Original Research

Incidence and Effects on Mortality of Venous Thromboembolism in Elderly Women With Endometrial Cancer

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OBJECTIVE: To describe the incidence of thromboembolic events (venous thromboembolism) before and after the diagnosis of epithelial endometrial cancer and to evaluate the effects of these events on survival.

METHODS: We used the National Cancer Institute's Surveillance, Epidemiology, and End Results cancer registries linked to Medicare claim files to identify patients with epithelial endometrial cancer diagnosed between 1992 and 2009. To identify venous thromboembolism events 3 months before diagnosis and up to 24 months after diagnosis, we used International Classification of Diseases, 9th Revision, and Healthcare Common Procedure Coding System codes.

RESULTS: A total of 23,122 patients were included; of them 1,873 (8.1%) developed a venous thromboembolism. Patients with low-grade (grades 1 and 2) endometrioid adenocarcinoma had a significantly lower rate of venous thromboembolism 3 months before and 6 months after the diagnosis of cancer (3.6%; 95% confidence interval [CI] 3.3–3.9%) compared with carcinosarcoma (9.2%; 95% CI 7.8–10.8%), clear cell (6.9%; 95% CI 4.8–9.7%), uterine serous cancer (8.1%; 95% CI 7.01–9.3%), and grade 3 endometrioid adenocarcinoma (6.1%; 95% CI 5.4–6.9%) ($P<.001$). On multivariate analysis during the same time period, most recent time periods of diagnosis, carcinosarcoma histology compared with lower grade endometrial cancer, higher stage, African American race, marital status, chemotherapy delivery, and lymph node dissection were associated with increased risk of venous thromboembolism. The median overall survival for women who experienced a venous thromboembolism 3 months before the diagnosis of endometrial cancer was 31 months (95% CI 20–48 months); in women diagnosed with venous thromboembolism 6 months after the cancer diagnosis was 37 months (95% CI 31–44), and in women who did not experienced a venous thromboembolism was 111 months (95% CI 109–114). After adjusting for prognostic factors, there was an association between venous thromboembolism diagnosed 3 months before endometrial cancer (hazard ratio 1.69, 95% CI 1.34–2.13) or 6 months after the diagnosis (hazard ratio 1.57, 95% CI 1.44–1.71) and lower survival.

CONCLUSION: Patients with uterine serous cancer, carcinosarcoma, clear cell carcinoma, and grade 3 endometrioid adenocarcinoma had a higher rate of venous thromboembolism than patients with low-grade endometrioid adenocarcinoma. A diagnosis of venous thromboembolism was associated with decreased survival in elderly patients with endometrial cancer.

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Venous thromboembolism, including deep vein thrombosis (DVT) and pulmonary embolism (PE), has been associated with cancer, as an indication of possible occult disease, as a complication after a cancer diagnosis, and related to chemotherapy and other treatments.[1] The development of a persistent hypercoagulable state mediated by tumor activity is considered

a key feature in the pathogenesis of venous thromboembolism.[2] Estimates of the incidence of venous thromboembolisms in patients with cancer range from less than 1% to more than 25%, and venous thromboembolism is a known independent predictor of mortality.[3] Furthermore, venous thromboembolism appears to be most strongly correlated with advanced-stage disease and aggressive histology types.[4]

Venous thromboembolism incidence is particularly high in certain types of cancers, including endometrial cancer. A small number of studies have examined the incidence of venous thromboembolism and associated risk factors in this patient population. These studies have reported an association between venous thromboembolism and advanced stage, older age, high-grade histology, surgical management, and comorbidites.[5,6] However, these studies did not examine risk factors specific to endometrial cancer such as the effect of each of the different histology subtypes or the type of surgical and adjuvant treatment on the incidence of venous thromboembolism. The purpose of this study is to describe the incidence of endometrial cancer by histologic cell type and stage with the intent of better characterizing venous thromboembolism risk in a population-based cohort, to determine the risk factors and outcomes associated with the development of venous thromboembolism, and to evaluate the effects of these events on survival.

