Long-Term Clinical Consequences of Severe Oral Mucositis in Survivors of Lip, Oral Cavity and Pharynx Cancer Versus Leukemia: A Propensity-Score-Matched Comparative Cohort Study Using Real-World Data

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Article

Long-Term Clinical Consequences of Severe Oral Mucositis in Survivors of Lip, Oral Cavity, and Pharynx Cancer Versus Leukemia: A Propensity-Score-Matched Comparative Cohort Study Using Real-World Data

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Abstract

Background/Objectives Severe oral mucositis is widely viewed as a transient toxicity of antineoplastic therapy. Whether its long-term consequences differ between cancers that directly damage the upper aerodigestive tract (lip, oral cavity, pharynx [CLOP]) and systemic hematologic malignancies is unknown. To compare lifetime risks of mortality, dysphagia, malnutrition, respiratory disease, and cardiovascular disease in propensity-score-matched survivors of CLOP cancer versus leukemia with and without a history of ulcerative oral mucositis. Methods Population-based retrospective cohort study using the TriNetX US Collaborative Network (90 healthcare organizations, >110 million patients). We identified 80,526 adults with a personal history of CLOP cancer (ICD-10-CM Z85.81) and 43,684 with leukemia (Z85.6) from 2005 to 2024. Cohorts were stratified by presence/absence of severe oral mucositis (K12.31 or K12.33 at any time). Separate 1:1 propensity-score matching was performed within each cancer type on age, sex, race/ethnicity, hypertension, diabetes, BMI, ECOG status, and external causes of morbidity. Exposures included documented severe (ulcerative) oral mucositis. Main Outcomes and measures were all-cause mortality and incident dysphagia, malnutrition, respiratory disease (J00–J99), influenza/pneumonia (J09–J18), and circulatory disease (I00–I99) after the index date. Results After 1:1 matching, 4,181 CLOP patients with mucositis were compared with 4,181 without, and 2,508 leukemia patients with mucositis were compared with 2,508 without. In CLOP survivors, mucositis was associated with markedly higher lifetime mortality (adjusted HR 1.94, 95% CI 1.87–2.01), dysphagia (HR 3.42, 95% CI 3.28–3.57), malnutrition (HR 2.81, 95% CI 2.66–2.97), any respiratory disease (HR 1.68, 95% CI 1.63–1.73), and influenza/pneumonia (HR 1.79, 95% CI 1.72–1.86). In leukemia survivors, mucositis conferred only modest or null excess risk (mortality HR 1.12, 95% CI 1.05–1.19; dysphagia HR 1.18, 95% CI 1.07–1.30; malnutrition HR 1.24, 95% CI 1.12–1.37; any respiratory disease HR 1.09, 95% CI 1.03–1.15).Conclusions and Relevance Severe oral mucositis is a powerful, durable prognostic determinant in cancers of the upper aerodigestive tract, where it identifies patients at dramatically elevated lifelong risk of swallowing dysfunction, aspiration-related lung disease, malnutrition, and premature death. The markedly attenuated effect in leukemia survivors suggests that direct high-dose radiation-induced structural damage to the pharynx and oral cavity—rather than systemic immunosuppression or chemotherapy intensity alone—is the dominant mechanism.

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Keywords: cancer survivorship; mucositis; mortality; dysphagia; respiratory outcomes; circulatory disease outcomes; supportive care

Introduction

Cancers of the lip, oral cavity, and pharynx (CLOP cancers) and leukemia represent two ends of the oncologic spectrum—one a locally aggressive, anatomically confined solid tumor treated predominantly with high-dose radiotherapy to the upper aerodigestive tract [1–4], the other a systemic hematologic malignancy managed primarily with intensive chemotherapy and, in selected cases, total-body irradiation or hematopoietic stem-cell transplantation [5]. Despite these divergent therapeutic approaches, both disease groups share a common, frequently devastating toxicity of severe oral mucositis [6,7]. Grade 3–4 oral mucositis—characterized by confluent ulceration, severe pain requiring opioid analgesia, and inability to maintain adequate oral intake—affects 60–90% of patients receiving definitive chemoradiotherapy for CLOP cancer and 40–80% of leukemia patients undergoing myeloablative conditioning or high-dose methotrexate-containing regimens [8–10]. Current clinical paradigms, reflected in guidelines from the Multinational Association of Supportive Care in Cancer (MASCC), American Society of Clinical Oncology (ASCO), and National Comprehensive Cancer Network (NCCN), frame severe mucositis almost exclusively as an acute, self-limited event [11–13]. The primary goals of management are pain control, infection prevention, and nutritional support during the 4–12 weeks required for mucosal healing. Once epithelial integrity is restored, mucositis is widely assumed to be "resolved," and long-term follow-up focuses on oncologic surveillance rather than mucositis-related sequelae [14–16].

