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Sepsis Involvement in Cancer-Attributed and Noncancer-Attributed Deaths in the United States, 1999–2024

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Abstract

Background/Objectives: Population-based mortality rates do not show how frequently sepsis is recorded among deaths attributed to cancer. We compared temporal trends in recorded sepsis involvement among cancer-attributed and noncancer-attributed deaths in the United States from 1999 to 2024. **Methods:** This national repeated cross-sectional study analyzed death certificates using age–sex standardization and grouped-binomial regression with flexible calendar-time modeling. **Results:** Among 69,714,059 deaths, 15,091,681 were cancer-attributed. Sepsis was recorded in 572,524 cancer-attributed and 4,095,662 noncancer-attributed deaths. Standardized sepsis involvement increased from 3.21% to 4.69% in cancer-attributed deaths (+1.48 percentage points) and from 6.75% to 7.89% in noncancer-attributed deaths (+1.15 percentage points). The differential change was +0.34 percentage points (95% confidence interval, 0.24–0.43; interaction $p < 0.001$). When restricted to 1999–2019, the model-based differential endpoint change was 0.00 percentage points (95% confidence interval, −0.20 to 0.20). Hematologic malignancies had higher absolute sepsis involvement, whereas solid malignancies showed larger relative increases. **Conclusions:** Recorded sepsis involvement rose in both groups, with the modestly greater overall increase among cancer-attributed deaths concentrated after 2019. These death-certificate findings do not establish individual-level sepsis risk or causal effects.

Keywords: cancer mortality; sepsis; multiple cause of death; population-based study; temporal trends

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1. Introduction

Sepsis remains a major cause of morbidity and mortality and an important complication across the cancer care continuum. Malignancy and its treatment can impair host immunity

and increase susceptibility to severe infection [1–3]. In a 2025 multicenter prospective cohort, sepsis developed in 9.1% of hospitalized patients with cancer, while a recent meta-analysis reported pooled hospital mortality of 54% among patients with cancer admitted to intensive care with sepsis [2,3]. Although outcomes have improved in some critical-care cohorts, the clinical burden of sepsis in patients with cancer remains substantial [3,4].

Population-level mortality data provide a complementary perspective by capturing sepsis when recorded among multiple causes of death (MCD). Prior United States (US) studies using national death-certificate data have primarily evaluated sepsis-related mortality relative to the general population [5], and a recent Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) analysis examined deaths with co-recorded cancer and sepsis using age-adjusted mortality rates per 100,000 population [6]. However, population-based mortality rates do not directly quantify how frequently sepsis is recorded among deaths attributed to cancer or whether temporal changes differ from those among deaths attributed to other underlying causes. Such comparisons also require careful interpretation because death-certificate ascertainment may be influenced by secular changes in sepsis recognition, documentation, and coding [7]. In this context, cancer-attributed deaths refer specifically to deaths in which cancer was designated as the underlying cause of death (UCD) and therefore do not represent all deaths occurring among individuals with cancer; conversely, noncancer-attributed deaths comprise deaths assigned to other underlying causes and should not be interpreted as a cancer-free population. Thus, unlike analyses centered on population-based mortality rates, our study uses mutually exclusive cancer-attributed and noncancer-attributed death groups defined by UCD and a common fixed age–sex standardization framework to compare changes in the proportion of deaths with recorded sepsis involvement.

In the current study, we used US MCD data from 1999 through 2024 to characterize temporal trends in recorded sepsis involvement among cancer-attributed deaths and to compare these trends with those among noncancer-attributed deaths. We further examined variation by age, sex, malignancy class, and major cancer site and assessed the consistency of findings across alternative temporal, standardization, pandemic-period, sepsis-definition, and comparator-definition specifications. Our objective was to characterize population-level temporal patterns in recorded sepsis involvement rather than to estimate individual-level sepsis risk or to compare people with and without cancer.

2. Methods

2.1. Study Design and Data Source

We conducted a national repeated cross-sectional analysis of US death-certificate data using the CDC WONDER MCD database. Deaths recorded from 1999 through 2024 were analyzed; data were accessed on 13 August 2026. Calendar years 1999–2017 were obtained from the final MCD 1999–2020 dataset and 2018–2024 from the final MCD 2018–2024 Single Race dataset [8,9]. The overlapping years 2018–2020 were extracted from both datasets solely for cross-dataset validation and were included only once in the final analytic series. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement, using the cross-sectional framework where applicable [10].

Cancer-attributed deaths were defined as deaths in which malignant neoplasms (International Classification of Diseases, Tenth Revision [ICD-10], C00–C97) were recorded as the UCD. Sepsis involvement was defined as ICD-10 A40–A41 recorded among the MCD fields. The primary descriptive estimand was the proportion of cancer-attributed deaths in which sepsis was recorded among the MCD. This estimand represents recorded sepsis

involvement within cancer-attributed mortality and should not be interpreted as sepsis incidence, individual-level sepsis risk, or mortality among all individuals with cancer.

2.2. Construction of Cancer and Noncancer Groups

For each calendar year, age group, and sex stratum, we obtained cancer-attributed deaths involving sepsis, all cancer-attributed deaths, all deaths involving sepsis, and all deaths. Noncancer-attributed deaths and corresponding sepsis-involved deaths were derived by subtracting cancer-attributed counts from the corresponding all-death counts, thereby creating mutually exclusive groups within the same national mortality universe. Accordingly, the noncancer-attributed group comprised deaths in which cancer was not designated as the UCD and should not be interpreted as a cancer-free population; it could include deaths among individuals with cancer when another condition was assigned as the underlying cause.

Primary analyses used nine age groups: 0–14, 15–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, and ≥85 years, stratified by sex. Records with age reported as "Not Stated" were retained in overall counts but excluded from standardization and regression. Suppressed cells were neither assigned zero nor imputed; required aggregates were directly re-queried from CDC WONDER. Detailed query construction, age aggregation, suppression handling, and overlap validation are provided in the Supplementary Methods and Supplementary Tables S1 and S2. Because the source datasets used different race-classification frameworks, race and ethnicity were not included in longitudinal analyses.

2.3. Direct Standardization

Annual crude sepsis-involvement proportions were calculated separately for cancer-attributed and noncancer-attributed deaths. Direct age-sex standardization used the fixed pooled 1999–2024 age-sex distribution of all deaths with stated age as the reference distribution, with identical weights applied to both mortality groups. Ninety-five percent confidence intervals (CIs) for standardized proportions were calculated using stratum-specific binomial variances and fixed reference weights.

