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Risk factors of death from vascular events among cancer survivors: A SEER database analysis

Jian Wang, Xin Yan, Wei Feng, Wenhua Shi, Qingting Wang, Qianqian Zhang, Limin Chai, Pengtao Liu, Yuqian Chen, Cong Li, Manxiang Li*

Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi 710061, PR China

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ABSTRACT

Introduction: Cancer is the most important leading cause of death in the world and vascular events are the second-leading cause of death in cancer patients after cancer itself. Understanding related risk factors associated with vascular events may help clinicians develop appropriate treatment strategies. However, few large-scale population-based studies have investigated the risk factors for vascular events among cancer patients.
Materials and methods: The study involved a retrospective evaluation of medical records from the SEER database. Ten most common cancers in the past 20 years were extracted from the database. Cox proportional hazards model was used to analyze risk factors affecting vascular events that caused death among cancer patients.
Results: This study revealed that cancer patients had a serious risk of vascular events caused death, the 1-year, 3-year, 5-year and the overall rates of mortality from vascular events were 6.0%, 10.8%, 17.9% and 25.8%, respectively. The results showed that male, black race, elderly, AJCC stage II, stage III and stage IV, with no multiple primary cancers and no surgical treatment were associated with a significantly increased risk of vascular events caused death.
Discussion: We hope this research can alert clinicians and help them select high-risk cancer patients who may die from vascular events. And for those patients, we recommend that clinicians regularly monitor the patient's coagulation function and perform individualized thromboprophylaxis promptly to reduce the risk of death from vascular events.

Factores de riesgo de muerte por episodios vascular es entre los supervivientes de cáncer: análisis de la base de datos SEER

Palabras clave:
Cáncer
Tromboembolismo
Sangrado
Factor de riesgo
Base de datos SEER

RESUMEN

Introducción: El cáncer es la causa más importante de muerte a nivel mundial, y los episodios vasculares son la segunda causa más importante de muerte en los pacientes de cáncer, tras la enfermedad en sí misma. Comprender los factores de riesgo relacionados con los episodios vasculares puede ayudar a los facultativos a desarrollar estrategias terapéuticas adecuadas. Sin embargo, son pocos los estudios a gran escala basados en población que investigan los factores de riesgo de los episodios vasculares entre los pacientes de cáncer.
Materiales y métodos: El estudio incluyó la evaluación retrospectiva de las historias médicas de la base de datos SEER, de donde se extrajeron los 10 tipos de cáncer más comunes en los últimos 20 años. Se utilizó el modelo de regresión de Cox para analizar los factores de riesgo que afectan a los episodios vasculares que causaron la muerte entre los pacientes de cáncer.

* Corresponding author.
E-mail address: manxiangli@hotmail.com (M. Li).

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Resultados: Este estudio reveló que los pacientes de cáncer tenían un riesgo grave de muerte causada por episodios vasculares. Las tasas de mortalidad causada por episodios vasculares a 1, 3, 5 años y global, fueron del 6, 10,8, 17,9 y 25,8%, respectivamente. Los resultados reflejaron que los varones, de raza negra, mayores, con AJCC estadios II, III y IV, sin cánceres primarios múltiples y sin tratamiento quirúrgico estaban relacionados con el incremento del riesgo significativo de muertes causadas por episodios vasculares.
Discusión: Esperamos que esta investigación pueda alertar a los clínicos, y ayudarles a seleccionar a los pacientes de cáncer con alto riesgo de muerte causada por episodios vasculares. Y recomendamos también que los facultativos supervisen regularmente la función de coagulación de dichos pacientes, realizando tromboprofilaxis individualizada para reducir el riesgo de muertes causadas por episodios vasculares.

Introduction

Cancer is one of the leading causes of death in the world, and the burden of cancer is increasing, posing a threat to human development. According to reports, there were 17.2 million cancer cases worldwide and 8.9 million cancer deaths in 2016, and cancer cases increased by 28% between 2006 and 2016.[1] Although the diagnosis, treatment, and prognosis of cancer have evolved over the decades, the overall survival rates of cancer patients remain low.[1] Indeed, the death of cancer patients caused by vascular events has always been an important research hotspot in this field.