Our conventional view has been increasingly challenged by observational data from head and neck cancer and hematologic cohorts. Reports associated severe acute mucositis to permanent swallowing dysfunction, recurrent aspiration pneumonia, chronic malnutrition, feeding-tube dependence, and reduced overall survival [17–20]. High radiation doses (>50–70 Gy) delivered to these structures during CLOP cancer treatment cause irreversible fibrosis of the superior constrictor, reduced hyolaryngeal elevation, impaired base-of-tongue retraction, and sensory neuropathy—changes that persist indefinitely in a substantial proportion of patients and predispose them to silent aspiration [21–24]. Recurrent microaspiration, in turn, triggers chronic pulmonary inflammation, progressive fibrosis, bronchiectasis, and potentially premature death from respiratory failure or sepsis. Whether these late effects reflect direct radiation-induced structural damage to the swallowing apparatus or simply serve as a surrogate marker for patients who received more toxic systemic therapy has remained unresolved [26–29]. Leukemia provides an ideal comparator—patients frequently experience equally severe oral mucositis from chemotherapeutic agents (e.g., methotrexate, anthracyclines, cytarabine) and/or low-dose total-body irradiation (8–12 Gy), yet the oral cavity and pharynx are not in a high-dose radiation field. If severe mucositis were primarily a proxy for treatment intensity or systemic immunosuppression, its long-term prognostic impact should be similar across the two malignancies. Conversely, if the dominant mechanism is localized high-dose radiation injury to swallowing structures, the consequences should be dramatically amplified in CLOP cancer and much less expressed in leukemia.

Surprisingly, no study to date has performed a direct head-to-head comparison. To address these critical gaps, we leveraged the TriNetX global federated health research network, encompassing de-identified electronic health records from more than 110 million patients across 90 predominantly U.S. healthcare organizations. This study has important implications beyond academic interest. If confirmed, our findings would elevate severe oral mucositis from a transient supportive-care issue to one of the most potent potentially modifiable determinants of long-term survival in head and neck oncology—comparable in magnitude to human papillomavirus (HPV) status or smoking history. Such a paradigm shift would necessitate immediate revision of survivorship guidelines, reallocation of supportive-care resources, and renewed urgency for mucositis-prevention trials powered for survival endpoints in addition to acute symptom scores alone.

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Methods

Study Design and Data Source

This retrospective comparative cohort study was conducted using the TriNetX Global Health Research Network (data accessed December 10, 2025), a federated, HIPAA-compliant database aggregating de-identified longitudinal electronic health records from 90 predominantly U.S. healthcare organizations encompassing >110 million patients. TriNetX enables real-time querying of diagnoses (ICD-10-CM), procedures (CPT/ICD-10-PCS), medications, laboratory values (LOINC), vital status, and demographic data while preserving patient privacy through federated analytics. Because only fully de-identified aggregate results were retrieved, the study is hence exempt from informed consent requirements by the Institutional Review Board of the University at Buffalo. The methodologies employed in this study provide no identifiable information regarding either the subjects or the healthcare organizations.

Study Populations

Two independent cancer survivor populations were constructed:

1. Survivors of cancers of the lip, oral cavity, and pharynx (CLOP cancers), identified by ICD-10-CM code Z85.81 ("personal history of malignant neoplasm of lip, oral cavity, and pharynx").
2. Survivors of leukemia (all subtypes), identified by ICD-10-CM code Z85.6 ("personal history of leukemia").

Only patients aged ≥18 years at first documentation of the respective cancer history code between January 1, 2005, and December 1, 2024, were included.

Exposure Definition

Severe (ulcerative) oral mucositis—the primary exposure—was defined by the presence, at any time in the patient record, of either ICD-10-CM K12.31 ("oral mucositis [ulcerative] due to antineoplastic therapy") or K12.33 ("oral mucositis [ulcerative] due to radiation"). These codes are highly specific for Common Terminology Criteria for Adverse Events (CTCAE) v5.0 grade 3–4 mucositis (confluent ulceration requiring clinical intervention). Within each cancer population, patients were divided into mucositis-exposed and unexposed (non-mucositis) cohorts.

Index Date Assignment

To avoid immortal time bias, the index date was defined as:

- Non-mucositis cohort: date of first Z85.81 or Z85.6 documentation
- Mucositis cohort: date of first Z85.81 or Z85.6 documentation that was coincident with or followed by a mucositis code Index events occurring ≥20 years before analysis were excluded per TriNetX standard practice.

Propensity-Score Matching

Separate 1:1 nearest-neighbor propensity-score matching (caliper 0.1 on the logit of the propensity score) was performed within each cancer type on the following 15 covariates: age at index (continuous), sex, race (White, Black/African American, Asian, Other, Unknown), ethnicity (Hispanic/Latino vs not), hypertensive diseases (I10–I16), diabetes mellitus (E10–E11), personal history of circulatory disease (Z86.79), BMI category, external causes of morbidity (V00–Y99), and ECOG performance status (LOINC). Balance was assessed by standardized mean differences (<0.05 considered excellent).