Absolute temporal change was defined as the difference between the 2024 and 1999 standardized proportions, and relative change was calculated relative to the 1999 value. Annual cancer-minus-noncancer differences and cancer-to-noncancer standardized proportion ratios were also calculated. Differential change was defined as the absolute 1999–2024 change in the cancer-attributed group minus the corresponding absolute change in the noncancer-attributed group. Delta-method variance estimates were used for absolute contrasts, whereas relative measures were evaluated on the log scale.

2.4. Primary Temporal Analysis

The primary inferential analysis used grouped-binomial logistic regression, with sepsis-involved deaths as the numerator and total deaths as the denominator within each calendar year × age group × sex × cancer-status stratum. Calendar year was modeled using a centered natural cubic spline with 4 degrees of freedom (df) to allow nonlinear temporal variation while limiting model complexity across the 26 annual observations [11]. Alternative linear, 3-df, and 5-df temporal specifications were evaluated in sensitivity analyses (Supplementary Table S8). The model included the full cancer status × age group × sex factorial structure and cancer status × calendar-time spline interactions. The primary comparative estimand was the difference in temporal trajectories of recorded sepsis involvement between cancer-attributed and noncancer-attributed deaths. The primary inferential test was the global 4-df cancer status × calendar-time interaction. Residual overdispersion was assessed using the Pearson chi-square statistic divided by the residual degrees of freedom (14.402 for the

primary model), and the model covariance matrix was adjusted using the estimated Pearson dispersion scale [12].

Model-based marginal predictions were standardized to the same fixed pooled 1999–2024 age-sex reference distribution used in the direct standardization analyses. These predictions provided model-based estimates of the temporal trajectories and endpoint contrasts, whereas the directly standardized observed proportions were descriptive estimates calculated without temporal smoothing. The two were therefore reported separately. The directly standardized endpoint contrast was prioritized for describing the magnitude of the observed 1999–2024 change, whereas the spline model was used for inference regarding the overall temporal trajectories and for model-based marginal predictions.

2.5. Segmented Temporal Analysis

Annual directly standardized proportions were additionally analyzed separately for cancer-attributed and noncancer-attributed deaths using weighted segmented log-linear regression. Models containing 0–3 joinpoints were evaluated without prespecified breakpoints; admissible joinpoints were restricted to observed calendar years, and the model with the lowest Bayesian information criterion (BIC) was retained [13,14]. Annual percent change (APC) was calculated from segment-specific log-linear slopes. Joinpoint-location 95% CIs were estimated using 10,000 parametric bootstrap replicates. Because joinpoints were estimated separately by mortality group, segment-specific APCs were used only for within-group temporal description; formal inference regarding differences in temporal trajectories between mortality groups was based on the primary grouped-binomial spline model. Full specifications are provided in the Supplementary Methods.

2.6. Secondary and Sensitivity Analyses

Secondary analyses examined age-specific patterns, solid versus hematologic malignancies, and seven major cancer sites: lung, colorectal, female breast, male prostate, pancreas, liver and intrahepatic bile duct, and stomach. Solid malignancies were defined as ICD-10 C00–C80 or C97 and hematologic malignancies as C81–C96. Malignancy-class comparisons used the grouped-binomial 4-df spline framework with a malignancy class × calendar-time interaction. Site-specific temporal associations were evaluated separately, with Benjamini–Hochberg correction across the seven global temporal tests [15]. No formal pooled site × calendar-time heterogeneity test was performed.

Sensitivity analyses evaluated linear calendar time; 3- and 5-df spline specifications; Huber–White robust covariance; generalized estimating equations; restriction to 1999–2019; exclusion of 2020 or 2020–2022; a full-period model including a 2020–2022 indicator and its interaction with cancer status; alternative 1999, 2010, and 2019 standardization reference distributions; and an A41.0–A41.9-only sepsis definition. An additional comparator-definition sensitivity analysis excluded deaths in which sepsis (ICD-10 A40–A41) was the underlying cause from the noncancer-attributed comparator, thereby restricting both mortality groups to deaths in which sepsis, when present, was recorded as a non-underlying multiple cause. Detailed specifications are reported in the Supplementary Methods and Supplementary Table S12.

2.7. Statistical Software

All statistical tests were two-sided, with $p < 0.05$ considered statistically significant. Given the large sample size, interpretation emphasized effect estimates and 95% CIs in addition to statistical significance. Analyses were performed in Python 3.13.5 using pandas 2.2.3, NumPy 2.3.5, SciPy 1.17.0, patsy 1.0.2, and statsmodels 0.14.6; graphics were generated using Matplotlib 3.10.8.

3. Results

3.1. Study Population and Sepsis Involvement

During 1999–2024, the analytic series included 69,714,059 deaths, comprising 15,091,681 cancer-attributed and 54,622,378 noncancer-attributed deaths. Sepsis was recorded among the multiple causes of death in 572,524 cancer-attributed deaths and 4,095,662 noncancer-attributed deaths. The corresponding period-wide crude sepsis-involvement proportions were 3.79% and 7.50%, respectively (Table 1; Figure 1). Annual death counts and crude sepsis-involvement proportions are reported in Supplementary Table S3.

Table 1. Characteristics of cancer-attributed and noncancer-attributed deaths and recorded sepsis involvement in the United States, 1999–2024.

Characteristic	Cancer-Attributed Deaths	Noncancer-Attributed Deaths	All Deaths
Mortality cohort			
Deaths, *n*	15,091,681	54,622,378	69,714,059
Deaths involving sepsis, *n*	572,524	4,095,662	4,668,186
Sepsis involvement, %	**3.79**	**7.50**	**6.70**
Characteristics of deaths involving sepsis *			
Male, *n (%)*	313,460 (54.8)	1,967,027 (48.0)	2,280,487 (48.9)
Female, *n (%)*	259,050 (45.2)	2,128,493 (52.0)	2,387,543 (51.1)
Age group, *n (%)*			
0–14 y	2422 (0.4)	26,029 (0.6)	28,451 (0.6)
15–24 y	3634 (0.6)	15,306 (0.4)	18,940 (0.4)
25–34 y	6673 (1.2)	43,440 (1.1)	50,113 (1.1)
35–44 y	16,774 (2.9)	106,900 (2.6)	123,674 (2.6)
45–54 y	50,197 (8.8)	266,742 (6.5)	316,939 (6.8)
55–64 y	119,990 (21.0)	543,797 (13.3)	663,787 (14.2)
65–74 y	168,939 (29.5)	847,297 (20.7)	1,016,236 (21.8)
75–84 y	143,861 (25.1)	1,155,357 (28.2)	1,299,218 (27.8)
≥85 y	60,020 (10.5)	1,090,652 (26.6)	1,150,672 (24.7)