It has long been proposed that changes in coagulation factors, increased platelet adhesion and decreased fibrinolysis may cause the formation of cancer-associated thrombosis, and a decrease in platelets after chemotherapy may cause an increased risk of bleeding. Pranav et al. have reported that patients with cancer have an annual venous thromboembolism risk of 1.3%, which is six times higher than patients without cancer.[2] And the risk of venous thromboembolism recurrence in patients with cancer can reach 29% at one year.[3] Besides, cancer also conveys a high risk of major bleeding-up to 20% at one year for patients with both cancer and venous thromboembolism .[4] Thus, thromboprophylaxis is not routinely recommended for cancer patients because clinicians concern more about high risk of bleeding. This ultimately leads to cancer patients not being able to prevent cancer-related thrombosis and bleeding timely and effectively.

Few large-scale population-based studies investigated the relationship between cancer and vascular events, including hemorrhage and thrombosis, such as cerebrovascular disease, cardiovascular disease and other vascular disorders.[5] In fact, the occurrence of vascular events in cancer patients has a significant impact on prognosis and leads to extremely poor outcomes. Thus, the aim of our study was to summarize the risk of vascular events caused death among cancer survivors who were diagnosed initially with any of the 10 most common cancers[1] in recent 20 years (1997–2016) and to identify potential risk factors associated with death from vascular events and help clinicians identify high-risk patients to prevent potential thromboembolism and bleeding risks.

Materials and methods

Data source

The study involved a retrospective evaluation of medical records from Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov), SEER*Stat Database (with additional treatment fields), Nov 2018 Sub (1975–2016 varying), National Cancer Institute, DCCPS, Surveillance Research Program, released April 2019, based on the November 2018 submission. SEER is a population based registry sponsored by the National Cancer Institute, and analysis of the data does not require IRB approval or informed consent from patients. We have got permission to access the research data file in the SEER program by National Cancer Institute, USA with the reference number 12263-Nov2018.

Data extraction

The data for this study were extracted utilizing the SEER*Stat software Version 8.3.6. To identify eligible patients diagnosed with one of the 10 most common cancers, the following parameters were selected in the selection tab of the SEER*Stat: (Site and Morphology. Site recode ICD-O-3/WHO 2008 = 'Stomach' 'Colon and Rectum' 'Liver' 'Lung and Bronchus' 'Other Non-Epithelial Skin' 'Breast' 'Cervix Uteri' 'Prostate' 'Non-Hodgkin Lymphoma' 'Leukemia'). The included patients were further restricted to those diagnosed initially in recent 20 years (1997–2016). The first endpoint of the present study was the survival status, which was categorized into the vascular events caused death and others (alive or non-vascular events related death) in the Frequency Session. While in the Case Listing Session, the survival status was divided into death triggered by vascular events and alive. The vascular events caused death included deaths from cerebrovascular disease, cardiovascular disease and other vascular disorders. The secondly endpoint was the overall survival. The variables include the site of the primary tumor, survival time, survival status, age at diagnosis, gender, races, AJCC stage, co-existing primary cancer, surgery, chemotherapy and radiotherapy.

Statistical analysis

Categorical data were represented by a number (n) and percentage (%). Cox proportional hazards model was used to conduct univariate and multivariate analyses of factors affecting vascular events caused death among cancer patients. Stratification analysis against survival time was performed to determine if the tumor survival influenced the identified associations. Statistical significance was declared with a two-sided p-value < 0.05. All of the statistical analyses were conducted with SPSS Statistics (version 22.0) as well as the SEER*Stat program (version 8.3.6); Microsoft excel was also utilized to produce figures. The study cutoff is the date of submission of most recent SEER data (December 2016).

Results

Characteristics of study subject

In the Frequency Session, we identified a total of 4,619,746 patients with the 10 most common cancers in the SEER database registered from 1997 to 2016. The cohort of cancer patients included 278,352 individuals died because of vascular events. Demographic data for all patients are shown in Table 1 (more detailed data were shown in Table S1). For patients of the evaluated 10 cancers, breast cancer (23.7%) and prostate cancer (22.3%) were the two most common cancers. Male represented the

Table 1
Basic characteristics of study population.