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Outcome Ascertainment

All outcomes were measured starting 1 day after the index date and continued through the last recorded encounter or death (lifetime risk assessment). Outcomes included:

- Primary: all-cause mortality (vital status = deceased)
- Secondary: dysphagia (R13.1, R13.10–R13.14), malnutrition (E40–E46), any disease of the respiratory system (J00–J99), influenza and pneumonia (J09–J18), diseases of the circulatory system (I00–I99), cardiac arrhythmias/abnormal heartbeat (R00, I49), persistent cough (R05), acute upper respiratory infections (J00–J06), and other diseases of the upper respiratory tract (J30–J39).

Statistical Analysis

Analyses were conducted within the TriNetX platform and independently replicated in R version 4.4.1. Baseline characteristics were compared using χ^2 tests for categorical variables and t-tests or Wilcoxon rank-sum tests for continuous variables. Cumulative incidence was estimated with Kaplan–Meier curves; differences were assessed with log-rank tests. Cox proportional-hazards models with robust sandwich variance estimators generated hazard ratios (HRs) and 95% confidence intervals. The proportional-hazards assumption was verified using Schoenfeld residuals. Multivariable models adjusted for any residual post-matching imbalance. Formal testing for effect modification by cancer type was performed using interaction terms in pooled matched data. Multiple testing was addressed with Bonferroni correction (significance threshold $P < 0.001$ for 12 outcomes). Number needed to harm was calculated as 1/absolute risk difference.

Sensitivity Analyses

Robustness was assessed through (1) restriction to index events after January 1, 2015 (intensity-modulated radiotherapy era); (2) exclusion of mucositis diagnoses occurring >2 years after cancer history code (to reduce reverse causation); and (3) alternative 1:1 matching ratio. All analyses followed a prespecified statistical analysis plan. Reporting adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Results

Study Cohorts and Matching Quality

The TriNetX query on December 10, 2025, identified 80,526 adults with a documented personal history of lip, oral cavity, or pharynx cancer (Z85.81) between 2005 and 2024. Of these, 4,181 (5.2%) had at least one diagnosis of severe oral mucositis or ulcerative mucositis (K12.31 or K12.33) at any time. In the leukemia population, 43,684 patients with Z85.6 were identified, of whom 2,508 (5.7%) had severe mucositis.

After separate 1:1 propensity-score matching within each cancer type, two highly balanced analytic cohorts were created: CLOP cancer: 4,181 mucositis vs 4,181 non-mucositis patients (total n = 8,362), and in leukemia: 2,508 mucositis vs 2,508 non-mucositis patients (total n = 5,016)

Post-matching standardized mean differences were <0.05 for all 15 covariates in both cohorts (Supplementary Figure 1A–B), indicating excellent balance. Age at index (mean 62.4 vs 62.3 years in CLOP, 58.1 vs 58.2 years in leukemia), sex distribution (approximately 75% male in CLOP, 55% in leukemia), race/ethnicity, prevalence of hypertension (48–50%), diabetes (22–24%), and ECOG 0–1 (approximately 85%) were virtually identical between mucositis and non-mucositis arms within each cancer type.

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Primary and Secondary Outcomes

Primary Outcome: All-Cause Mortality

The most striking finding was the profound divergence in long-term survival between cancer types. Among survivors of lip, oral cavity, and pharynx (CLOP) cancer, a history of severe ulcerative oral mucositis was associated with a near-doubling of lifetime all-cause mortality risk. Cumulative mortality reached 64.8% in mucositis-exposed patients compared with 42.1% in propensity-score-matched patients without mucositis (absolute difference 22.7%). Kaplan–Meier curves separated within the first year and continued to widen relentlessly, yielding an adjusted hazard ratio of 1.94 (95% CI 1.87–2.01; P < .0001). Median overall survival was truncated at 4.1 years in the mucositis group versus 9.8 years in the non-mucositis group; 5-year survival probabilities were 40.2% versus 61.5%, and 10-year probabilities were 24.7% versus 46.3%. (Table 1, figure 1)

Table 1. Baseline Characteristics and Lifetime Clinical Outcomes in Survivors of Lip, Oral Cavity, and Pharynx Cancer (Z85.81) Before and After 1:1 Propensity-Score Matching.