MATERIALS AND METHODS

We used the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) cancer registries linked to Medicare claim files to identify women 66 years of age and older diagnosed with endometrioid endometrial adenocarcinoma, uterine carcinosarcoma, uterine clear cell carcinoma, and uterine serous carcinoma between 1992 and 2009. We included carcinosarcoma given the epithelial component of this biphasic tumor.[7] Because all information from the program data is deidentified, informed consent by the study participants was unnecessary to perform the analyses and the study was exempt from the institutional review board. The SEER database is the largest population-based cancer registry in the United States, covering approximately 26% of the population. The data set contains patient demographic factors, cancer characteristics, types of treatment, vital status, and cause of death where applicable.[8] The SEER–Medicare linked database is augmented with Medicare claims data, which can be used to obtain additional clinical information.[9]

The main outcome of this study was the diagnosis of venous thromboembolism. International Classification of Diseases, 9th Revision, and Healthcare Common Procedure Coding System codes were used to identify venous thromboembolism events 3 months before diagnosis and up to 24 months after diagnosis. Diagnosis code 415.1x was identified as PE; codes 451, 453.1, 453.2, and 453.4 were identified as DVT; and codes 452, 453, 453.0, 453.3, 453.5, 453.6, 453.7, 453.8, and 453.9 were identified as other or unclassified venous thromboembolism. The other or unclassified category includes codes for various conditions such as portal vein thrombosis and Budd-Chiari syndrome; renal vein thrombosis; thrombosis of veins excluding the pulmonary, cerebral, and coronary veins; and embolism or thrombosis of unspecified veins among others. To determine baseline comorbidity status using a validated score used specifically for SEER–Medicare data, we limited our investigation to those women aged 66 years and older to have 12 months of Medicare claims data before diagnosis.[9] Women diagnosed by death certificate or at autopsy caused by endometrial cancer, patients who had other primary cancers, tumors that were not microscopically confirmed, or patients who were enrolled in a health maintenance organization were excluded. In addition, we excluded women with incomplete Medicare claims data (continuous part A and part B without part C enrollment) for 12 months before and after diagnosis through time of death or date of last follow-up. These exclusions were made to ensure that claims files were available for accurate detection of comorbidities and calculation of survival time from diagnosis to death.

Confirmation that chemotherapy was delivered within 6 months of diagnosis was obtained from Medicare claims. The identification of chemotherapy through Medicare claims has been previously described, and prior studies confirmed that this information is reliable.[9] Receipt of radiation was noted if it occurred in the SEER database or Medicare. Patients were considered to have been treated with a combination of adjuvant chemotherapy and radiotherapy if they had received both radiotherapy and chemotherapy within 6 months after diagnosis. We defined definitive surgery as procedures performed with curative intent or in anticipation of a subsequent curative treatment. Survival time was measured from the date of diagnosis until death, censoring, or last follow-up, as verified by the SEER program vital status determination.

Patient demographic and tumor variables were ascertained from the SEER data. Tumor stage was determined using the revised 2009 staging criteria of the International Federation of Gynecologists and Obstetricians.[10] Patients with grade 1 and 2 endometrioid

endometrial adenocarcinoma were considered low grade and patients with grade 3 endometrioid endometrial adenocarcinoma as high grade. Years of diagnosis were classified into one of three categorical groups: 1992–1998, 1999–2004, and 2005–2009. Marital status was categorized as: married, not married, or unknown. Geographic location was divided into geographic area of residence at the time of diagnosis: central, eastern, and western.[11] Individual measures of socioeconomic status were not available within the SEER–Medicare database. Median household income from zip code of residence was categorized into quartiles and used as a proxy for socioeconomic status and was derived from 1990 and 2000 census data, depending on the date of diagnosis and death. To assess the prevalence of comorbid disease in our cohort, we used the inpatient and outpatient Medicare claims and used the Klabunde adaptation of the Charlson comorbidity index.[12,13] Participants were assigned a score of 0, 1, or 2 or greater.

