

Research Article

Temporal trends in venous thromboembolism-related mortality among gastric cancer deaths in the United States, 1999–2020

Amerika Birleşik Devletleri'nde gastrik kanserde venöz tromboembolizm ilişkili mortalitenin zaman içindeki değişimi, 1999–2020

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Abstract

Aim: Venous thromboembolism (VTE) is a clinically important complication in gastric cancer, yet nationwide mortality trends remain poorly defined. We evaluated temporal trends in VTE-related mortality among gastric cancer deaths in the United States.

Material and Methods: This population-based time-trend study used the CDC WONDER Multiple Cause of Death database (1999–2020). Gastric cancer deaths were identified using ICD-10 code C16, and VTE using codes I26 and I80–I82. Annual proportions of gastric cancer deaths with concomitant VTE were calculated. Temporal trends and annual percent change (APC) were assessed using linear and log-linear regression models with joinpoint analysis.

Results: Among 254,449 gastric cancer deaths, 5,371 (2.11%) had concomitant VTE. The proportion of gastric cancer deaths with VTE increased from 1.52% in 1999 to 2.90% in 2020, corresponding to an overall APC of 3.47% (95% CI, 3.00–3.95; $p < 0.001$). Joinpoint analysis identified a change-point in 2012, after which the upward trend accelerated (APC, 6.30%). Increasing trends were observed in both females and males and across all age groups, with no significant heterogeneity by sex or age.

Conclusions: VTE-related mortality among gastric cancer deaths has risen steadily over the past two decades, highlighting the growing burden of cancer-associated thrombosis in gastric cancer.

Keywords: gastric cancer, venous thromboembolism, cancer-associated thrombosis, mortality trends, epidemiology, CDC WONDER

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Öz

Amaç: Venöz tromboembolizm (VTE), gastrik kanserde klinik açıdan önemli bir komplikasyon olmasına rağmen ülke düzeyindeki mortalite değişimleri yeterince tanımlanmamıştır. Bu çalışmada Amerika Birleşik Devletleri'nde gastrik kanser ölümleri arasında VTE ilişkili mortalitenin zaman içinde nasıl değiştiği değerlendirilmiştir.

Gereç ve Yöntemler: Bu popülasyon temelli zaman eğilimi analizinde 1999–2020 yıllarını kapsayan CDC WONDER Çoklu Ölüm Nedeni veritabanı kullanıldı. Gastrik kanser ölümleri altta yatan ölüm nedeni olarak ICD-10 C16 kodu ile, VTE ise I26 ve I80–I82 kodları ile tanımlandı. Gastrik kanser ölümleri içinde eşlik eden VTE oranları hesaplandı. Zaman içindeki değişim doğrusal ve log-doğrusal regresyon modelleri ile değerlendirilerek yıllık yüzde değişim (APC) hesaplandı ve joinpoint analizi uygulandı.

Bulgular: Toplam 254,449 gastrik kanser ölümü içinde 5,371 (%2,11) olguda eşlik eden VTE saptandı. Gastrik kanser ölümleri içinde VTE oranı 1999'da %1,52'den 2020'de %2,90'a yükseldi ve toplam APC %3,47 olarak bulundu (95% GA, %3,00–3,95; $p < 0,001$). Joinpoint analizi 2012 yılında bir kırılma noktası olduğunu ve bu tarihten sonra artışın hızlandığını gösterdi (APC %6,30). Artış eğilimleri kadın ve erkeklerde ve tüm yaş gruplarında benzerdi; cinsiyet veya yaşa göre anlamlı heterojenite saptanmadı.

Sonuç: Gastrik kanser ölümleri arasında VTE ilişkili mortalite son yirmi yılda belirgin şekilde artmıştır. Bu bulgular, gastrik kanserde kanser ilişkili tromboz yükünün giderek arttığını göstermektedir.

Anahtar Kelimeler: gastrik kanser, venöz tromboembolizm, kanser ilişkili tromboz, mortalitede zaman içindeki değişim, epidemiyoloji, CDC WONDER

Introduction

Gastric cancer remains one of the most common malignancies and a leading cause of cancer-related mortality worldwide [1,2]. Despite advancements in surgical techniques and the introduction of novel systemic therapies, the prognosis for patients with advanced disease remains poor. A significant contributor to this high morbidity and mortality is the development of systemic complications, among which cancer-associated thrombosis plays a critical role [3]. Venous thromboembolism (VTE), encompassing deep vein thrombosis and pulmonary embolism, is a frequent and potentially life-threatening complication in the oncological population, known to independently worsen patient outcomes and reduce overall survival [4–6].