Survival status	Cancer survivors in recent 20 years, *n* (%)		
	Vascular events (*n* = 278,352)	Other (*n* = 4,341,394)	Total (*n* = 4,619,746)
Cancer type			
Stomach	5885 (2.1%)	113,633 (2.6%)	119,518 (2.6%)
Colon and rectum	58,937 (21.2%)	655,633 (15.1%)	714,570 (15.5%)
Liver	2786 (1.0%)	108,071 (2.5%)	110,857 (2.4%)
Lung and bronchus	38,606 (13.9%)	896,348 (20.6%)	934,954 (20.2%)
Non-Epithelial skin	2955 (1.1%)	27,342 (0.6%)	30,297 (0.7%)
Breast	55,617 (20.0%)	1,037,152 (23.9%)	1,092,769 (23.7%)
Cervix uteri	1734 (0.6%)	63,986 (1.5%)	65,720 (1.4%)
Prostate	82,304 (29.6%)	949,929 (21.9%)	1,032,233 (22.3%)
Non-Hodgkin lymphoma	18,091 (6.5%)	289,862 (6.7%)	307,953 (6.7%)
Leukemia	11,437 (4.1%)	199,438 (4.6%)	210,875 (4.6%)
Gender			
Male	159,161 (57.2%)	2,207,706 (50.9%)	2,366,867 (51.2%)
Female	119,191 (42.8%)	2,133,688 (49.1%)	2,252,879 (48.8%)
Races			
White	231,531 (83.2%)	3,484,112 (80.3%)	3,715,643 (80.4%)
Black	32,445 (11.7%)	495,566 (11.4%)	528,011 (11.4%)
Other	13,883 (5.0%)	316,562 (7.3%)	330,445 (7.2%)
Unknown	493 (0.2%)	45,154 (1.0%)	45,647 (1.0%)
Age at diagnosis			
<40	670 (0.2%)	168,127 (3.9%)	168,797 (3.7%)
40–69	68,664 (24.7%)	2,441,514 (56.2%)	2,510,178 (54.3%)
≥70	209,018 (75.1%)	1,731,753 (39.9%)	1,940,771 (42.0%)
AJCC stage			
0	2012 (0.7%)	20,108 (0.5%)	22,120 (0.5%)
I	61,438 (22.1%)	925,892 (21.3%)	987,330 (21.4%)
II	69,330 (24.9%)	1,000,779 (23.1%)	1,070,109 (23.2%)
III	29,093 (10.5%)	555,076 (12.8%)	584,169 (12.6%)
IV	22,435 (8.1%)	702,479 (16.2%)	724,914 (15.7%)
Unknown	94,044 (33.8%)	1,137,060 (26.2%)	1,231,104 (26.6%)
Multiple primary cancers			
Yes	59,231 (21.3%)	859,672 (19.8%)	918,903 (19.9%)
No	218,121 (78.4%)	3,481,722 (80.2%)	3,699,843 (80.1%)
Surgery			
Yes	145,769 (52.4%)	2,276,179 (52.4%)	2,421,948 (52.4%)
No	125,732 (45.2%)	1,972,380 (45.4%)	2,098,112 (45.4%)
Unknown	6851 (2.5%)	92,835 (2.1%)	99,686 (2.2%)
Chemotherapy			
Yes	39,237 (14.1%)	1,370,942 (31.6%)	1,410,179 (30.5%)
No/unknown	239,115 (85.9%)	2,970,452 (68.4%)	3,209,567 (69.5%)
Radiotherapy			
Yes	65,798 (23.6%)	1,333,804 (30.7%)	1,399,602 (30.2%)
No/unknown	212,554 (76.4%)	3,007,590 (69.3%)	3,220,144 (69.8%)

majority of the patients (51.2%) and 80.4% patients were white. For the age at diagnosis, most patients were over 70 years old. Regarding the AJCC stage, the majority of identified patients were at stage I (21.4%) and stage II (23.2%). Additionally, 19.9% of patients had multiple primary cancers. For the treatment strategy, 52.4% of the patients received surgery, 30.5% received chemotherapy, and 30.2% received radiotherapy.

The incidence of vascular events caused death

As shown in Fig. 1, patients with the 10 most common cancers had seriously risk of vascular events triggered death, especially for patients who had survived for more than three years (Fig. 1a). The 1-year, 3-year, 5-year and the overall rates of mortality from vascular events for patients with the 10 cancers were 6.0%, 10.8%, 17.9% and 25.8% (Fig. 1b), respectively. And for Non-Epithelial Skin cancer, Prostate cancer and Colon and Rectum cancer, the overall rates of vascular events triggered death were even reached to 43.6%, 36.1% and 33.2%, respectively (detailed data were shown in Table S2).