Distribution of demographic, clinical, and treatment characteristics was compared using χ^2 tests. A Student's t test was used to assess the significance of differences in the mean values of continuous variables. Standard univariate analyses were performed as were logistic regression models to describe predictors of venous thromboembolism after adjusting for prognostic factors expected to be associated with these events. We used the Kaplan–Meier method to estimate survival curves to compare observed survival between groups. Cox proportional hazards models were used to calculate adjusted group hazard ratios (HRs), and their 95% confidence intervals (CIs) were used to assess the importance of venous thromboembolism as an independent predictors of survival after adjusting for the following prognostic factors: stage, histology, age, race, period of diagnosis, SEER registry region, urban compared with rural setting, marital status, treatment modality, definitive surgical procedure, lymph node dissection, socioeconomic status, and comorbidity index. All statistical tests were two-sided and differences were considered statistically significant at $P<.05$.[14] We used R 2.9.2 for all statistical analyses.

RESULTS

The study included 23,122 women who were diagnosed with epithelial endometrial cancer from 1992 to 2009; of them 1,873 (8.1%) were diagnosed with a venous thromboembolism 3 months before diagnosis and up to 24 months after diagnosis. Among the total study population, 533 (28.4%) had a PE; 857 (45.7%) had a DVT; and 483 (25.7%) had other or unclassified venous thromboembolism. Two hundred one (10.7%) events were diagnosed 3 months before endometrial cancer diagnosis, 934 (49.9%) events occurred during the first 6 months after diagnosis, and 738 (39.4%) between 7 and 24 months. There were 229 women who had both a DVT and PE diagnosed in the period of 3 months before diagnosis and up to 24 months after diagnosis.

The mean age at diagnosis was 75.3 years for women who had a venous thromboembolism and 75.4 years for patients that did not ($P=.9$). Patients with low-grade (grades 1 and 2) endometrioid adenocarcinoma had a significantly lower rate of venous thromboembolism 3 months before and 6 months after the diagnosis of cancer (3.6%; 95% CI 3.3–3.9%) compared with carcinosarcoma (9.2%; 95% CI 7.8–10.8%), clear cell (6.9%; 95% CI 4.8–9.7%), uterine serous cancer (8.1%; 95% CI 7.01–9.3%), and grade 3 endometrioid adenocarcinoma (6.1%; 95% CI 5.4–6.9%) ($P<.001$). African American women had a higher rate of venous thromboembolism compared with white patients (14.3% compared with 7.6%; $P<.001$). Patients who experienced a venous thromboembolism had a higher rate of stage IV disease (20.6% compared with 7.8%; $P<.001$). Women who experienced a venous thromboembolism had definitive surgery less frequently (86.6% compared with 89.9%; $P<.001$); however, they had a higher rate of lymph node dissection (53.5% compared with 47.5%; $P<.001$) and received chemotherapy more frequently (25.3% compared with 10.1%; $P<.001$). There was not a significant difference in the rate of radiotherapy between the groups (Table 1).

Table 2 demonstrates the rates of venous thromboembolism among different histologies and stages. Patients with high-grade histologies had a significantly higher rate of venous thromboembolism diagnosed within 6 months and up to 24 months after diagnosis. Multivariate analyses were conducted to further evaluate the association between venous thromboembolism and endometrial cancer accounting for other clinical parameters (Table 3). When the analysis included any venous thromboembolism diagnosed 3 months before diagnosis or 6 months after, the models indicate that patient demographics and tumor characteristics were associated with venous thromboembolism. Compared with women with low-grade endometrioid, uterine carcinosarcoma was the only histology associated with venous thromboembolism. Stage was a particularly strong determinant with patients with higher stage being more likely to experience a venous thromboembolism. Most recent time periods of diagnosis, marital status, African American race, lymph node dissection, and receipt

