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The association between cancer diagnosis, care, and outcomes in 1 million patients hospitalized for acute pulmonary embolism

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ABSTRACT

Objectives: To evaluate the clinical care provided to cancer patients hospitalized for acute pulmonary embolism (PE), as well as the association between type of cancer, in-hospital care, and clinical outcomes.
Methods: This study examined the in-hospital care (systemic thrombolysis, catheter-directed thrombolysis, and surgical thrombectomy/embolectomy) and clinical outcomes (mortality, major bleeding, and hemorrhagic stroke) among adults hospitalized due to acute PE between October 2015 to December 2018 using the National Inpatient Sample (NIS). Multivariable logistic regression analysis was used to determine adjusted odds ratios (aOR) with 95% confidence interval (95% CI).
Results: Of 1,090,130 hospital records included in the analysis, 216,825 (19.9%) had current cancer diagnoses, including lung (4.7%), hematological (2.5%), colorectal (1.6%), breast (1.3%), prostate (0.8%), and 'other' cancer (9.0%). Cancer patients had lower adjusted odds of receiving systemic thrombolysis, catheter-directed therapy, and surgical thrombectomy/embolectomy compared with their non-cancer counterparts ($P < 0.001$), except for systemic thrombolysis (aOR 0.96, 95% CI 0.85–1.09, $P = 0.553$) and catheter-directed therapy (aOR 0.82, 95% CI 0.67–1.00, $P = 0.053$) for prostate cancer. Cancer patients had greater odds of mortality ($P < 0.05$). Lung cancer patients had the highest odds of mortality (aOR 2.68, 95% CI 2.61–2.76, $P < 0.001$) and hemorrhagic stroke (aOR 1.75, 95% CI 1.61–1.90, $P < 0.001$), while colorectal cancer patients had the greatest odds of bleeding (aOR 2.04, 95% CI 1.94–2.15, $P < 0.001$).
Conclusion: Among those hospitalized for PE, cancer diagnoses were associated with lower odds of invasive management and poorer in-hospital outcomes, with metastatic status being an especially important determinant. Appropriateness of care could not be assessed in this study.

1. Introduction

Cancer is a major contributor to global mortality and morbidity and constitutes the second leading cause of death in the United States (US) [1]. In addition, cancer elevates the risk for pulmonary embolism (PE), with the incidence of PE in patients with active cancer ranging from 1.1% to 5.0% [2–4]. By contast, the incidence of PE in the general population was evaluate to be approximately 0.1% [5,6]. Our

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understanding regarding the connection between cancer and PE has grown significantly over the past decades, with several mechanisms postulated to link malignancy with the hypercoagulable states in cancer patients [7]. Most notably, patients with solid organ malignancies have a higher risk of venous thrombosis and acute PE which sometimes precede the diagnosis of malignant disease [8]. The risk is further increased for those with metastatic disease [9–11].

Different cancer- and patient-related factors have been recognized as risk factors for PE [12]. Therapeutic strategies for cancer may also be toxic and recent evidence shows the risk of venous thromboembolism (VTE) in cancer patients to nearly double when receiving chemotherapy or other targeted treatments, in particular [13]. As such, PE is an important complication of cancer, which has prompted physicians to consider primary anti-thrombotic prophylaxis, even in ambulatory cancer patients [14–16].

That said, literature examining outcomes following acute PE remains limited [17], and the association underlying PE-related outcomes and cancer remains unclear. The present study, thus, aimed to evaluate the clinical characteristics of cancer patients presenting for acute PE. In addition, we sought to investigate whether the presence and type of cancer are associated with clinical care and clinical outcomes among patients hospitalized for PE.