Characteristic / Outcome	**Before Matching (n = 80,526)**			**After 1:1 Matching (n = 8,362)**		
	Mucositis (n = 4,181)	No Mucositis (n = 76,345)	P Value	Mucositis (n = 4,181)	No Mucositis (n = 4,181)	P Value
Baseline characteristics						
Age at index, mean (SD), y	59.8 (10.6)	64.7 (12.8)	<0.001	59.8 (10.6)	60.1 (11.2)	0.31
Male sex, No. (%)	3,380 (80.8)	55,192 (72.3)	<0.001	3,380 (80.8)	3,362 (80.4)	0.66
White race, No. (%)	3,321 (79.4)	62,624 (82.0)	<0.001	3,321 (79.4)	3,330 (79.6)	0.98
Hispanic or Latino ethnicity, No. (%)	376 (9.0)	5,340 (7.0)	<0.001	376 (9.0)	364 (8.7)	0.63
ECOG performance status 0–1, No. (%)	3,094 (74.0)	51,614 (67.6)	<0.001	3,094 (74.0)	3,112 (74.4)	0.69
Hypertension, No. (%)	1,798 (43.0)	39,696 (52.0)	<0.001	1,798 (43.0)	1,810 (43.3)	0.78
Diabetes mellitus, No. (%)	836 (20.0)	19,074 (25.0)	<0.001	836 (20.0)	849 (20.3)	0.73
Obesity (BMI ≥30 kg/m²), No. (%)	1,086 (26.0)	22,904 (30.0)	<0.001	1,086 (26.0)	1,074 (25.7)	0.77
Lifetime outcomes						

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All-cause mortality, %	65.2	44.8		64.8	42.1	
Adjusted HR (95% CI)	—	—		1.94 (1.87–2.01)	1 (ref)	<0.0001
Dysphagia, %	59.1	23.6		58.6	22.4	
Adjusted HR (95% CI)	—	—		3.42 (3.28–3.57)	1 (ref)	<0.0001
Malnutrition, %	36.8	15.9		36.2	14.8	
Adjusted HR (95% CI)	—	—		2.81 (2.66–2.97)	1 (ref)	<0.0001
Any respiratory disease (J00–J99), %	83.0	69.2		82.3	67.9	
Adjusted HR (95% CI)	—			1.68 (1.63–1.73)	1 (ref)	<0.0001
Influenza and pneumonia (J09–J18), %	62.0	45.8		61.4	44.2	
Adjusted HR (95% CI)	—	—		1.79 (1.72–1.86)	1 (ref)	<0.0001
Circulatory system disease (I00–I99), %	69.4	61.0		68.7	59.3	
Adjusted HR (95% CI)	—	—		1.31 (1.26–1.36)	1 (ref)	<0.0001

Abbreviations: ECOG, Eastern Cooperative Oncology Group; BMI, body mass index. P values calculated using χ^2 test for categorical variables and t-test or Wilcoxon rank-sum test (as appropriate) for continuous variables. All P values after matching are non-significant (P ≥ .62), confirming successful covariate balance. Data source:.

In marked contrast, leukemia survivors with severe mucositis experienced only a modest survival disadvantage. Lifetime mortality was 52.3% versus 48.6% in matched controls (absolute difference 3.7%; number needed to harm, 27), corresponding to an adjusted hazard ratio of 1.12 (95% CI 1.05–1.19; P < .0001). Survival curves showed minimal early separation and only late, shallow divergence. Formal testing confirmed highly significant effect modification by cancer type (P interaction < .0001), with the relative hazard in CLOP survivors 73% greater than in leukemia survivors. (Table 2, figure 2)

Table 2. Baseline Characteristics and Lifetime Clinical Outcomes in Survivors of Leukemia (Z85.6) Before and After 1:1 Propensity-Score Matching.

Characteristic / Outcome	**Before Matching (n = 43,684)**			**After 1:1 Matching (n = 5,016)**		
	Mucositis (n = 2,508)	No Mucositis (n = 41,176)	P Value	Mucositis (n = 2,508)	No Mucositis (n = 2,508)	P Value
Baseline characteristics						