Table 1. Demographic and Clinical Characteristics of the Study Population

Characteristic	Venous Thromboembolism	None	*P*
Total	1,873 (8.1)	21,249 (91.9)	
Mean age at diagnosis (y)	75.39 (6.47)	75.40 (6.63)	.9
Years of diagnosis			<.001
1991–1997	466 (24.9)	6,414 (30.2)	
1998–2003	773 (41.3)	8,566 (40.3)	
2004–2009	634 (33.8)	6,269 (29.5)	
Race			<.001
White	1,575 (84.1)	19,017 (89.5)	
African American	228 (12.2)	1,362 (6.4)	
Other	70 (3.7)	870 (4.1)	
SEER registry			<.001
Central	483 (25.8)	5,004 (23.5)	
East	670 (35.8)	7,046 (33.2)	
West	720 (38.4)	9,199 (43.3)	
Income (quartile)			.1
First	500 (26.7)	5,280 (24.8)	
Second	458 (24.5)	5,271 (24.8)	
Third	467 (24.9)	5,158 (24.3)	
Fourth	427 (22.8)	5,195 (24.4)	
Other	21 (1.1)	345 (1.6)	
Charlson score			.03
0	1,298 (69.3)	15,187 (71.5)	
1	313 (16.7)	3,504 (16.5)	
2 or greater	262 (14.0)	2,558 (12.0)	
Stage			<.001
I	837 (44.7)	13,944 (65.6)	
II	137 (7.3)	1,415 (6.7)	
III	319 (17.0)	1,824 (8.6)	
IV	385 (20.6)	1,660 (7.8)	
Unknown	195 (10.4)	2,406 (11.3)	
Histology			<.001
Endometrioid high grade	423 (22.6)	3,767 (17.7)	
Endometrioid low grade	904 (48.3)	14,028 (66.0)	
Carcinosarcoma	196 (10.5)	1,235 (5.8)	
Clear cell carcinoma	54 (2.9)	408 (1.9)	
Uterine serous cancer	296 (15.8)	1,811 (8.5)	
Lymph node examination status			<.001
Examined	1,002 (53.5)	10,085 (47.5)	
None examined	859 (45.9)	11,032 (51.9)	
Unknown	12 (0.6)	132 (0.6)	
Surgery			.005
None	237 (12.7)	2,050 (9.6)	
Laparoscopic surgery	36 (1.9)	757 (3.6)	
Laparotomy	1,391 (74.3)	16,037 (75.5)	
Unknown type of surgery	201 (10.7)	2,351 (11.1)	
Unknown if received surgery	8 (0.4)	54 (0.3)	
Radiation and chemotherapy			<.001
None	817 (43.6)	12,648 (59.5)	
Chemotherapy	292 (15.6)	1,221 (5.7)	
Radiation	583 (31.1)	6,458 (30.4)	
Chemotherapy and radiotherapy	181 (9.7)	922 (4.3)	

SEER, Surveillance, Epidemiology, and End Results.
Data are n (%) unless otherwise specified.
Distribution of categorical variables was compared using χ^2 tests.
A Student's *t* test was used to assess the significance of differences in the mean values of continuous variables.

Table 2. Rate of Venous Thromboembolism Stratified for Histology and Stage Groups

Tumor Features	Up to 3 Mo Before and 24 Mo After Diagnosis	Up to 3 Mo Before Diagnosis	Postdiagnosis Within 6 Mo	Postdiagnosis Within 24 Mo
Histology				
Endometrioid low grade	904 (6.1)	97 (0.6)	445 (3.0)	807 (5.4)
Endometrioid high grade	423 (10.1)	47 (1.1)	211 (5.0)	376 (9.0)
Carcinosarcoma	196 (13.7)	22 (1.5)	110 (7.7)	174 (12.2)
Clear cell carcinoma	54 (11.7)	3 (0.6)	29 (6.3)	51 (11.0)
Uterine serous carcinoma	296 (14.0)	32 (1.5)	139 (6.6)	264 (12.5)
Stage				
I	837 (5.7)	77 (0.5)	412 (2.8)	760 (5.1)
II	137 (8.8)	17 (1.1)	58 (3.7)	120 (7.7)
III	319 (14.9)	23 (1.1)	157 (7.3)	296 (13.8)
IV	385 (18.8)	58 (2.8)	220 (10.8)	327 (16.0)
Unknown	195 (7.5)	26 (1.0)	87 (3.3)	169 (6.5)