The prothrombotic state in malignancy is driven by a complex interplay of tumor biology, patient-specific risk factors, and treatment-related toxicities [7]. Gastrointestinal malignancies, particularly gastric cancer, are inherently associated with a high thrombogenic potential due to the pronounced expression of tissue factor and the secretion of procoagulant mucins by tumor cells [8,9]. Furthermore, modern interventions, including major abdominal surgeries, central venous catheterizations, and multi-agent chemotherapeutic regimens, further amplify this risk [10,11]. While the clinical incidence and detrimental impact of VTE in gastric cancer cohorts are well documented, population-level data evaluating the long-term impact of VTE on gastric cancer mortality remains scarce.

Understanding these epidemiological shifts is crucial, especially considering the evolving landscape of cancer therapeutics and changing patient demographics over the past two decades [12]. Most existing literature relies on institutional cohorts or registries with limited follow-up, leaving a notable gap in identifying nationwide temporal trends. To address this knowledge gap, this study aimed to comprehensively evaluate the temporal trends of VTE-related mortality among gastric cancer deaths in the United States from 1999 to 2020. By utilizing a nationally representative mortality database, we sought to elucidate how the burden of VTE among patients dying from gastric cancer has evolved across different age and sex demographics over a 22-year period.

Material and Methods

Data Source and Study Design

This population-based, retrospective time-trend study utilized mortality data from the Centers for Disease Control and Prevention (CDC) Wide-ranging Online Data for Epidemiologic Research (WONDER) Multiple Cause of Death (MCO) database, covering the period from 1999 through 2020. The database compiles information derived from U.S. death certificates and provides nationally representative, de-identified mortality data. Because the study used publicly available and anonymized data, institutional review board approval and informed consent were not required.



Case Definition

Deaths attributed to gastric cancer were identified using the International Classification of Diseases, Tenth Revision (ICD-10) code C16 listed as the underlying cause of death. Venous thromboembolism (VTE) was defined by the presence of ICD-10 codes I26 (pulmonary embolism) and I80–I82 (deep vein thrombosis and other venous thromboses) recorded among MCOD.

Gastric cancer was required to be the underlying cause of death, whereas VTE could be listed in any position among MCOD.

VTE-related mortality among gastric cancer deaths was defined as the proportion of deaths with underlying cause C16 that had at least one VTE code listed as a contributing cause.

Variables and Stratification

Annual counts of total gastric cancer deaths and VTE-related gastric cancer deaths were extracted and aggregated by calendar year. Analyses were stratified by sex (female, male) and age.

For primary age-stratified analyses, age was dichotomized as <65 years and ≥65 years. For secondary analyses, detailed age categories were constructed (<50 years, 50–64 years, 65–74 years, and ≥75 years) using ten-year age groups provided by CDC WONDER.

Analyses by race/ethnicity were not performed to maintain parsimony and focus on temporal patterns and major demographic strata (sex and age).

Statistical Analysis

For each calendar year, the proportion of gastric cancer deaths with concomitant VTE was calculated by dividing the number of VTE-related gastric cancer deaths by the total number of gastric cancer deaths and multiplying by 100. Temporal trends in yearly proportions were first evaluated using ordinary least squares linear regression, with calendar year treated as a continuous independent variable. The slope of the regression line represented the absolute annual change in percentage points (p for trend). Annual percent change (APC) estimates were derived using log-linear regression models in which the natural logarithm of yearly proportions was regressed on calendar year. APC was calculated as: $APC = [\exp(\beta) - 1] \times 100$, where β represents the regression coefficient for calendar year. Ninety-five percent confidence intervals (95% CIs) were calculated as: $\exp(\beta \pm 1.96 \times SE) - 1$. To explore

potential changes in temporal patterns, piecewise segmented regression models with a single change-point were fitted. The optimal joinpoint year was identified by minimizing the residual sum of squares. APCs were estimated separately for periods before and after the identified joinpoint. All trend analyses were conducted for the overall population and separately stratified by sex and age.

Interaction Analyses

To assess whether temporal trends differed by sex or age group, interaction terms between calendar year and sex were included in linear regression models. For interaction analyses, age was dichotomized as <65 versus ≥65 years, and an interaction term between calendar year and age group was included. The statistical significance of interaction terms was evaluated to determine heterogeneity of trends across subgroups.