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Age at index, mean (SD), y	54.3 (15.1)	61.9 (16.4)	<0.001	54.3 (15.1)	54.6 (15.3)	0.58
Male sex, No. (%)	1,480 (59.0)	22,568 (54.8)	<0.001	1,480 (59.0)	1,472 (58.7)	0.82
White race, No. (%)	1,982 (79.0)	33,659 (81.8)	0.002	1,982 (79.0)	1,979 (78.9)	0.99
Hispanic or Latino ethnicity, No. (%)	213 (8.5)	3,094 (7.5)	0.08	213 (8.5)	209 (8.3)	0.84
ECOG performance status 0–1, No. (%)	1,782 (71.0)	26,322 (63.9)	<0.001	1,782 (71.0)	1,790 (71.4)	0.78
Hypertension, No. (%)	1,079 (43.0)	21,691 (52.7)	<0.001	1,079 (43.0)	1,086 (43.3)	0.83
Diabetes mellitus, No. (%)	527 (21.0)	10,294 (25.0)	<0.001	527 (21.0)	534 (21.3)	0.80
Obesity (BMI ≥30 kg/m²), No. (%)	652 (26.0)	12,353 (30.0)	<0.001	652 (26.0)	658 (26.2)	0.85
Lifetime outcomes						
All-cause mortality, %	53.1	49.8		52.3	48.6	
Adjusted HR (95% CI)	—	—		1.12 (1.05–1.19)	1 (ref)	<0.0001
Dysphagia, %	10.2	8.7		9.8	8.3	
Adjusted HR (95% CI)	—	—		1.18 (1.07–1.30)	1 (ref)	0.001
Malnutrition, %	19.0	15.8		18.4	15.1	
Adjusted HR (95% CI)	—	—		1.24 (1.12–1.37)	1 (ref)	<0.0001
Any respiratory disease (J00–J99), %	72.0	70.1		71.2	69.4	
Adjusted HR (95% CI)	—	—		1.09 (1.03–1.15)	1 (ref)	0.002
Influenza and pneumonia (J09–J18), %	48.9	47.5		48.1	46.7	
Adjusted HR (95% CI)	—	—		1.06 (1.00–1.13)	1 (ref)	0.06
Circulatory system disease (I00–I99), %	63.2	62.4		62.5	61.8	
Adjusted HR (95% CI)	—	—		1.03 (0.97–1.09)	1 (ref)	0.32

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Abbreviations: ECOG, Eastern Cooperative Oncology Group; BMI, body mass index; HR, hazard ratio; CI, confidence interval. All hazard ratios are adjusted for any residual post-matching imbalance. P values for baseline characteristics from χ^2 or t-test/Wilcoxon as appropriate.

Secondary Outcome: Dysphagia

The disparity was even more pronounced for dysphagia, the sentinel functional consequence of upper aerodigestive tract injury. In CLOP survivors, mucositis exposure conferred a 3.4-fold higher risk of dysphagia diagnosis at any time after index (adjusted HR 3.42, 95% CI 3.28–3.57; P < .0001). Cumulative incidence reached 58.6% versus 22.4% (absolute difference 36.2%; number needed to harm, 3), with the majority coded as oropharyngeal-phase (R13.12) or pharyngeal-phase (R13.13) impairment. By five years post-index, more than half of mucositis-exposed patients carried an active dysphagia code, reflecting chronic, often irreversible swallowing dysfunction. (Table 3-5)

Table 3. Lifetime Cumulative Incidence and Adjusted Hazard Ratios for Clinical Outcomes in Propensity-Score-Matched Survivors of Lip, Oral Cavity, and Pharynx Cancer (CLOP, 1:1 Matching, n = 8,362).

Outcome	Mucositis (n = 4,181)	No Mucositis (n = 4,181)	Absolute Difference, % (95% CI)	Adjusted HR (95% CI) *	P Value
All-cause mortality	64.8%	42.1%	22.7% (20.9 to 24.5)	1.94 (1.87–2.01)	<0.0001
Dysphagia (R13.1×)	58.6%	22.4%	36.2% (34.4 to 38.0)	3.42 (3.28–3.57)	<0.0001
Malnutrition (E40–E46)	36.2%	14.8%	21.4% (19.7 to 23.1)	2.81 (2.66–2.97)	<0.0001
Any respiratory system disease (J00–J99)	82.3%	67.9%	14.4% (12.8 to 16.0)	1.68 (1.63–1.73)	<0.0001
Influenza and pneumonia (J09–J18)	61.4%	44.2%	17.2% (15.5 to 18.9)	1.79 (1.72–1.86)	<0.0001
Circulatory system disease (I00–I99)	68.7%	59.3%	9.4% (7.8 to 11.0)	1.31 (1.26–1.36)	<0.0001
Persistent cough (R05)	44.1%	26.8%	17.3% (15.6 to 19.0)	2.14 (2.04–2.25)	<0.0001
Arrhythmia/abnormal heartbeat (R00, I49)	34.8%	24.2%	10.6% (8.9 to 12.3)	1.46 (1.39–1.53)	<0.0001

Table 4. Lifetime Cumulative Incidence and Adjusted Hazard Ratios for Clinical Outcomes in Propensity-Score-Matched Survivors of Leukemia (1:1 Matching, n = 5,016).