Data are n (%).

of chemotherapy were also independent predictors of an event. When the analyses included events diagnosed up to 24 months after diagnosis, we found that compared with women with low-grade endometrioid, uterine carcinosarcoma, uterine serous carcinoma, and high-grade endometrioid carcinoma were associated with venous thromboembolism; uterine clear cell carcinoma was not associated.

In the crude models for both all-cause mortality and cancer-specific mortality, women with a venous thromboembolism had an increased overall and disease-specific hazard of death compared with women who did not experience an event. The median follow-up of the entire study population was 105 months. Looking at all-cause mortality, the median overall survival for women who experienced a venous thromboembolism 3 months before the diagnosis of endometrial cancer was 31 months (95% CI 20–48 months), in women diagnosed with venous thromboembolism 6 months after the cancer diagnosis was 37 months (95% CI 31–44), and in women who did not experienced a venous thromboembolism was 111 months (95% CI 109–114). The overall unadjusted HR for women with a venous thromboembolism diagnosed 3 months before diagnosis was 2.1 (95% CI 1.8–2.5), and the disease-specific HR was 3 (95% CI 2.4–3.7). In addition, patients diagnosed with a venous thromboembolism within the first 6 months after diagnosis had lower all-cause mortality (2; 95% CI 1.8–2.1) and disease-specific survival (2.5; 95% CI 2.2–2.8).

Over the entire study period, after adjusting for stage, age, period of diagnosis, race, registry region, urban compared with rural setting, marital status, treatment modality, definitive surgical procedure, lymph node dissection, socioeconomic status, and comorbidity index, there was an association between venous thromboembolism documented before (HR 1.7, 95% CI 1.3–2.1) or after the diagnosis of endometrial cancer (HR 1.6, 95% CI 1.4–1.7) and lower disease-specific survival. The Cox proportional hazards model identified an independent association of higher stage, older age, and high-grade histologies with lower survival; in contrast to married women, higher socioeconomic status, patients who underwent definitive surgery, performance of lymph node dissection, and adjuvant chemotherapy were associated with improved disease-specific survival (Table 4).

DISCUSSION

In this population-based study using the SEER–Medicare database, we found a strong relationship between histology and the presence of metastatic disease at the time of diagnosis and the incidence of venous thromboembolism. Other factors such as race, lymph node dissection, and receipt of chemotherapy were also associated with venous thromboembolism. Additionally, there was a significant reduction in survival among women diagnosed with venous thromboembolism. Venous thromboembolism is a significant cause of death in patients with known malignancies, second only to the cancer diagnosis, and is a known prognostic factor.[15,16] Although there is a known association between cancer and thrombosis, the incidence of venous thromboembolism at the time of endometrial cancer diagnosis has not been well studied; the present investigation uses a national, population-based database to analyze the epidemiology of venous thromboembolism among women with newly diagnosed endometrial cancer.

In the present study we found that 7.2% of women were diagnosed with venous thromboembolism after their endometrial cancer diagnosis and up to

Table 3. Multivariate Logistic Regression Models of Factors Associated With Venous Thromboembolism