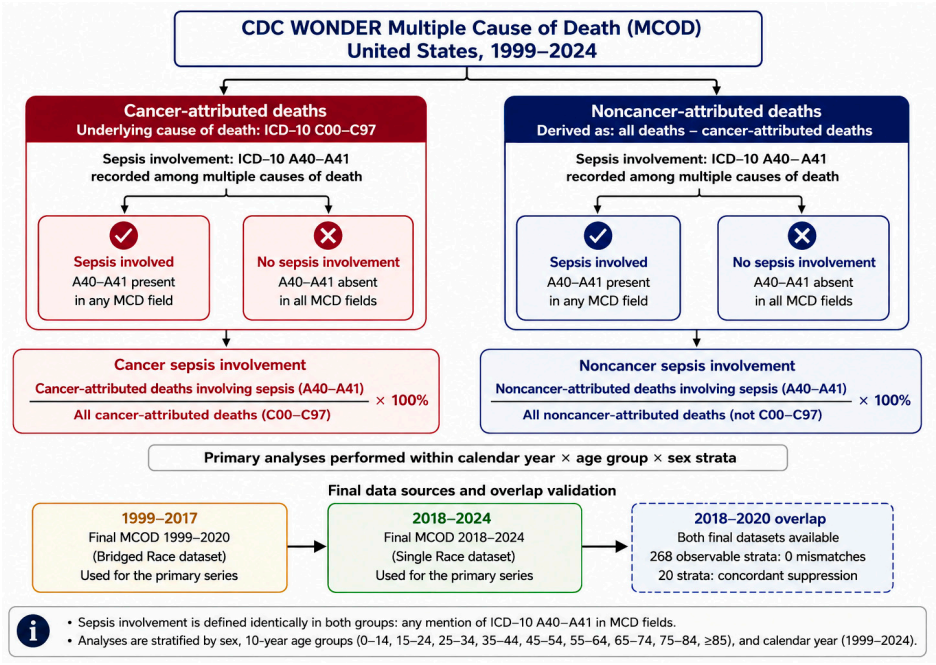

Figure 1. Study design and denominator framework.

Cancer-attributed deaths were defined as deaths with malignant neoplasms (ICD-10 C00–C97) recorded as the underlying cause of death. Sepsis involvement was defined by the presence of ICD-10 codes A40–A41 among the multiple causes of death. Noncancer-attributed deaths were derived by subtracting cancer-attributed deaths from all-cause deaths; the corresponding sepsis-involved counts were derived analogously.

* Demographic distributions were calculated among sepsis-involved deaths with stated age. Age was not stated for 14 cancer-attributed, 142 noncancer-attributed, and 156 total sepsis-involved deaths (<0.01% in each group); these records were excluded from sex- and age-distribution percentages because exact sex allocation of suppressed age-not-stated cells could not be reconstructed. Accordingly, the demographic denominators were 572,510, 4,095,520, and 4,668,030, respectively.

Final CDC WONDER Multiple Cause of Death data were combined using 1999–2017 observations from the 1999–2020 final dataset and 2018–2024 observations from the 2018–2024 Single Race final dataset. Death counts were identical across the two sources during the overlapping 2018–2020 period.

Cancer-attributed deaths were defined as deaths with malignant neoplasms (ICD-10 C00–C97) recorded as the underlying cause of death. Sepsis involvement was defined by ICD-10 A40–A41 recorded among multiple causes of death. Noncancer-attributed deaths were derived by subtracting cancer-attributed deaths from all deaths, and noncancer deaths involving sepsis were derived by subtracting cancer-attributed deaths involving sepsis from all deaths involving sepsis. Analyses were conducted within calendar year, age-group, and sex strata. Data for 1999–2017 were obtained from the final 1999–2020 Multiple Cause of Death dataset and data for 2018–2024 from the final 2018–2024 Single Race dataset. The overlapping 2018–2020 period was used for cross-dataset validation; all 268 strata with observable counts matched exactly, while the remaining 20 paired strata showed concordant suppression.

3.2. Temporal Trends in Cancer- and Noncancer-Attributed Deaths

After age-sex standardization, sepsis involvement among cancer-attributed deaths increased from 3.21% (95% CI, 3.16–3.27%) in 1999 to 4.69% (95% CI, 4.63–4.76%) in 2024, corresponding to an absolute change of +1.48 percentage points (95% CI, 1.40–1.57) and a relative change of +46.1% (95% CI, 43.0–49.4%). Among noncancer-attributed deaths, the standardized proportion increased from 6.75% (95% CI, 6.71–6.78%) to 7.89% (95% CI, 7.86–7.93%), corresponding to an absolute change of +1.15 percentage points (95% CI, 1.10–1.20) and a relative change of +17.0% (95% CI, 16.2–17.8%). The between-group differential absolute change was +0.34 percentage points (95% CI, 0.24–0.43), and the ratio of the 2024-to-1999 proportional changes between cancer-attributed and noncancer-attributed deaths was 1.249 (95% CI, 1.221–1.278). The global cancer status × calendar-time interaction was significant (Wald χ^2 [4] = 525.13; $p < 0.001$) (Table 2; Figures 2 and 3; Supplementary Table S4). Crude and directly standardized annual trajectories are shown together in Supplementary Figure S1. The primary spline model yielded a model-based differential change of +0.61 percentage points (95% CI, 0.39–0.83), compared with the directly standardized observed differential change of +0.34 percentage points (95% CI, 0.24–0.43). This difference reflects the fitted temporal trajectories, which produce endpoint predictions that differ from the directly standardized observed values despite using the same age–sex reference distribution. The directly standardized estimate was therefore used to describe the magnitude of the observed endpoint change, while the spline model was used to assess differences across the full temporal trajectories (Supplementary Tables S8 and S10).

The standardized cancer-minus-noncancer difference was −3.54 percentage points (95% CI, −3.60 to −3.47) in 1999, −4.51 percentage points (95% CI, −4.58 to −4.45) in

2015, and −3.20 percentage points (95% CI, −3.27 to −3.13) in 2024. The corresponding standardized cancer-to-noncancer proportion ratios were 0.476 (95% CI, 0.467–0.485), 0.460 (95% CI, 0.453–0.467), and 0.595 (95% CI, 0.587–0.603), respectively (Table 2).