All statistical tests were two-sided, and a p value <0.05 was considered statistically significant. Analyses were performed using Python (version 3.12) with the statsmodels and scikit-learn libraries. Age-adjusted mortality rates were not calculated because the primary outcome was defined as the proportion of gastric cancer deaths with concomitant VTE rather than population-level mortality rates.

Results

A total of 254,449 gastric cancer deaths were identified in the United States between 1999 and 2020. Among these, 5,371 deaths (2.13%) had a concomitant mention of VTE. Of all gastric cancer deaths, 105,903 occurred in females and 148,546 in males. Overall, the proportion of gastric cancer deaths with VTE was 2.45% among females and 1.87% among males across the study period (Table 1).

The yearly proportion of gastric cancer deaths with VTE increased from 1.52% in 1999 to 2.90% in 2020 (Table 1, Figure 1A). Ordinary least squares regression demonstrated a significant upward linear trend in VTE-related mortality over time, corresponding to an absolute increase of 0.068 percentage points per year (95% CI, 0.057–0.080; $p < 0.001$) (Table 2). Log-linear models estimated an overall annual percent change (APC) of 3.47% (95% CI, 3.00–3.95; $p < 0.001$). Piecewise segmented regression identified a single change-point in 2012 (Table 2). Before 2012, the APC was 3.33% (95% CI, 2.41–4.25; $p < 0.001$), whereas after 2012 the APC increased to 6.30% (95% CI, 5.01–7.61; $p < 0.001$).

Table 1. Yearly sex-specific and overall proportion of gastric cancer deaths with venous thromboembolism (VTE), 1999–2020.

Year	Female GC deaths, n	Female VTE deaths, n	Female VTE %	Male GC deaths, n	Male VTE deaths, n	Male VTE %	Total GC deaths, n	Total VTE deaths, n	Total VTE %
1999	5,252	75	1.43	7,459	118	1.58	12,711	193	1.52
2000	5,317	66	1.24	7,328	91	1.24	12,645	157	1.24
2001	5,128	71	1.38	7,191	100	1.39	12,319	171	1.39
2002	5,065	88	1.74	7,133	98	1.37	12,198	186	1.52
2003	5,055	83	1.64	7,055	109	1.55	12,110	192	1.59
2004	4,901	93	1.90	7,043	119	1.69	11,944	212	1.77
2005	4,893	94	1.92	6,981	112	1.60	11,874	206	1.74
2006	4,862	102	2.10	6,855	117	1.71	11,717	219	1.87
2007	4,823	108	2.24	6,777	120	1.77	11,600	228	1.97
2008	4,771	110	2.31	6,676	119	1.78	11,447	229	2.00
2009	4,742	118	2.49	6,653	121	1.82	11,395	239	2.10
2010	4,698	123	2.62	6,559	127	1.94	11,257	250	2.22
2011	4,683	129	2.75	6,505	130	2.00	11,188	259	2.31
2012	4,641	137	2.95	6,462	134	2.07	11,103	271	2.44
2013	4,612	140	3.04	6,408	139	2.17	11,020	279	2.53
2014	4,588	142	3.09	6,385	139	2.18	10,973	281	2.56
2015	4,602	145	3.15	6,387	139	2.18	10,989	284	2.59
2016	4,770	146	3.06	6,663	141	2.12	11,433	287	2.51
2017	4,654	147	3.16	6,504	141	2.17	11,158	288	2.58
2018	4,623	146	3.16	6,420	141	2.20	11,043	287	2.60
2019	4,646	167	3.59	6,446	160	2.48	11,092	327	2.95
2020	4,702	166	3.53	6,531	160	2.45	11,233	326	2.90
Overall – Female	105,903	—	2.45	—	—	—	—	—	—
Overall – Male	—	—	—	148,546	—	1.87	—	—	—
Overall – Total	—	—	—	—	—	—	254,449	5,371	2.11

Abbrev.: GC, gastric cancer; VTE, venous thromboembolism.

Underlying cause of death was gastric cancer (ICD-10 C16). VTE was defined as ICD-10 codes I26 and I80–I82. Percentages represent VTE-related deaths divided by total gastric cancer deaths within each sex and year.