Risk factors for vascular events caused death

In the Case Listing Session, after removing cases with incomplete data, we found 176,609 patients who died due to vascular events and 1,666,294 living patients. Gender, race, age at diagnosis, AJCC stage, situation of co-existing primary cancers and surgery strategy were identified as risk factors, and then those variables were analyzed by using multivariate Cox regression. As shown in Table 2, male (hazard ratio [HR] = 1.40, 95% confidence interval [95% CI] = 1.38–1.42, $p < 0.001$), black race (HR = 1.34, 95% CI = 1.32–1.36, $p < 0.001$), diagnosed at 40–69 years old (HR = 8.15, 95% CI = 7.35–9.04, $p < 0.001$) and 70 years older (HR = 59.02, 95% CI = 53.24–65.44, $p < 0.001$), AJCC stage II (HR = 1.25, 95% CI = 1.19–1.31, $p < 0.001$) and stage III (HR = 1.47, 95% CI = 1.40–1.54, $p < 0.001$) and stage IV (HR = 2.91, 95% CI = 2.77–3.05, $p < 0.001$), no-multiple primary cancers (HR = 1.02, 95% CI = 1.01–1.04, $p < 0.001$) and no-surgery treatment (HR = 2.19, 95% CI = 2.15–2.22, $p < 0.001$) were associated with significantly increased risk of vascular events triggered death. On the other hand, other races (American Indian/AK Native, Asian/Pacific Islander) (HR = 0.64, 95%