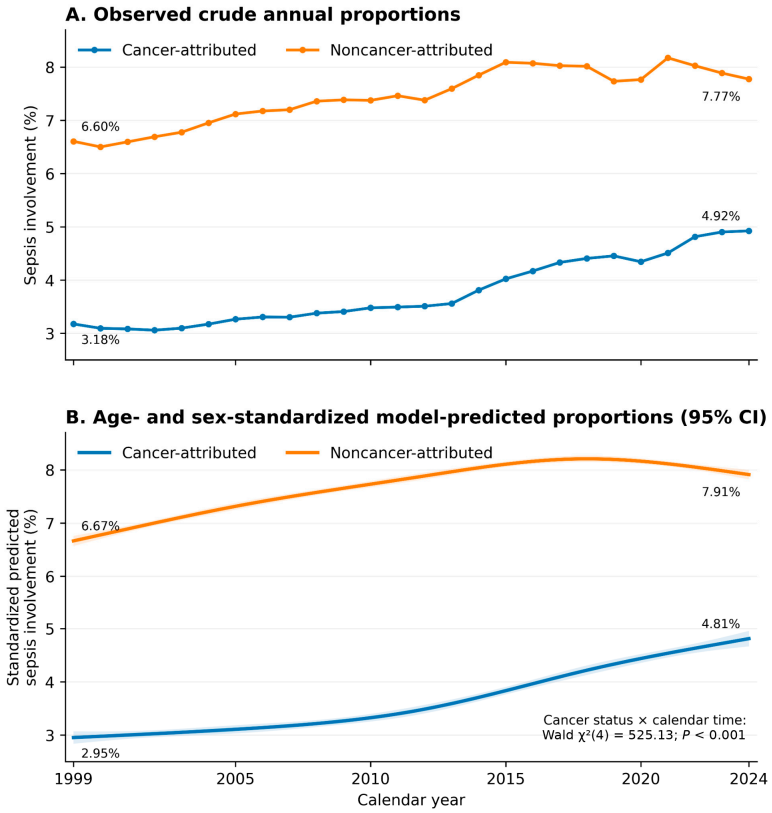

Figure 2. Age- and sex-standardized temporal trends in sepsis involvement among cancer-attributed and noncancer-attributed deaths, 1999–2024. Panel (**A**) shows observed annual crude proportions of deaths involving sepsis among cancer-attributed and noncancer-attributed deaths. Panel (**B**) shows age- and sex-standardized marginal predictions with 95% confidence intervals from the primary grouped-binomial logistic regression model, in which calendar year was modeled using a 4-df centered natural cubic spline and baseline cancer status × age group × sex effects were fully saturated. The global cancer status × calendar-time interaction was significant (Wald χ^2 [4] = 525.13; $p < 0.001$). No calendar breakpoint was prespecified or displayed.

Table 2. Temporal changes in sepsis involvement among cancer-attributed and noncancer-attributed deaths in the United States, 1999–2024.

Panel A. Observed and age- and sex-standardized sepsis involvement						
Year	**Cancer crude, %**	**Cancer standardized, % (95% CI)**	**Noncancer crude, %**	**Noncancer standardized, % (95% CI)**	**Absolute difference, pp (95% CI) ***	**Standardized proportion ratio (95% CI) †**
1999	3.18	3.21 (3.16–3.27)	6.60	6.75 (6.71–6.78)	−3.54 (−3.60 to −3.47)	0.476 (0.467–0.485)
2005	3.26	3.23 (3.17–3.28)	7.12	7.38 (7.34–7.42)	−4.15 (−4.21 to −4.08)	0.438 (0.430–0.446)
2010	3.48	3.42 (3.36–3.47)	7.37	7.66 (7.62–7.70)	−4.25 (−4.32 to −4.18)	0.446 (0.438–0.453)
2015	4.02	3.84 (3.78–3.90)	8.09	8.35 (8.32–8.39)	−4.51 (−4.58 to −4.45)	0.460 (0.453–0.467)
2019	4.45	4.27 (4.21–4.33)	7.73	7.93 (7.90–7.97)	−3.67 (−3.74 to −3.60)	0.538 (0.530–0.546)
2020	4.34	4.08 (4.02–4.14)	7.77	7.92 (7.89–7.95)	−3.85 (−3.91 to −3.78)	0.515 (0.507–0.522)

Table 2. *Cont.*

Panel A. Observed and age- and sex-standardized sepsis involvement						
Year	**Cancer crude, %**	**Cancer standardized, % (95% CI)**	**Noncancer crude, %**	**Noncancer standardized, % (95% CI)**	**Absolute difference, pp (95% CI) ***	**Standardized proportion ratio (95% CI) †**
2022	4.81	4.55 (4.49–4.61)	8.03	8.15 (8.12–8.19)	−3.60 (−3.67 to −3.53)	0.558 (0.551–0.566)
2024	4.92	4.69 (4.63–4.76)	7.77	7.89 (7.86–7.93)	−3.20 (−3.27 to −3.13)	0.595 (0.587–0.603)

Panel B. Change from 1999 to 2024 and primary temporal interaction			
Measure	**Cancer-attributed deaths**	**Noncancer-attributed deaths**	**Between-group comparison**
Standardized proportion, 1999, %	3.21 (3.16–3.27)	6.75 (6.71–6.78)	—
Standardized proportion, 2024, %	4.69 (4.63–4.76)	7.89 (7.86–7.93)	—
Absolute change, pp	+1.48 (1.40–1.57)	+1.15 (1.10–1.20)	Differential change: +0.34 (0.24–0.43)
Relative change, %	+46.1 (43.0–49.4)	+17.0 (16.2–17.8)	Ratio of relative changes: 1.249 (1.221–1.278)
Cancer status × calendar time interaction	—	—	Wald χ^2 (4) = 525.13; $p <$ 0.001

Abbreviations: CI, confidence interval; df, degrees of freedom; ICD-10, International Classification of Diseases, Tenth Revision; pp, percentage points. Cancer-attributed deaths were defined as deaths with malignant neoplasms (ICD-10 C00–C97) recorded as the underlying cause of death. Sepsis involvement was defined by the presence of ICD-10 codes A40–A41 among the multiple causes of death. Noncancer-attributed deaths and corresponding sepsis-involved deaths were derived by subtracting cancer-attributed counts from all-cause counts. Age- and sex-standardized proportions were standardized to a fixed pooled 1999–2024 age-sex distribution of all deaths using the following age categories: 0–14, 15–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, and ≥85 years. Dedicated year-by-sex queries combining ages <1, 1–4, and 5–14 years were used to construct the 0–14-year stratum and minimize suppression of small pediatric cells. The primary inferential analysis used grouped-binomial logistic regression with calendar year modeled using a natural cubic spline with 4 df, including a cancer status × calendar time interaction, with fully saturated baseline cancer status × age group × sex effects. Because residual overdispersion was identified, inference used Pearson scale correction. The global cancer status × calendar time interaction was evaluated using a Wald test. * Absolute difference was calculated as the standardized proportion among cancer-attributed deaths minus the standardized proportion among noncancer-attributed deaths; negative values therefore indicate lower absolute sepsis involvement among cancer-attributed deaths. † Standardized proportion ratio was calculated as the standardized proportion among cancer-attributed deaths divided by that among noncancer-attributed deaths.