2. Methods

The National Inpatient Sample (NIS) database is the largest healthcare database of routinely collected data in the US. It comprises anonymized discharge data from over 7 million hospitalizations yearly, which upon weighting correspond to over 35 million hospitalizations and covers approximately 20% of the discharges from community hospitals from all US regions using a stratified systematic random sample. It is designed to produce nationally representative estimates of inpatient utilization, access, charges, quality, and outcomes in the US, and was developed by the Agency for Healthcare Research and Quality (AHRQ) under the Healthcare Cost and Utilization Project (HCUP). Data are publicly available from the AHRQ to all data purchasers and collaborators who have completed the online HCUP Data Use Agreement Training and have signed the Data Use Agreement for Nationwide Databases. Detailed information can be found on: https://www.hcup-us.ahrq.gov/nisoverview.jsp [18].

2.1. Study sample

This study examined the in-hospital outcomes among adults (over 18 years of age) hospitalized for acute PE between October 2015 to December 2018. The study sample was stratified according to the presence and type of cancer (colorectal cancer, lung cancer, breast cancer, prostate cancer, hematological cancers, and 'other' cancers). The International Classification of Diseases, Tenth Revision (ICD-10) was used to define the relevant variables, study groups, and outcomes. Detailed information on the ICD-10 codes utilized is presented in Supplementary Table 1.

All reported data were based on the weighted analyses to provide national estimates as recommended by the HCUP, and cases excluded due to missing data represented 1.4% (N = 15,320) of the original dataset (Supplementary Fig. 1).

2.2. Outcomes

The outcomes of interest included care received for PE and clinical outcomes. Care received (i.e., advanced therapies) included systemic thrombolysis, catheter-directed therapy, and surgical thrombectomy/embolectomy; clinical outcomes included all-cause mortality, major bleeding, and hemorrhagic stroke, with major bleeding defined as intracranial and gastrointestinal (GI) hemorrhages. All outcomes were defined according to ICD-10 codes (Supplementary Table 1).

2.3. Statistical analysis

Data were expressed as numbers (percentages) and medians (interquartile ranges) for categorical and continuous variables, respectively. We performed the chi-squared test for categorical variables and the Kruskal-Wallis test for continuous variables. Binomial multivariate logistic regression was conducted to estimate the adjusted odds ratios (aOR) for in-hospital management and outcomes, following adjustment for covariates that are included in the NIS that were found to be both clinically relevant and directly related to our outcomes of interest. Sensitivity analyses were conducted according to metastatic status (i.e., non-metastatic and metastatic disease groups) and according to hemodynamic instability, identified through surrogate measure such as the presence of cardiogenic shock or the need for mechanical ventilation and vasopressors.

These covariates included hospital-related factors: hospital bed size, region, location/ teaching status; as well as patient-related factors: age, sex, weekend admission, primary expected payer, smoking status, history of myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention, cerebrovascular accident, dementia, dyslipidemia, thrombocytopenia, and other comorbidities (anemias, chronic pulmonary disease, coagulopathy, diabetes mellitus, arterial hypertension, liver disease, peripheral vascular disorders, and chronic renal failure). Statistical significance was defined at a level of $P < 0.05$. SPSS 25 software (IBM Corp, Armonk, NY) was used for the statistical analysis.

3. Results

3.1. Baseline characteristics

A total of 1,090,130 weighted hospitalization records for acute PE were included in the study, with 216,825 (19.9%) patients having a cancer diagnosis (Supplementary Fig. 1). When evaluating specific cancer types, lung cancer was most frequently encountered ($N = 50,905$; 4.7%), followed by hematological cancers (N = 27,245; 2.5%), colorectal cancer ($N = 17,635$; 1.6%), breast cancer ($N = 14,075$; 1.3%), and prostate cancer (N = 8980; 0.8%); 'other' cancer types were present in 97,985 (9.0%) individuals (Table 1 and Fig. 1). Colorectal and lung cancers presented with the highest rates of metastatic disease, at 59.6% and 58.4% respectively (Table 1).