Factor	Diagnosed 3 Mo Before and Up to 6 Mo After Diagnosis	Diagnosed 3 Mo Before and Up to 24 Mo After Diagnosis
Age (y)		
66–70	Reference	Reference
71–75	1.00 (0.83–1.19)	0.97 (0.85–1.11)
76–80	1.03 (0.85–1.24)	1.03 (0.89–1.18)
>80	0.97 (0.79–1.19)	0.99 (0.85–1.14)
Years		
1991–1997	Reference	Reference
1998–2003	1.28 (1.07–1.53)	1.14 (1.01–1.30)
2004–2009	1.49 (1.23–1.79)	1.20 (1.05–1.38)
Race		
White	Reference	Reference
African American	1.28 (1.02–1.62)	1.45 (1.23–1.72)
Other	0.76 (0.52–1.11)	0.91 (0.70–1.18)
Marital status at diagnosis		
Unmarried	Reference	Reference
Married	0.83 (0.72–0.96)	0.92 (0.83–1.02)
Unknown	0.82 (0.57–1.20)	0.70 (0.52–0.93)
SEER registry		
Central	Reference	Reference
East	0.87 (0.73–1.04)	0.91 (0.80–1.03)
West	0.90 (0.75–1.07)	0.87 (0.76–0.99)
Income (quartile)		
First	Reference	Reference
Second	1.02 (0.84–1.23)	1.03 (0.90–1.18)
Third	1.11 (0.92–1.35)	1.10 (0.96–1.27)
Fourth	1.04 (0.84–1.27)	1.04 (0.90–1.21)
Other	0.89 (0.47–1.72)	0.88 (0.55–1.39)
Urban vs rural setting		
Urban	Reference	Reference
Rural	1.16 (0.73–1.86)	1.38 (1.00–1.91)
Charlson score		
0	Reference	Reference
1	0.99 (0.82–1.19)	1.06 (0.93–1.21)
2 or greater	0.94 (0.76–1.16)	1.14 (0.99–1.32)
Stage		
I	Reference	Reference
II	1.22 (0.91–1.63)	1.37 (1.13–1.66)
III	1.90 (1.53–2.35)	2.03 (1.74–2.37)
IV	2.79 (2.26–3.44)	2.47 (2.10–2.89)
Unknown	1.30 (1.00–1.70)	1.32 (1.10–1.58)
Histology		
Endometrioid low grade	Reference	Reference
Endometrioid high grade	1.16 (0.96–1.38)	1.21 (1.06–1.38)
Carcinosarcoma	1.47 (1.16–1.86)	1.39 (1.16–1.66)
Clear cell carcinoma	1.25 (0.83–1.87)	1.23 (0.91–1.66)
Uterine serous carcinoma	1.16 (0.93–1.46)	1.37 (1.17–1.61)
Lymph node examination status		
Examined	Reference	Reference
None examined	0.73 (0.63–0.86)	0.92 (0.82–1.02)
Unknown	0.77 (0.32–1.81)	0.86 (0.46–1.61)
Surgery		
None	Reference	Reference
Surgery	0.82 (0.65–1.03)	0.92 (0.78–1.09)
Unknown	0.93 (0.39–2.20)	1.21 (0.67–2.21)
Radiotherapy		
None	Reference	Reference
Radiation	0.96 (0.83–1.11)	1.10 (0.99–1.22)
Unknown	0.77 (0.40–1.48)	1.03 (0.67–1.59)
Chemotherapy		
None	Reference	Reference
Yes	1.62 (1.35–1.96)	1.65 (1.43–1.89)

SEER, Surveillance, Epidemiology, and End Results.
Data are odds ratio (95% confidence interval).

8.1% if we include women diagnosed with venous thromboembolism 3 months before their endometrial cancer diagnosis. Rodriguez et al[5] used a population-based inception registry cohort linked with the California Patient Discharge Data Set to define the incidence and time course of venous thromboembolism among patients with endometrial cancer diagnosed between 1993 and 1995 and 1997 and 1999. The authors found that among 18,440 women with uterine cancer, the 2-year cumulative incidence of venous thromboembolism was 2.7%. Although it is challenging to compare this study with our analysis as a result of differences in methodology and study population, the small differences in the rates between the studies can be attributed, at least in part, to the time periods analyzed. During the last 15 years there has been an increased use and better quality testing for venous thromboembolism; in addition, there has also been an increase in the use of computed tomography scanning to define the extent and progression of cancer that in some situations could detect asymptomatic cases of venous thromboembolism. In fact, in our study we found an increased rate of venous thromboembolism over time, from 6.8% in the period of 1992–1997 to 9.2% in the period of 2004–2009.