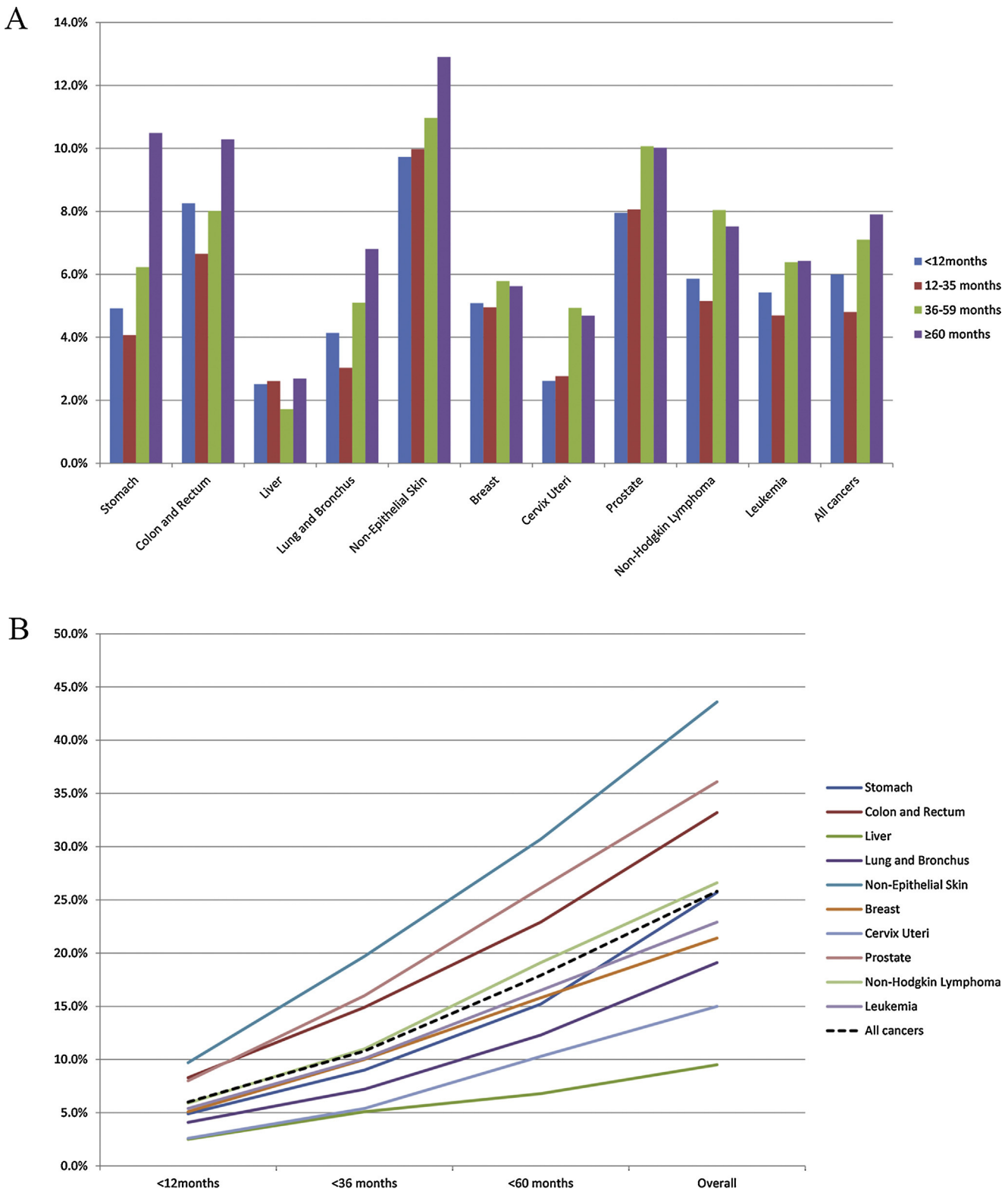

Fig. 1. (a) Bar chart of the mortality from vascular events among cancer survivors stratified by the time from diagnosis. (b) Bar chart of the cumulative mortality from vascular events among cancer survivors.

CI = 0.63–0.66, $p < 0.001$) were associated with lower risk of mortality due to vascular events. However, radiotherapy and chemotherapy were not available to be incorporated in the Cox proportional hazards regression analysis due to patients who have not received and patients who are unknown whether they have received radiotherapy or chemotherapy are combined as "no/unknown" in SEER database.

Discussion

Since cancer is the most important leading cause of death in the world and venous thromboembolism is the second-leading cause of death in cancer patients after cancer itself,[6] understanding the susceptibility and related risk factors associated with the development of vascular events in cancer patients may help guide

Table 2
Multivariate hazard regression analysis of risk factors for vascular events caused death.

Variable	HR (95%CI)	*p*-Value
Gender		
Female	Reference	
Male	**1.40 (1.38, 1.42)**	**<0.001**
Races		
White	Reference	
Black	**1.34 (1.32, 1.36)**	**<0.001**
Other	0.64 (0.63, 0.66)	<0.001
Age at diagnosis		
<40	Reference	
40–69	**8.15 (7.35, 9.04)**	**<0.001**
≥70	**59.02 (53.24, 65.44)**	**<0.001**
AJCC stage		
0	Reference	
I	1.00 (0.96, 1.06)	–
II	**1.25 (1.19, 1.31)**	**<0.001**
III	**1.47 (1.40, 1.54)**	**<0.001**
IV	**2.91 (2.77, 3.05)**	**<0.001**
Multiple primary cancers		
Yes	Reference	
No	**1.02 (1.01, 1.04)**	**<0.001**
Surgery		
Yes	Reference	
No	**2.19 (2.15, 2.22)**	**<0.001**

C-index = 0.826.
HR, hazard ratio; CI, confidence interval.
Significant risk factors were shown in bold face.

clinicians develop appropriate treatment strategy. While, due to few large-scale population-based studies investigated the risk factors of vascular events among cancer patients, this study aimed to estimate the incidence of vascular events caused death in 10 most common cancers and determine potential risk factors associated with this mortality. In our study, we found that patients with the 10 most common cancers had seriously risk of vascular events triggered death, the 1-year, 3-year, 5-year and the overall rates of mortality from vascular events for cancer patients were 6.0%, 10.8%, 17.9% and 25.8%, respectively.