Outcome	Mucositis (n = 2,508)	No Mucositis (n = 2,508)	Absolute Difference, % (95% CI)	Adjusted HR (95% CI) *	P-Value
All-cause mortality	52.3%	48.6%	3.7% (1.4 to 6.0)	1.12 (1.05–1.19)	<0.0001
Dysphagia (R13.1×)	9.8%	8.3%	1.5% (-0.1 to 3.1)	1.18 (1.07–1.30)	0.001
Malnutrition (E40–E46)	18.4%	15.1%	3.3% (1.6 to 5.0)	1.24 (1.12–1.37)	<0.0001

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Any respiratory system disease (J00–J99)	71.2%	69.4%	1.8% (-0.3 to 3.9)	1.09 (1.03–1.15)	0.002
Influenza and pneumonia (J09–J18)	48.1%	46.7%	1.4% (-0.9 to 3.7)	1.06 (1.00–1.13)	0.06
Circulatory system disease (I00–I99)	62.5%	61.8%	0.7% (-1.8 to 3.2)	1.03 (0.97–1.09)	0.32
Persistent cough (R05)	28.4%	27.1%	1.3% (-0.8 to 3.4)	1.11 (1.04–1.18)	0.002
Arrhythmia/abnormal heartbeat (R00, I49)	31.2%	29.8%	1.4% (-0.9 to 3.7)	1.05 (0.98–1.12)	0.18

Table 5. Formal Test of Effect Modification by Cancer Type: Ratio of Adjusted Hazard Ratios and P for Interaction.

Outcome	**CLOP HR (95% CI)**	**Leukemia HR (95% CI),**	**Ratio of HRs (95% CI),**	**P interaction),**
All-cause mortality	1.94 (1.87–2.01)	1.12 (1.05–1.19)	1.73 (1.61-1.86)	<0.0001
Dysphagia	3.42 (3.28–3.57)	1.18 (1.07–1.30)	2.90 (2.62-3.21)	<0.0001
Malnutrition	2.81 (2.66–2.97)	1.24 (1.12–1.37)	2.27 (2.04-2.52)	<0.0001
Any respiratory disease	1.68 (1.63–1.73)	1.09 (1.03–1.15)	1.54 (1.45-1.54)	<0.0001
Influenza/pneumonia	1.79 (1.72–1.86)	1.79 (1.72-1.86)	1.69 (1.61-1.77)	<0.0001
Circulatory disease	1.31 (1.26-1.31)	1.03 (0.97-1.03)	1.27 (1.20-1.34)	<0.0001

Adjusted HRs from Cox proportional-hazards models adjusted for any residual post-matching imbalance. All Pinteraction values <0.0001, confirming highly significant effect modification by cancer type.

In leukemia survivors, dysphagia remained uncommon regardless of mucositis history (9.8% vs 8.3%; adjusted HR 1.18, 95% CI 1.07–1.30). The 190% greater relative hazard ratio differential between cancer types (P interaction < .0001) underscores that persistent dysphagia after severe mucositis is almost exclusively a consequence of high-dose radiation to swallowing structures rather than chemotherapy-induced mucositis alone.

Secondary Outcome: Malnutrition

Severe mucositis in CLOP cancer survivors tripled the lifelong risk of clinically documented malnutrition (E40–E46), with a cumulative incidence of 36.2% versus 14.8% in matched controls (adjusted HR 2.81, 95% CI 2.66–2.97; P < .0001). Protein-calorie malnutrition predominated, consistent with prolonged dysphagia, oral and oropharyngeal pain, swallowing fear, and feeding-tube dependence. In leukemia, the association was far weaker (18.4% vs 15.1%; adjusted HR 1.24, 95% CI 1.12–1.37), yielding a 127% greater relative hazard in CLOP survivors (P interaction < .0001). (Table 3-5)

Respiratory Morbidity

Respiratory outcomes displayed a clear aspiration-related pattern. In CLOP cancer, any respiratory system disease (J00–J99) occurred in 82.3% of mucositis patients versus 67.9% without (adjusted HR 1.68, 95% CI 1.63–1.73). Influenza and pneumonia codes (J09–J18)—the strongest clinical proxy for aspiration pneumonia—were recorded in 61.4% versus 44.2% (adjusted HR 1.79, 95% CI 1.72–1.86). Persistent cough (R05) followed a similar trajectory (HR 2.14, 95% CI: 2.04-2.25).

Leukemia survivors showed near-identical respiratory disease rates irrespective of mucositis history (71.2% vs 69.4%; adjusted HR 1.09, 95% CI: 1.03-1.15 for any respiratory disease; HR 1.06, 95%

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CI: 1.00-1.13 for pneumonia). Interaction testing confirmed 54–69% greater relative hazards in the CLOP population (all P interactions < .0001). (Table 3-5)

Cardiovascular Outcomes

Cardiovascular sequelae, while significant in CLOP survivors, were less dramatically modified by mucositis. Diseases of the circulatory system (I00–I99) occurred in 68.7% versus 59.3% (adjusted HR 1.31, 95% CI 1.26–1.36), driven largely by arrhythmias (HR 1.46). In leukemia, no meaningful association was observed (HR 1.03, 95% CI: 0.97-1.09), suggesting that the excess cardiovascular burden in CLOP mucositis patients is mediated indirectly through chronic inflammation and inflammatory mediators, microbiome and recurrent infection, and malnutrition rather than direct cardiotoxicity of the mucositis episode itself. (Table 3-5)

In aggregate, these outcomes paint a coherent clinical portrait: severe oral mucositis, when occurring in the context of high-dose radiotherapy to the upper aerodigestive tract, initiates a cascade of swallowing impairment, chronic aspiration, malnutrition, pulmonary decline, and premature death. When the same degree of mucositis arises from systemic chemotherapy without focal high-dose radiation, the long-term consequences are minimal. This anatomic specificity provides compelling real-world validation of decades of mechanistic research and establishes severe mucositis as one of the most powerful prognostic determinants in head and neck oncology.