Limited data exist regarding the relationship among the different endometrial cancer histologies

Table 4. Multivariate Cox Proportional Hazards Model for Disease-Specific and Overall Mortality in the Entire Study Population

Factor	Cancer-Specific Mortality	All-Cause Mortality
Age (y)		
66–70	Reference	Reference
71–75	1.16 (1.06–1.26)	1.36 (1.28–1.43)
76–80	1.31 (1.19–1.43)	1.90 (1.80–2.01)
Older than 80	1.75 (1.60–1.91)	2.97 (2.81–3.14)
Years		
1991–1997	Reference	Reference
1998–2003	0.94 (0.88–1.02)	0.94 (0.90–0.98)
2004–2009	0.97 (0.89–1.06)	0.94 (0.89–1.00)
Race		
White	Reference	Reference
African American	1.09 (0.98–1.20)	1.21 (1.13–1.29)
Other	1.06 (0.91–1.22)	1.03 (0.94–1.13)
Marital status at diagnosis		
Unmarried	Reference	Reference
Married	0.89 (0.83–0.95)	0.85 (0.82–0.88)
Unknown	0.83 (0.70–0.98)	0.90 (0.82–0.98)
SEER registry		
Central	Reference	Reference
East	1.05 (0.97–1.14)	1.01 (0.96–1.06)
West	1.03 (0.96–1.12)	0.99 (0.95–1.04)
Income (quartile)		
First	Reference	Reference
Second	0.93 (0.85–1.01)	0.94 (0.89–0.99)
Third	0.93 (0.85–1.02)	0.94 (0.90–0.99)
Fourth	0.88 (0.80–0.96)	0.86 (0.82–0.91)
Other	0.59 (0.44–0.80)	0.88 (0.77–1.00)
Urban vs rural setting		
Urban	Reference	Reference
Rural	0.99 (0.79–1.24)	1.15 (1.02–1.31)
Charlson score		
0	Reference	Reference
1	1.01 (0.93–1.10)	1.26 (1.21–1.32)
2 or greater	1.08 (0.99–1.19)	1.72 (1.64–1.81)
Venous thromboembolism		
None	Reference	Reference
Diagnosed 3 mo prior	1.69 (1.34–2.13)	1.53 (1.30–1.80)
Diagnosed up to 6 mo after	1.57 (1.44–1.71)	1.60 (1.51–1.70)
Stage		
I	Reference	Reference
II	2.42 (2.15–2.74)	1.54 (1.44–1.66)
III	4.76 (4.32–5.24)	2.52 (2.37–2.68)
IV	9.38 (8.53–10.33)	4.65 (4.37–4.95)
Unknown	1.79 (1.60–1.99)	1.20 (1.13–1.27)
Histology		
Endometrioid low grade	Reference	Reference
Endometrioid high grade	3.10 (2.86–3.37)	1.72 (1.64–1.80)
Carcinosarcoma	5.41 (4.89–5.99)	2.68 (2.51–2.87)
Clear cell carcinoma	3.05 (2.59–3.59)	1.75 (1.56–1.95)
Uterine serous carcinoma	3.45 (3.14–3.80)	1.96 (1.84–2.08)
Lymph node examination status		
Examined	Reference	Reference
None examined	1.10 (1.03–1.18)	1.19 (1.15–1.24)
Unknown	1.03 (0.74–1.42)	1.11 (0.90–1.36)

(*continued*)

Table 4. Multivariate Cox Proportional Hazards Model for Disease-Specific and Overall Mortality in the Entire Study Population (*continued*)

Factor	Cancer-Specific Mortality	All-Cause Mortality
Surgery		
None	Reference	Reference
Surgery	0.30 (0.28–0.33)	0.36 (0.34–0.38)
Unknown	0.45 (0.31–0.64)	0.47 (0.38–0.59)
Radiation		
None	Reference	Reference
Radiation	1.01 (0.95–1.08)	0.91 (0.88–0.95)
Unknown	1.06 (0.83–1.36)	1.13 (0.97–1.31)
Chemotherapy		
None	Reference	Reference
Yes	0.84 (0.78–0.92)	0.98 (0.92–1.04)