Vascular events, including hemorrhage and thrombosis, are always triggered first by venous thromboembolism in cancer patients. Venous thromboembolism is common and may occur before or at the same time as cancer diagnosis.[7] The development of venous thromboembolism in cancer patients increases the morbidity, mortality, and medical costs.[7,8] Currently, although consensus guidelines encourage the prevention of thrombosis, it is still difficult to develop the treatment strategy due to clinician's concern about high risk of bleeding.[4,7,9] It is reported that 25% of cancer patients have to be hospitalized again due to bleeding or thrombosis recurrence.[10] In fact, a meta-analysis of 11 randomized controlled trials has shown that cancer patients could benefit from anticoagulant therapy.[11] Thus, it is important to identify high-risk patients and make appropriate treatment modalities to prevent potential thromboembolism and bleeding risks. Actually, the incidence of cancer-related vascular events varies due to patient-related factors (e.g. gender, race and age at diagnosis) and tumor-related factors (e.g. AJCC stage, co-existing primary cancers and treatment strategies). In this study, we found that male cancer patients had a higher risk of vascular events triggered death; this is in line with the finding of non-small cell lung cancer study.[5] It is possible that hormonal differences may responsible for this, but detailed mechanisms about this difference associated to gender on cancer-related vascular events are not yet fully defined.[12] Our study also showed that black race is more likely to experience vascular events caused death compared to other races. This is consistent with published studies.[5,13] Patel R.K. et al. have shown that black cancer patients had significantly increased risk of venous thromboembolism when compared with Caucasians.[13] It is believed that elevated levels of Factor VIII may be responsible for the increased risk in black population.[13] However, it is uncertain whether this is the cause of the increased risk of vascular events caused death in cancer patients. Additionally, this study showed that elderly cancer patients are more prone to death triggered by vascular events. This result is in line with expectations, as this age group has a higher probability of comorbidities, which may lead to a higher risk of vascular events.

Moreover, apart from patient-related factors, tumor-related factors including primary site, AJCC stage, co-existing primary cancers and treatment strategies, also play an important role in the mortality caused by vascular events. It is reported that the types of cancer associated with a high risk of venous thromboembolism include gastric cancer, lung cancer, gynecological cancers and hematological malignancies.[14–18] Interestingly, in this study, we have found that the cumulative risk of vascular events triggered death was much higher in Non-Epithelial Skin cancer (43.6%), Prostate cancer (36.1%), Colon and Rectum cancer (33.2%) and Non-Hodgkin Lymphoma (26.6%) patients. This may be explained by the difference source of study population. In addition, this analysis demonstrated that cancer patients in AJCC stage II, stage III and stage IV were more likely to suffer from vascular events caused death. This may be explained by the fact that the risk of mortality due to vascular events depends on the severity of the stage of cancer. Regarding of patients with or without co-existing primary cancers, our study found that patients with a single primary tumor were more likely to die from vascular events. This result is in line with previously published study,[5] it is possible that patients with multiple primary cancers may receive more diverse treatment. However, data regarding chemotherapy and radiotherapy were not available to be incorporated in the Cox proportional hazards model. But, we do have analyzed the impact of surgery on death due to vascular events in cancer patients. Although many studies have confirmed that surgery may lead to a significant increase in the risk of venous thromboembolism,[19,20] the study of Trinh V. Q. et al. confirmed that the frequency of venous thromboembolic-related death after major cancer surgery is indeed reduced.[21] In our study, we found that cancer patients who did not undergo surgery had a significantly increased risk of death from vascular events (HR = 2.19). This may be explained that patients who have not undergone surgery are often patients with significant tumor progression, and those patients always have a higher risk of death.

There are some limitations of this study. First, the research data of our study is derived from the SEER database only. Secondly, given the study cutoff of 2016, some recently diagnosed patients did not have sufficient follow-up time. Thirdly, data of chemotherapy and radiotherapy are unavailable in the Cox proportional hazards model, and this may cause potential bias in our results, as studies have shown that chemotherapy and radiotherapy do increase the risk of venous thromboembolism in cancer patients.[22,23] Considering above limitations, the results of this analysis should be interpreted carefully.

In conclusion, we hope this research can alert clinicians and help them select high-risk cancer patients who may die from vascular events, such as those male, elderly, non-surgical, AJCC stage IV cancer patients, especially for black race. For patients with high-risk factors, we recommend that clinicians should regularly monitor the patient's coagulation function and timely perform individualized thromboprophylaxis to reduce the risk of cancer death caused by vascular events.

Authors' contributions

Wang J, Yan X, Feng W and Li MX planned this study. Wang J, Shi WH, Liu PT, Chen YQ and Li C extracted data. Wang J, Yan X, Wang QT, Zhang QQ and Chai LM analyzed data. Wang J, Yan X, Feng W and Shi WH wrote the paper. Wang QT, Zhang QQ, Chai LM, Liu PT, Chen YQ, Li C and Li MX made critical revisions to this article. All authors have approved to submit this final version to your journal and agreed to be accountable for all aspects of this work.

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Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.medcli.2020.02.007.

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