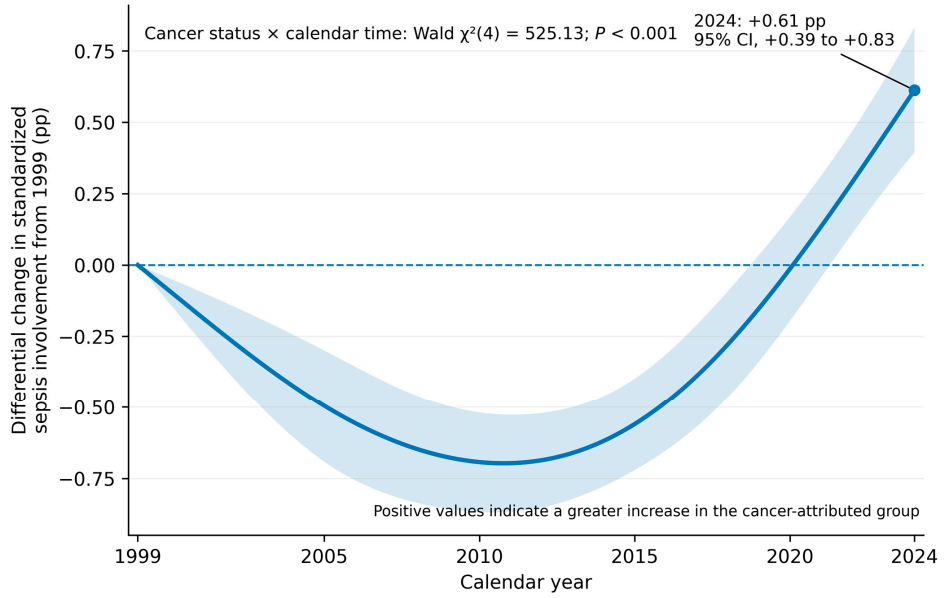

Figure 3. Differential change in standardized sepsis involvement between cancer-attributed and noncancer-attributed deaths, 1999–2024. The curve represents the model-based difference in temporal

change from the 1999 reference year, calculated as [(cancer proportion at year *t*—cancer proportion in 1999)—(noncancer proportion at year *t*—noncancer proportion in 1999)]. Shaded bands indicate 95% confidence intervals derived using the delta method. Positive values indicate a greater increase in standardized sepsis involvement among cancer-attributed than noncancer-attributed deaths relative to 1999. The global cancer status × calendar-time interaction was significant (Wald χ^2 [4] = 525.13; $p < 0.001$). No calendar breakpoint was prespecified.

3.3. Data-Driven Temporal Changes

In segmented analyses, three joinpoints were selected for each mortality group according to the minimum BIC (Table 3; Figure 4). Among cancer-attributed deaths, standardized sepsis involvement increased during 1999–2013 (APC, +0.82%; 95% CI, +0.60% to +1.05%; $p < 0.001$) and 2013–2017 (APC, +4.99%; 95% CI, +4.19% to +5.80%; $p < 0.001$), showed no statistically significant change during 2017–2020 (APC, −0.20%; 95% CI, −1.35% to +0.96%; $p = 0.723$), and increased during 2020–2024 (APC, +3.47%; 95% CI, +2.51% to +4.43%; $p < 0.001$). The estimated joinpoints were 2013, 2017, and 2020.

Table 3. Group-specific data-driven temporal trends in age- and sex-standardized sepsis involvement among cancer-attributed and noncancer-attributed deaths in the United States, 1999–2024.

Panel A. Segment-specific temporal trends

Group	Segment	Calendar period	APC, % (95% CI)	*p* value	Joinpoint year (95% CI)
Cancer-attributed deaths	1	1999–2013	+0.82 (+0.60 to +1.05)	<0.001	2013 (2011–2014)
	2	2013–2017	+4.99 (+4.19 to +5.80)	<0.001	2017 (2016–2018)
	3	2017–2020	−0.20 (−1.35 to +0.96)	0.723	2020 (2019–2021)
	4	2020–2024	+3.47 (+2.51 to +4.43)	<0.001	—
Noncancer-attributed deaths	1	1999–2008	+1.64 (+1.34 to +1.94)	<0.001	2008 (2003–2009)
	2	2008–2012	+0.09 (−0.55 to +0.73)	0.780	2012 (2010–2015)
	3	2012–2015	+2.65 (+1.82 to +3.48)	<0.001	2015 (2014–2019)
	4	2015–2024	−0.49 (−0.74 to −0.24)	<0.001	—

Panel B. Model selection according to the number of joinpoints

Number of joinpoints	Cancer-attributed deaths, BIC	ΔBIC	Noncancer-attributed deaths, BIC	ΔBIC
0	−86.052	39.432	−97.763	44.651
1	−109.140	16.344	−134.261	8.153
2	−117.258	8.226	−134.212	8.202
3	−125.484	0	−142.414	0

Abbreviations: APC, annual percent change; BIC, Bayesian information criterion; CI, confidence interval; df, degrees of freedom.

Annual directly age- and sex-standardized sepsis-involvement proportions were analyzed separately for cancer-attributed and noncancer-attributed deaths using weighted segmented log-linear regression. Candidate models containing 0 to 3 joinpoints were evaluated without prespecifying calendar breakpoints. Joinpoint locations were restricted to the observed annual grid, with at least two annual observations between adjacent joinpoints

and between a joinpoint and either endpoint. Models were fitted by weighted least squares to the logarithm of the annual standardized proportion using inverse-variance weights based on the corresponding annual standard errors. For each specified number of joinpoints, the lowest BIC among all admissible joinpoint configurations is reported in Panel B; the BIC difference was calculated relative to the lowest BIC within each mortality group. The overall model with the lowest BIC was retained, resulting in three joinpoints for each group. APC was calculated as $100 \times [\exp(\text{beta}) - 1]$, where beta represents the segment-specific log-linear slope. Ninety-five percent CIs and two-sided p values for APCs were derived from the fitted-model covariance matrix using the residual degrees of freedom. Ninety-five percent CIs for joinpoint locations were estimated using 10,000 parametric bootstrap replicates, conditional on the selected number of joinpoints, with joinpoint locations re-estimated over the same admissible annual grid in each replicate. Because joinpoints were estimated separately within each mortality group, the resulting calendar segments were not constrained to coincide between cancer-attributed and noncancer-attributed deaths. Accordingly, segment-specific APCs describe within-group temporal trajectories and were not used for formal between-group slope comparisons. The formal comparison of temporal trajectories was performed in the primary grouped-binomial spline model using the global cancer status x calendar-time interaction (Wald chi-square [4 df] = 525.13; $p < 0.001$).