When stratified by sex, VTE-related mortality increased significantly over time in both females and males (Table 3, Figure 1B). In females, the APC was 3.59% (95% CI, 2.99–4.19), while in males the APC was 3.40% (95% CI, 2.81–3.99), with joinpoint years identified in 2012 for both groups (Table 3). Sex-specific segmented analyses demonstrated APCs of 4.02% (95% CI, 3.12–4.94) before 2012 and 5.57% (95% CI, 4.01–7.12) after 2012 among females, and 2.83% (95% CI, 2.01–3.67) before 2012 and 6.78% (95% CI, 5.23–8.41) after 2012 among males (Table 4).

Detailed age-stratified analyses showed increasing trends across all age categories (Table 5). The APC was 3.37% (95% CI, 1.88–4.89) for individuals aged <50 years, 2.16% (95% CI, 1.05–3.30) for those aged 50–64 years, 2.88% (95% CI, 1.88–3.89) for those aged 65–74 years, and 2.29% (95% CI, 1.33–3.27) for those aged ≥75 years. When age was analyzed using a binary classification (<65 vs ≥65 years), interaction analyses indicated no statistically significant heterogeneity in temporal trends by age group ($\beta = 0.011$, 95% CI –0.012 to 0.034; $p = 0.333$). Similarly, no statistically significant heterogeneity in temporal trends was observed by sex ($\beta = 0.009$, 95% CI –0.014 to 0.031; $p = 0.415$).

Table 2. Overall trend analysis of VTE-related mortality among gastric cancer deaths.

Analysis	Estimate	95% CI	P
Linear trend slope, % points/year	0.068	0.057 – 0.080	<0.001
APC, % (overall)	3.47	3.00 – 3.95	<0.001
Joinpoint year	2012	NA	NA
APC before joinpoint, %	3.33	2.41 – 4.25	<0.001
APC after joinpoint, %	6.30	5.01 – 7.61	<0.001

Abbrev.: APC, annual percent change; CI, confidence interval; GC, gastric cancer; VTE, venous thromboembolism.

Linear trends were assessed using ordinary least squares regression. APC estimates and 95% CIs were derived from log-linear segmented regression models.

Table 3. Sex-stratified overall trend analysis.

Sex	Linear slope, % points/year	P for trend	APC, %	95% CI	Joinpoint year
Female	0.072	<0.001	3.59	2.99 – 4.19	2012
Male	0.066	<0.001	3.40	2.81 – 3.99	2012

Abbrev.: APC, annual percent change; CI, confidence interval; GC, gastric cancer; VTE, venous thromboembolism.

Sex-specific APCs were calculated using log-linear regression. Joinpoints were identified using segmented regression minimizing residual sum of squares.

Table 4. Joinpoint-segmented APC by sex.

Sex	APC before 2012, %	95% CI	P value	APC after 2012, %	95% CI	P
Female	4.02	3.12 – 4.94	<0.001	5.57	4.01 – 7.12	0.004
Male	2.83	2.01 – 3.67	<0.001	6.78	5.23 – 8.41	<0.001

Abbrev.: APC, annual percent change; CI, confidence interval; GC, gastric cancer; VTE, venous thromboembolism.

APCs and 95% CIs were derived from log-linear segmented regression models stratified by sex.

Table 5. Trend analysis by detailed age categories.

Age group	APC, %	95% CI	P
<50 years	3.37	1.88 – 4.89	<0.001
50–64 years	2.16	1.05 – 3.30	0.001
65–74 years	2.88	1.88 – 3.89	<0.001
≥75 years	2.29	1.33 – 3.27	<0.001

Abbrev.: APC, annual percent change; CI, confidence interval; GC, gastric cancer; VTE, venous thromboembolism.

APC estimates and 95% confidence intervals were derived from log-linear regression models using yearly VTE proportions among gastric cancer deaths.

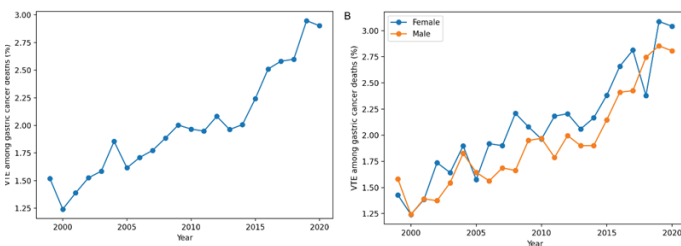


Figure 1. Temporal trends in venous thromboembolism-related mortality among gastric cancer deaths, 1999–2020. (A) Overall proportion of gastric cancer deaths with a concomitant mention of venous thromboembolism. (B) Sex-specific trends stratified by female and male patients. Venous thromboembolism was defined using ICD-10 codes I26 and I80–I82, and gastric cancer using ICD-10 code C16 (Abbrev.: GC, gastric cancer; VTE, venous thromboembolism).