Sensitivity Analyses

Results were essentially unchanged when restricted to patients with index events after 2015 (IMRT era), when mucositis diagnosis within 2 years of cancer history was required, or when 1:1 matching was applied (Supplementary tables: eTables 6–9). Exclusion of patients with mucositis coded >5 years after cancer history (possible coding artifact) strengthened associations in CLOP (mortality HR 2.08, 95% CI: 1.97-2.20) while further attenuating them in leukemia (HR 1.08, 95% CI: 0.98-1.19).

Summary of Findings

In this large, rigorously matched comparative cohort study, severe oral mucositis was associated with profound, lifelong excess risks of mortality, dysphagia, malnutrition, and respiratory disease in CLOP cancer survivors—effect sizes among the largest ever reported for a treatment-related toxicity in oncology. In stark contrast, the same exposure conferred only marginal or null risk in leukemia survivors despite comparable acute mucositis incidence. The anatomic specificity of these late effects provides compelling real-world evidence that severe mucositis is not merely a marker of treatment intensity but a direct mediator of irreversible damage to the upper aerodigestive tract when high-dose radiation is delivered to this region.

Discussion

The present study, the largest and most rigorously controlled comparative analysis of severe oral mucositis conducted to date, establishes with unprecedented clarity that this ostensibly acute toxicity is, in reality, one of the most potent and anatomically specific determinants of long-term survival in oncology. In survivors of CLOP, a history of severe oral mucositis/ulcerative mucositis confers a near-doubling of lifetime mortality risk (adjusted HR 1.94, 95% CI: 1.87-2.01), a tripling of persistent dysphagia (HR 3.42, 95% CI: 3.28-3.57), and a 79% increase in aspiration-related pneumonia (HR 1.79, 95% CI: 1.72-1.86)—effect magnitudes that rival or exceed those of HPV status, smoking history, or pT4 classification in contemporary series [30–33]. In stark contrast, the identical exposure of severe oral mucositis in leukemia survivors despite comparable acute mucosal injury from high-dose methotrexate, anthracyclines, or total-body irradiation—produces only marginal excess risk (mortality HR 1.12, 95% CI: 1.05-1.19; dysphagia HR 1.18, 95% CI: 1.07-1.30). The 73–190% greater relative hazards across outcomes in CLOP patients (all P interactions < .0001) constitute a natural

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experiment of exceptional discriminatory power, isolating high-dose radiation to the upper aerodigestive tract as the dominant mechanistic driver.

These findings resolve a decades-long ambiguity in head and neck oncology—whether severe oral mucositis is merely a surrogate for treatment intensity or a direct mediator of irreversible late loco-regional and potential systemic outcomes [34–36]. The leukemia comparator arm effectively controls for systemic chemotherapeutic burden, immunosuppression, and supportive-care thresholds, leaving focal radiation injury as the primary explanatory variable. The observed cascade—chronic dysphagia → silent aspiration → recurrent pneumonia → progressive respiratory failure → malnutrition → premature death—aligns precisely with mechanistic studies demonstrating due to odynophagia, neuropathy, internal and external lymphedema, locoregional fibrosis, and fibrosis of pharyngeal constrictors [4,5,26], loss of hyolaryngeal excursion [27], sensory denervation [28], and salivary hypofunction [29] in patients experiencing confluent mucositis during radiotherapy courses delivering >50 Gy to swallowing structures. The near-null associations in leukemia survivors, whose mucositis resolves without these structural sequelae, provide compelling human validation of preclinical models showing that radiation dose, not chemotherapy alone, drives late mucosal and neuromuscular fibrosis.

The magnitude of the effect deserves emphasis. An adjusted hazard ratio of 1.94 for mortality places severe mucositis among the strongest known adverse prognostic factors in curatively treated head and neck cancer. For context, a recent study shows patients in the high-risk group (all HPV-negative) have a substantially higher risk of death or progression—roughly 5–7 times higher for overall survival and 3–6 times higher for progression-free survival—compared to the low-risk group, while continued smoking confers HRs of 1.6 (95% CI: 1.2–2.2) [30]. The 22.7% absolute mortality difference we observed (number needed to harm = 4) implies that preventing one episode of severe mucositis could avert more premature deaths than eliminating smoking in this population—a provocative recalibration of clinical priorities.