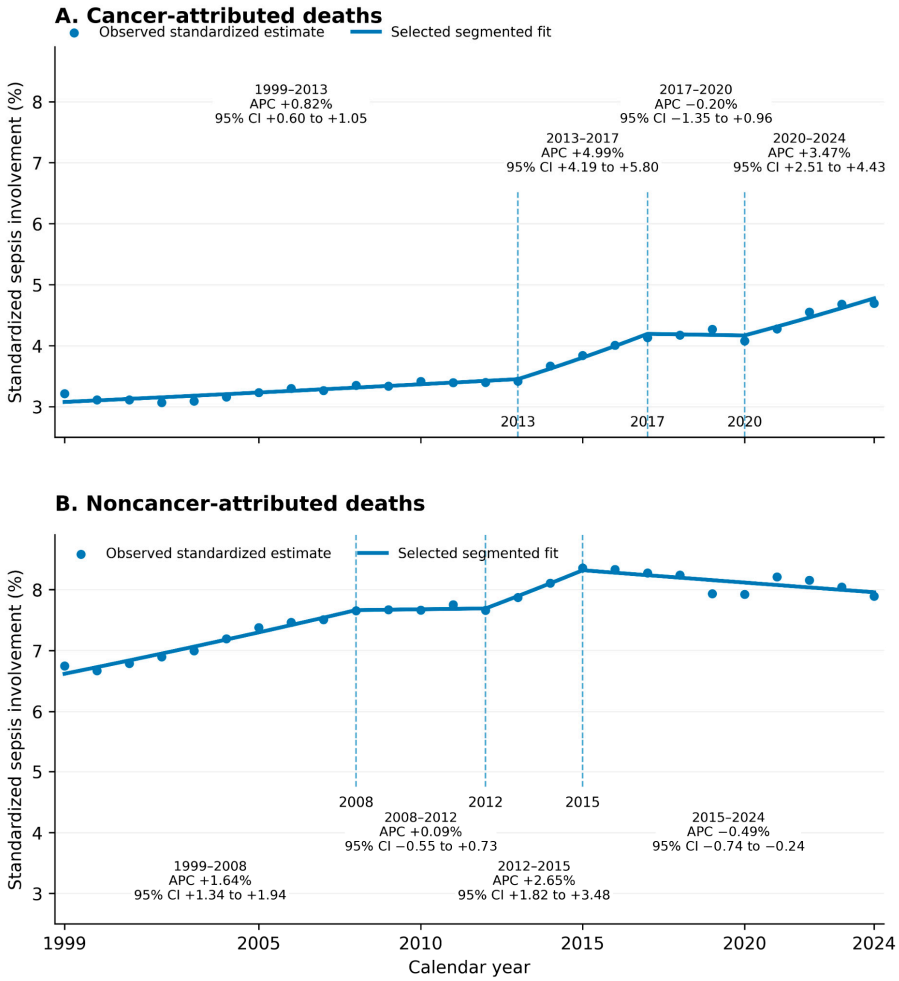

Figure 4. Data-driven temporal inflection points in age- and sex-standardized sepsis involvement, 1999–2024. Annual points represent directly age- and sex-standardized sepsis-involvement proportions among (**A**) cancer-attributed and (**B**) noncancer-attributed deaths. Solid lines represent the selected segmented log-linear models. Vertical dashed lines indicate data-driven joinpoints identified without prespecifying calendar breakpoints. Models allowing 0 to 3 joinpoints were compared using

the Bayesian information criterion, with the lowest-BIC model retained. Segment-specific annual percent changes (APCs) and 95% confidence intervals are displayed within each panel. Joinpoint-location confidence intervals and complete model estimates are reported in Table 3. Both panels use an identical y-axis scale to facilitate direct visual comparison.

Among noncancer-attributed deaths, standardized sepsis involvement increased during 1999–2008 (APC, +1.64%; 95% CI, +1.34% to +1.94%; $p < 0.001$), showed no statistically significant change during 2008–2012 (APC, +0.09%; 95% CI, −0.55% to +0.73%; $p = 0.780$), increased during 2012–2015 (APC, +2.65%; 95% CI, +1.82% to +3.48%; $p < 0.001$), and decreased during 2015–2024 (APC, −0.49%; 95% CI, −0.74% to −0.24%; $p < 0.001$). The estimated joinpoints were 2008, 2012, and 2015.

3.4. Age-, Malignancy Class-, and Cancer Site-Specific Analyses

Between 1999 and 2024, cancer-attributed sepsis-involvement proportions decreased in both sexes at ages 0–14 and 15–24 years and increased in both sexes across the 25–34 through 75–84-year age groups. At age ≥ 85 years, the absolute changes were +0.13 percentage points among females and +0.76 percentage points among males (Supplementary Table S5 and Supplementary Figure S2).

For solid malignancies, the standardized sepsis-involvement proportion increased from 2.37% (95% CI, 2.32–2.42%) in 1999 to 4.09% (95% CI, 4.03–4.15%) in 2024, an absolute change of +1.71 percentage points (95% CI, 1.64–1.79) and a relative change of +72.2% (95% CI, 67.8–76.7%). For hematologic malignancies, the corresponding proportions were 9.24% (95% CI, 8.99–9.48%) and 10.20% (95% CI, 9.93–10.47%), with an absolute change of +0.96 percentage points (95% CI, 0.60–1.32) and a relative change of +10.4% (95% CI, 6.3–14.6%). The malignancy class × calendar-time interaction was significant (Wald χ^2 [4] = 972.69; $p < 0.001$) (Supplementary Table S6).

Standardized sepsis involvement increased between 1999 and 2024 in each of the seven examined cancer sites. All seven global temporal tests were significant after Benjamini–Hochberg adjustment. Relative changes ranged from +44.8% for stomach cancer to +139.3% for lung cancer. Absolute changes ranged from +1.37 percentage points for stomach cancer to +2.31 percentage points for liver and intrahepatic bile duct cancer (Supplementary Table S7 and Supplementary Figure S3).

3.5. Sensitivity Analyses

The cancer status × calendar-time interaction was significant with 3-df and 5-df natural cubic splines, a linear-time specification, Huber–White robust covariance estimation, and generalized estimating equations (all $p < 0.001$). Model-based differential changes at 2024 ranged from +0.55 to +0.63 percentage points across these temporal and covariance specifications (Supplementary Table S8 and Supplementary Figure S4).