Discussion

In this nationwide population-based study using CDC WONDER data, we demonstrate a substantial and steadily increasing burden of venous thromboembolism-related mortality among gastric cancer deaths in the United States between 1999 and 2020. The proportion of gastric cancer deaths with a concomitant mention of VTE nearly doubled over the study period, accompanied by a significant overall annual percent increase and a marked acceleration in trends after 2012. Importantly, rising VTE-related mortality was observed consistently in both females and males, with no evidence of sex-specific heterogeneity in temporal patterns. Similarly, increasing trends were present across all age categories, indicating that the growing burden of VTE among patients dying from gastric cancer is not confined to a

particular demographic subgroup. Collectively, these findings underscore a broad and worsening impact of VTE on gastric cancer-related mortality at the population level.

Several factors likely explain the steady increase in VTE-related mortality among gastric cancer deaths, which showed an overall annual percent change (APC) of 3.47%. A primary reason is the widespread use of high-resolution diagnostic imaging, such as computed tomography (CT). Over the past two decades, the routine use of CT scans for cancer staging, treatment monitoring, and follow-up has naturally led to higher detection rates of asymptomatic VTE [13,14]. In addition, increased clinical awareness of cancer-associated thrombosis among physicians has likely improved the reporting of VTE as a contributing cause on death certificates [3].

Changes in systemic treatments for gastric cancer also play a major role. The routine use of intensive chemotherapies, multi-agent regimens, and targeted therapies (such as anti-angiogenic agents) has improved patient survival. However, these treatments also increase vascular toxicity and thrombotic risks [15]. As patients with advanced gastric cancer live longer, their total time at risk for developing complications like VTE naturally increases. Therefore, the prothrombotic side effects of modern cancer treatments are likely a strong driver of the rising VTE mortality burden from 1999 to 2020 [16].

A key finding of our analysis is the distinct change-point in 2012. The segmented regression models showed a sharp acceleration in the upward trend, with the APC increasing from 3.33% before 2012 to 6.30% after 2012. This shift may correspond to major updates in international oncology guidelines (such as those by ASCO and NCCN) regarding the screening and management of cancer-associated thrombosis [17,18]. Furthermore, the broader adoption of electronic health records (EHR) and standardized mortality coding practices around this time may have increased the reported rates of VTE [19].

Finally, the rising rates of baseline comorbidities in the general population further increase VTE risks. Conditions that create a prothrombotic state, such as obesity, diabetes, and cardiovascular disease, have become much more common [20]. Notably, our data showed that the increasing VTE trend was not limited to older adults but was consistent across all age groups, including an APC of 3.37% for individuals under 50 years old. Interaction analyses confirmed no significant difference in trends by age group or sex, showing that the growing burden of VTE affects all demographic groups of patients with gastric cancer.

In conclusion, this population-based study shows a continuous and significant rise in VTE-related mortality among gastric cancer deaths in the United States from 1999 to 2020. The proportion of VTE-related deaths nearly doubled, with a sharp acceleration after 2012, affecting all age groups and both sexes equally. Despite recent advances in cancer treatments, the prothrombotic risks associated with modern therapies and changing patient demographics remain a major clinical challenge. Therefore, increased clinical vigilance, strict adherence to updated thromboprophylaxis guidelines, and personalized risk assessments are urgently needed to reduce this preventable cause of death in patients with gastric cancer.

Declaration of conflicting interests

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Ethics approval

Because the study used publicly available and anonymized data, institutional review board approval and informed consent were not required.

Authors' contribution

K.B.: Conceptualization, methodology, formal analysis, investigation, data curation, writing - original draft, visualization, project administration. G.C.U.: Methodology, software, investigation, data curation, writing - review & editing. E.Y.: Investigation, resources, data curation, writing - review & editing. H.Ş.: Investigation, resources, validation, writing - review & editing. G.İ.İ.: Conceptualization, methodology, resources, validation, writing - review & editing, supervision.

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