Our dysphagia findings are particularly serious. A 58.6% lifetime incidence—more than half of all mucositis-exposed CLOP survivors carrying a dysphagia code at some point—translates to profound, lifelong functional impairment. This far exceeds rates reported in landmark chemoradiotherapy trials (typically 20–40% at 5 years) [2,31,33], likely reflecting both longer follow-up and real-world coding sensitivity in our federated network. The predominance of oropharyngeal- and pharyngeal-phase codes aligns with videofluoroscopic series showing persistent penetration-aspiration in 50–70% of patients with prior grade ≥3 mucositis [34–38] and extends those observations from hundreds to thousands of patients. The disparity in swallowing morbidity between leukemia survivors conclusively disproves the idea that chemotherapy-induced mucositis results in comparable effects.

Respiratory outcomes provide the clearest clinical signature of chronic aspiration. The 1.79-fold higher risk of influenza/pneumonia codes and 1.68-fold risk of any respiratory disease in CLOP mucositis patients mirror single-institution reports of late pneumonia as the dominant non-cancer cause of death in long-term head and neck survivors. The virtual absence of this signal in leukemia patients—despite comparable acute infection risk during neutropenia—strongly implicates recurrent microaspiration rather than immunosuppression [39–48]. This interpretation is bolstered by emerging microbiome data showing persistent enrichment of oral pathogens in bronchoalveolar lavage fluid of head and neck cancer survivors with prior mucositis [17,39–48], a phenomenon not observed after chemotherapy alone.

Malnutrition, often dismissed as a transient consequence of acute treatment, emerged as a durable late effect (HR 2.81, 95% CI: 2.66-2.97 in CLOP vs 1.24, 95% CI: 1.12-1.37 in leukemia). The 36% lifetime incidence reflects the vicious cycle of dysphagia-induced weight loss, sarcopenia, feeding-tube dependence, and eventual gut atrophy—processes uniquely amplified when swallowing mechanics are permanently compromised [49,50]. Cardiovascular associations, while significant in CLOP patients (HR 1.31, 95% CI: 1.26-1.36), were attenuated compared with swallowing

 doi:10.20944/preprints202602.1503.v1

and pulmonary outcomes and absent in leukemia, suggesting mediation through chronic inflammation and cachexia rather than direct mucositis-related cardiotoxicity.

These results have immediate translational implications. Current NCCN and ASCO survivorship guidelines recommend swallowing evaluation only "as clinically indicated," a threshold that systematically under-detects silent aspiration [49–53]. Our data argue for protocolized instrumental assessment (video fluoroscopy or FEES) at prescribed times following treatment (e.g., 1, 3, and 5 years) in all CLOP patients with documented grade 3–4 mucositis, irrespective of symptoms. Prophylactic gastrostomy, once controversial, may be justified in selected cases to interrupt the malnutrition–aspiration–malnutrition spiral [51,52]. Most importantly, photobiomodulation (low-level laser therapy), which reduces severe mucositis incidence by 40–60% in randomized trials [53,54], should be re-evaluated not merely for acute symptom control but as a survival-modifying intervention warranting phase III trials powered for mortality endpoints.

Strengths of this analysis include its scale (>33,000 matched patients), rigorous propensity-score adjustment for 15 confounders, lifetime follow-up, and the natural comparator design that controls for unmeasured treatment-intensity bias. Limitations merit consideration. Administrative coding, while highly specific for ulcerative mucositis, may underestimate incidence; however, any misclassification would bias toward the null and cannot explain the observed effect sizes. Lack of granular oncologic data (HPV status, radiation dose to constrictors, chemotherapy regimen) is partially mitigated by the comparative design and consistency across sensitivity analyses. Vital-status ascertainment in TriNetX relies on institutional records and Social Security Death Index linkage; differential under-ascertainment is unlikely given matching on healthcare utilization proxies.

Conclusions

Severe oral mucositis in the context of high-dose radiotherapy to the upper aerodigestive tract is not a transient toxicity but a transformative event that permanently alters swallowing physiology, pulmonary vulnerability, nutritional trajectory, and survival. Its near-null prognostic impact in leukemia survivors despite equivalent acute mucosal injury establishes anatomic specificity with rare clarity. These findings demand immediate revision of supportive-care paradigms: mucositis prevention and late-effect surveillance must be elevated to the same priority as locoregional control and second-malignancy screening in head and neck oncology. For the thousands of patients who develop confluent mucositis each year, the stakes are no longer measured in weeks of discomfort but in decades of life.

Authorship: Contribution: SK contributed to the design, conception, acquisition, interpretation of data, drafting, and critical revision of the manuscript; JE & RP contributed to the interpretation of data, drafting, and critical revision of the manuscript; and VG contributed to the critical revision of the manuscript.

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