Using the 1999, 2010, or 2019 all-death age-sex distributions as alternative standardization references yielded 1999–2024 differential changes of +0.30, +0.35, and +0.32 percentage points, respectively, compared with +0.34 percentage points using the primary pooled 1999–2024 reference distribution (Supplementary Table S9).

When the analysis was restricted to 1999–2019, the model-based differential change between the endpoints was 0.00 percentage points (95% CI, −0.20 to 0.20), despite a significant global cancer status × calendar-time interaction (Wald χ^2 [4] = 220.08; $p < 0.001$). The endpoint contrast captures the net differential change between 1999 and 2019, whereas the global interaction evaluates differences across the entire fitted temporal trajectories; therefore, the near-zero endpoint contrast does not imply identical temporal patterns between the mortality groups. After exclusion of 2020 alone, the 1999–2024 differential change was +0.61 percentage points (95% CI, 0.40–0.81); after exclusion of 2020–2022, it was +0.68 percentage

points (95% CI, 0.48–0.89). In the full-period pandemic-adjusted model, the corresponding differential change was +0.67 percentage points (95% CI, 0.44–0.90) (Supplementary Table S10).

With sepsis restricted to ICD-10 A41.0–A41.9, the standardized 1999–2024 change was +1.50 percentage points (95% CI, 1.41–1.58) among cancer-attributed deaths and +1.21 percentage points (95% CI, 1.16–1.26) among noncancer-attributed deaths, yielding a differential change of +0.29 percentage points (95% CI, 0.19–0.39). The global cancer status × calendar-time interaction was significant (Wald χ^2 [4] = 526.44; $p < 0.001$) (Supplementary Table S11).

Finally, after excluding deaths in which sepsis was the underlying cause from the noncancer comparator, the directly standardized differential change was +0.28 percentage points (95% CI, 0.19–0.38). In the corresponding grouped-binomial model, the mortality-group × calendar-time interaction was significant (Wald χ^2 [4] = 325.98; $p < 0.001$) (Supplementary Table S12).

4. Discussion

In this national analysis of nearly 70 million US deaths between 1999 and 2024, recorded sepsis involvement increased among both cancer-attributed and noncancer-attributed deaths. The absolute increase was modestly greater among cancer-attributed deaths (+1.48 vs. +1.15 percentage points), yielding a between-group differential of +0.34 percentage points. Importantly, the pre-pandemic analysis showed a near-zero net differential endpoint change between 1999 and 2019 despite differences in the overall temporal trajectories, whereas the full-period analysis showed a positive differential endpoint change by 2024. Patterns also differed by malignancy class: hematologic malignancies had higher absolute sepsis involvement, whereas solid malignancies showed the larger relative increase; increases were also observed across all seven cancer sites examined. Taken together, these findings indicate a modest but changing pattern of recorded sepsis involvement in cancer-attributed mortality and warrant cautious interpretation in light of potential changes in death-certificate ascertainment and coding practices.

Our findings extend prior work by shifting the focus from population-based cancer–sepsis mortality rates or outcomes after sepsis to the proportion of cancer-attributed deaths in which sepsis was recorded. A recent CDC WONDER analysis by Magsi et al. reported declining age-adjusted population mortality rates for deaths with co-recorded neoplasms and sepsis through 2023 [6]. In addition to using a population-based denominator, that study was restricted to adults aged ≥ 25 years and used ICD-10 codes C00–D48 for neoplasms and A41 for sepsis. In contrast, our analysis included all age groups, defined cancer-attributed deaths by malignant neoplasms (C00–C97) as UCD and identified recorded sepsis involvement using A40–A41. These differences in study populations, case definitions, and denominators limit direct comparison of the reported temporal trends. Beyond these differences in case definitions and denominators, our study extends previous research by directly comparing recorded sepsis involvement between mutually exclusive cancer-attributed and noncancer-attributed mortality groups within a common age–sex standardization framework. This approach enables a formal comparison of temporal trajectories and provides a complementary epidemiological perspective that cannot be obtained from population-based cancer–sepsis mortality rates alone. Similarly, a nationwide analysis of more than 19 million US sepsis hospitalizations found declining in-hospital mortality among patients both with and without cancer [16], while contemporary cancer cohorts continue to report substantial short-term mortality after sepsis and critical illness [17,18]. Collectively, these findings highlight that population mortality, hospital case fatality, and death-certificate

sepsis involvement capture distinct dimensions of the cancer–sepsis burden and should not be interpreted interchangeably.

The comparison between cancer-attributed and noncancer-attributed deaths provides important context for interpreting temporal changes in recorded sepsis involvement. Although sepsis involvement was consistently lower among cancer-attributed deaths, this finding should not be interpreted as indicating lower sepsis susceptibility among individuals with cancer, because the groups were defined by UCD rather than individual-level cancer status. Moreover, sepsis itself could be designated as the underlying cause within the noncancer comparator, introducing a structural difference between the mortality groups. The narrowing between-group difference and its persistence under the restricted comparator definition suggest that the observed temporal patterns were not solely attributable to this classification difference, although residual differences in death certification and sepsis ascertainment cannot be excluded. Previous studies have demonstrated that sepsis surveillance estimates are sensitive to case-identification methods and coding practices [7,19]. Accordingly, these findings are primarily relevant to interpreting national mortality surveillance rather than estimating individual-level sepsis risk or establishing changes in clinical sepsis incidence.

The concentration of the between-group divergence after 2019 warrants particular caution. Although the differential change persisted in analyses excluding 2020 alone or 2020–2022 and in a model explicitly accounting for the pandemic period, these sensitivity analyses cannot exclude persistent changes in sepsis recognition, documentation, or coding that may have followed the COVID-19 pandemic. Differences between clinical and code-based sepsis surveillance, together with potentially changing coding practices, further limit the interpretation of these death-certificate trends [7,19,20]. The contemporaneous noncancer comparator provides context for system-wide temporal changes, but it cannot fully account for differential ascertainment between mortality groups; cancer-attributed deaths may occur in settings with greater clinical surveillance or more detailed documentation of infectious complications. Accordingly, the post-2019 divergence should be interpreted as a difference in recorded sepsis involvement, without inferring a corresponding change in clinically occurring sepsis or a causal effect of the COVID-19 pandemic, cancer treatments, or health-system practices.

