N	N	N	N
Stomatitis necrotising	3.51(0.87,14.09)	3.51(0.87,14.09)	1.80(-0.75)	3.49(0.87)	N	N	N	N

Furthermore, EudraVigilance analysis identified exceptionally high signal intensity for "hemorrhagic stomatitis" (ROR = 11.96), a specific morphological endpoint consistent with the severe mucosal damage observed in FAERS, while also establishing significant associations for "aphthous ulcer" (ROR = 2.87) and "mucosal erosion" (ROR = 4.49)**(TableS1)**, which offer higher clinical granularity. Crucially, age-stratified analysis in EudraVigilance validated the increased risk in the elderly found in FAERS, showing a higher reporting density for classic mucosal erosion in the ≥65 age group**(TableS2)**.

Table S2 Analysis of Age-related Differences (Group 1: < 65 years; Group 2: ≥ 65 years)(EV)

PT	P Value	FDR_Pvalue
Stomatitis	1.42019E-05	0.002078206
Mouth ulceration	0.197976732	1
Aphthous ulcer	0.279895654	1
Oral mucosa erosion	1	1
Stomatitis haemorrhagic	0.856027197	1
Lip ulceration	0.856027197	1
Stomatitis necrotising	0.200621066	1

These consistent findings across databases, timeframes, and subgroups further underscore the high risk and clinical importance of fluorouracil-induced oral mucosal toxicity.

4. Discussion

This study conducted a comprehensive analysis of fluorouracil (5-FU)-related oral mucositis (OM) based on the FAERS database. Our results indicate that OM is a frequent and severe adverse drug reaction (ADR) associated with 5-FU. Signal detection revealed significant reporting odds ratios (RORs) for "Stomatitis" and "Stomatitis haemorrhagic." A key finding is that these adverse events are concentrated in the early post-treatment phase, with a median TTO of 13.5 days. This temporal pattern aligns with the pharmacological characteristics of 5-FU and established mucosal injury models 15.

As an antimetabolite, 5-FU primarily inhibits thymidylate synthase, thereby blocking DNA replication and exerting direct cytotoxic effects on the rapidly dividing cells of the oral mucosal basal layer16. Clinically, OM typically manifests as erythema 3–5 days after the initiation of chemotherapy, reaching a peak of ulceration between days 7 and 1417. The median onset of 13.5 days identified in this study coincides precisely with this ulcerative phase. This suggests that clinicians should prioritize monitoring during the second week of chemotherapy. Furthermore, we recommend implementing prophylactic cryotherapy during this window to reduce local drug distribution through vasoconstriction 18 19.

Demographic analysis showed that patients aged ≥65 years accounted for the largest proportion of cases (40.23%), supporting the view that advanced age is an independent risk factor for OM20. In elderly patients, the physiological decline in renal function reduces 5-FU clearance, leading to increased systemic exposure21. Additionally, age-related reductions in salivary secretion impair the self-repair capacity of the oral mucosa 21. While some studies suggest that females may be more susceptible to 5-FU toxicity due to lower dihydropyrimidine dehydrogenase (DPD) activity22, our study found similar reporting proportions and TTO across sexes. This discrepancy may reflect variations in real-world prescribing patterns rather than a lack of biological difference.

Notably, 95.51% of the cases in this study were

classified as serious adverse events, with 41.02% requiring hospitalization. While this high severity rate may be influenced by "reporting bias" inherent to the FAERS database, where severe cases are more likely to be documented23, it nonetheless underscores the clinical burden of high-grade OM. Severe ulceration causes debilitating pain, malnutrition, and systemic infection, often necessitating dose reductions or treatment interruptions, which ultimately compromise oncological outcomes24.

5. Limitations

As a spontaneous reporting system (SRS), FAERS lacks denominator data (the total number of patients exposed), preventing the calculation of true incidence rates. Additionally, the database is subject to missing information and potential duplicate reporting2325.

6. Conclusion

This study provides large-scale real-world evidence confirming a robust and statistically significant association between fluorouracil and severe oral mucosal toxicity across both FAERS and EudraVigilance databases. Our findings characterize oral mucositis as a high-severity adverse event with a distinctive early-onset pattern (median 13.5 days), predominantly affecting the geriatric population (≥65 years). Consequently, clinicians should prioritize intensive oral monitoring and proactive interventions, such as cryotherapy, during the critical high-risk window of the second week of treatment, particularly for elderly patients, to minimize the need for dose reductions and ensure the continuity of oncological therapy.

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Availability of Data and Materials: All the data for the present article can be found on the US FDA Adverse Event Reporting System (FAERS) database and the EudraVigilance (EV) database.

Authors' Contributions: IV NORA1 and Ung Rattanaricky collected, analyzed, and interpreted the data, wrote the manuscript. Pengkhun Nov and Qionglin Huang designed, revised, and supervised the study. All authors had reviewed and approved the final manuscript.

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Patient Consent for Publication: Not applicable.

Competing Interests: The authors declare that they have no competing interests.

Clinical Trial Number: Not Applicable.

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