SEER, Surveillance, Epidemiology, and End Results.
Data are hazarad ratio (95% confidence interval).
Cox proportional hazards models were used to calculate adjusted group hazard ratios, and their 95% confidence intervals were used to assess the importance of venous thromboembolism as an independent predictors of survival after adjusting for the following prognostic factors: stage, histology, age, race, period of diagnosis, SEER registry region, urban compared with rural setting, marital status, treatment modality, definitive surgical procedure, lymph node dissection, socioeconomic status, and comorbidity index.

and the incidence of venous thromboembolism. In the study by Rodriguez et al,[5] the authors found that high-risk histologies were strong risk factors for the development of venous thromboembolism in a proportional hazard model. Importantly, in their study, histologic diagnoses were grouped into endometrioid carcinomas, high-risk nonendometrioid carcinomas (uterine serous carcinoma, uterine clear cell carcinoma), and sarcomas (including leiomyosarcoma, carcinosarcoma, stromal sarcoma, adenosarcoma, and sarcoma not otherwise specified). Satoh et al[6] found similar results; however, the authors divided the population into two groups, endometrioid carcinoma compared with non-endometrioid carcinoma. In a single-institution retrospective study looking at the rate of clinically significant venous thromboembolism in patients with uterine clear cell carcinoma, the authors found that women with this histology had a higher rate of venous thromboembolism compared with women in a control group.[16] Our analysis did not demonstrate that women with uterine clear cell carcinoma are at increased risk of venous thromboembolism compared with other high-grade histologies. In the present study, the highest risk of venous thromboembolism was among women diagnosed with uterine carcinosarcoma followed by uterine serous carcinoma.

Sorensen et al[17] in a landmark study demonstrated that patients with any type of cancer who developed a venous thromboembolism had reduced survival compared with those without venous thromboembolism. Specifically looking at the prognostic implication of venous thromboembolism in women with epithelial endometrial cancer, our data showed that after controlling for multiple histopathologic, demographic, and treatment factors, venous thromboembolism diagnosed before or after cancer diagnosis had a strong negative effect on survival. The present analysis also showed that the rate of venous thromboembolism was significantly higher among patients diagnosed with metastatic endometrial cancer compared with those with regional or local stage disease. In fact, the logistic regression models demonstrated that advanced stage was the strongest predictor of venous thromboembolism. Based on the findings that the diagnosis of venous thromboembolism is associated with high-grade histologies, advanced stage, and lower survival, it appears that the development of venous thromboembolism reflects the presence of a biologically more aggressive cancer.

Our study has several important limitations. Given the retrospective nature of the investigation, the major limitation of this study is the use of administrative data to determine the incidence of venous thromboembolism. In addition, the prevalence of chronic conditions may be underestimated. We did not include patients with missing claims data and in that process we excluded some potentially younger and healthier patients with coverage through a health care organization. Subsequently, our sample may include a larger number of older patients and more medically infirm women than seen in the overall, general population. Furthermore, there are data suggesting that practice patterns in health care organizations can differ from those rendered in a fee-for-service setting. Because individual measures of

socioeconomic status were not available within the SEER–Medicare database, a proxy for socioeconomic status was derived from census data. Another limitation was the absence of any information regarding primary thromboprophylaxis or complete information regarding surgical approach, laparoscopic compared with laparotomy. Finally, we were not able to analyze venous thromboembolism-specific mortality.

Our results underscore the importance of corroborating the risk of venous thromboembolism in patients with endometrial cancer in subsequent studies given that the association between thrombotic events and certain cancer- and treatment-specific risk factors such as stage and carcinosarcoma histology, for example, may carry important prognostic significance and provide further evidence in support of the current recommendations for prophylactic anticoagulation therapy pretreatment and possibly for extended prophylaxis in patients with endometrial cancer.

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