The variation observed across age groups and malignancy types is consistent with prior population-based studies showing substantial heterogeneity in sepsis-related mortality according to patient and tumor characteristics [21–23]. In our analysis, recorded sepsis involvement decreased among cancer-attributed deaths in the 0–14 and 15–24-year age groups but increased across the older age groups, indicating variation in temporal patterns by age. Hematologic malignancies had substantially higher absolute sepsis involvement than solid tumors, whereas the relative increase over time was considerably greater for solid malignancies. This distinction is clinically relevant because previous comparative cohorts have also demonstrated differences in infectious burden between hematologic and solid malignancies, including more frequent bacteremia in hematologic cancers, although malignancy class itself has not consistently been associated with hospital mortality after sepsis [24]. Sepsis involvement also increased across all seven cancer sites examined. A recent CDC WONDER analysis of co-recorded lung cancer and sepsis among adults aged $\geq$ 45 years similarly examined temporal mortality trends through 2024, but evaluated population-based age-adjusted mortality rates rather than sepsis involvement among cancer-attributed deaths [25]. Taken together, these findings support consideration of age and malignancy type when characterizing the cancer–sepsis burden, while the site-specific results should be interpreted as within-site temporal trends rather than evidence of formal between-site heterogeneity.

Strengths and Limitations

This study has several strengths, including 26 years of national coverage, a death-based denominator aligned with the study question, a contemporaneous noncancer comparator, direct age–sex standardization, formal comparison of temporal trajectories, and extensive sensitivity analyses. Cross-dataset validation also demonstrated exact agreement across all observable strata during the 2018–2020 overlap period. Several limitations should be considered. First, death-certificate ascertainment using ICD-10 codes A40–A41 may miss clinically recognized sepsis that was not documented or coded, and changes in sepsis recognition, documentation, and coding over time, including potentially persistent post-pandemic changes, may influence the observed temporal patterns [7,19,20]. Although the A41-only sensitivity analysis yielded similar findings, it evaluated robustness to a narrower coding definition and could not establish the clinical sensitivity of death-certificate coding in the absence of an independent clinical reference standard. Second, ascertainment may differ between mortality groups; cancer-attributed deaths may occur in settings with greater clinical surveillance or more detailed documentation of infectious complications, and the contemporaneous noncancer comparator cannot fully eliminate this possibility. Third, clinical information on cancer stage, treatment exposure, neutropenia, comorbidities, microbiology, antimicrobial therapy, and acute illness severity was unavailable, precluding attribution of the observed trends to specific treatments, infection patterns, or care practices. Fourth, the noncancer-attributed comparator encompassed a heterogeneous range of underlying causes of death and should not be regarded as a clinically homogeneous population. Because the groups were defined by underlying cause of death, the noncancer-attributed group could also include individuals with cancer whose deaths were attributed to another condition. Cause-specific subgroup analyses were not performed within the noncancer-attributed group; consequently, we could not determine whether temporal patterns differed across underlying-cause categories or whether changes in their relative contributions influenced the aggregate findings. Although excluding deaths with sepsis as the underlying cause from the noncancer comparator reduced this particular structural asymmetry and yielded similar temporal findings, this sensitivity analysis did not resolve the heterogeneity of the remaining noncancer-attributed deaths or eliminate other differences arising from underlying-cause-of-death classification. Finally, the repeated cross-sectional design permits population-level temporal comparisons but does not support individual-level risk estimation or causal inference. Accordingly, the observed patterns should be interpreted as changes in recorded sepsis involvement on death certificates rather than as direct evidence of changes in sepsis incidence or the effects of specific cancer treatments or health-care practices.

5. Conclusions

Recorded sepsis involvement among cancer-attributed deaths increased between 1999 and 2024, with a modestly greater absolute increase than among noncancer-attributed deaths and most of the between-group divergence occurring after 2019. Temporal patterns also varied by age and malignancy type, with particularly high absolute involvement in hematologic malignancies but larger relative increases in solid tumors. These findings characterize temporal changes in recorded sepsis involvement specifically among deaths for which cancer was designated as the underlying cause, without establishing changes in sepsis incidence or the effects of cancer treatments or health-care practices. Future studies incorporating clinical, treatment, and infection-specific data are needed to clarify the factors underlying the observed post-2019 patterns.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/medsci14080822/s1. Supplementary Methods; Figure S1: Crude versus age- and sex-standardized proportions of sepsis involvement among cancer-attributed and noncancer-attributed deaths, 1999–2024; Figure S2: Age-specific temporal trends in sepsis involvement among cancer-attributed and noncancer-attributed deaths in the United States, 1999–2024; Figure S3: Cancer site-specific temporal trajectories of standardized sepsis involvement among cancer-attributed deaths in the United States, 1999–2024; Figure S4: Sensitivity of the differential temporal change in standardized sepsis involvement to alternative calendar-time model specifications, 1999–2024; Table S1: CDC WONDER query definitions and construction of the analytic dataset; Table S2: Overlap validation of the CDC WONDER final mortality datasets, 2018–2020; Table S3: Annual death counts and crude proportions of sepsis involvement among cancer-attributed and noncancer-attributed deaths in the United States, 1999–2024; Table S4: Full coefficients, global tests, and diagnostics from the primary grouped-binomial spline model of sepsis involvement, 1999–2024; Table S5: Age- and sex-specific proportions of sepsis involvement among cancer-attributed and noncancer-attributed deaths in the United States, 1999, 2010, 2019, and 2024; Table S6: Temporal changes in age- and sex-standardized sepsis involvement among solid and hematologic malignancy-attributed deaths in the United States, 1999–2024; Table S7: Site-specific temporal changes in standardized sepsis involvement among cancer-attributed deaths in the United States, 1999–2024; Table S8: Sensitivity analyses of the temporal model specification for sepsis involvement, 1999–2024; Table S9: Sensitivity analyses using alternative age-sex standardization reference distributions; Table S10: Sensitivity analyses addressing the COVID-19 pandemic period; Table S11: Sensitivity of temporal changes in sepsis involvement to an A41-only coding definition; Table S12: Sensitivity analysis restricting the comparator group to deaths in which sepsis was not the underlying cause.

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Informed Consent Statement: Not applicable. This study used publicly available, deidentified, aggregate mortality data and included no identifiable patient information.

Data Availability Statement: The data analyzed in this study are publicly available through the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) Multiple Cause of Death database (https://wonder.cdc.gov/mcd.html) (accessed on 13 August 2026). The analysis used the final Multiple Cause of Death 1999–2020 dataset and the final Multiple Cause of Death 2018–2024 Single Race dataset. Detailed query definitions, data extraction procedures, analytic dataset construction, statistical methods, and sensitivity analysis specifications are provided in the Supplementary Materials, including the Supplementary Methods and Tables S1–S12. The statistical code supporting the principal analyses is available through Zenodo (https://doi.org/10.5281/zenodo.21956261).

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