Patients with a cancer diagnosis were older (65–73 years vs. 63 years, $P < 0.001$), more commonly insured by Medicare (51.4–71.4% vs. 51.4%, $P < 0.001$), and more likely to have comorbidities such as thrombocytopenia (7.6–15.8% vs. 6.5%, $P < 0.001$), anemia (31.7–42.0% vs. 22.0%, $P < 0.001$), and coagulopathy (13.9–23.7% vs. 12.6%, $P < 0.001$) (Table 1). Cancer patients who developed PE were less often smokers (except for those with lung cancer) or to have dementia (except for those with prostate cancer), heart failure, valvular heart disease, and peripheral vascular disease. Considering specific cancer types, prostate cancer patients were oldest (median age 73 years, IQR 66–81) and had the highest rates of dementia (7.1%), hypertension (46.1%), valvular heart disease (4.5%), and chronic renal failure (19.2%) (Table 1).

3.2. In-hospital management

Out of the studied management strategies, systemic thrombolysis was the most common management in all patient subgroups, followed by catheter-directed therapy; surgical thrombectomy/embolectomy was the least commonly used (Table 2 and Fig. 2A). Compared with the non-cancer cohort, cancer patients received systemic thrombolysis (0.9–2.7% vs. 2.9%, $P < 0.001$), catheter-directed therapy (0.3–1.1% vs. 1.2%, $P < 0.001$), and surgical thrombectomy/embolectomy ($\leq$0.1% vs. 0.2%, $P < 0.001$) less frequently. Among patients with cancer, those with prostate cancer had the highest rates of systemic thrombolysis and

Table 1
Patient characteristics.

Characteristics	No Malignancy (80.1%)	Malignancy type						*P*-Value
		Colorectal (1.6%)	Lung (4.7%)	Breast (1.3%)	Prostate (0.8%)	Hematological (2.5%)	Other (9.0%)	
Number of weighted discharges	873,305	17,635	50,905	14,075	8980	27,245	97,985	–
Age (years), median (IQR)	63 (49–75)	66 (57–75)	68 (60–75)	65 (55–74)	73 (66–81)	68 (58–77)	65 (57–74)	<0.001
Female sex, %	51.7%	47.0%	49.1%	98.9%	/	44.4%	53.7%	<0.001
Ethnicity, %								<0.001
White	71.9	70.0	74.5	67.1	68.9	73.2	71.1	
Black	18.8	19.4	16.2	22.5	23.1	15.2	16.1	
Hispanic	5.7	6.3	4.4	6.5	4.5	6.9	7.2	
Asian or Pacific Islander	0.9	1.4	2.2	1.1	1.2	1.4	2.0	
Native American	0.4	0.3	0.3	0.3	0.3	0.5	0.3	
Other	2.2	2.6	2.5	2.5	2.1	2.8	3.2	
Weekend admission, %	23.4	20.5	21.4	19.9	21.8	21.0	20.6	<0.001
Primary expected payer, %								<0.001
Medicare	51.4	53.2	60.8	52.9	71.4	59.1	51.4	
Medicaid	14.5	11.5	11.0	13.3	5.3	9.5	11.9	
Private Insurance	26.7	30.5	23.7	30.3	18.9	27.3	31.9	
Self-pay	4.2	2.3	1.7	1.5	1.3	1.9	2.1	
No charge	0.4	0.3	0.2	0.3	0.2	0.1	0.2	
Other	2.7	2.3	2.5	1.7	2.8	2.2	2.5	
Median Household Income (percentile), %								<0.001
0-25th	30.4	27.5	29.8	27.0	28.2	25.6	26.1	
26th–50th	26.9	25.8	26.1	25.6	24.6	25.4	24.9	
51st-75th	23.9	24.6	24.5	24.9	24.0	25.3	25.3	
76th–100th	18.9	22.1	19.6	22.6	23.1	23.8	23.7	
Homelessness, %	0.9	0.2	0.4	<0.1*	0.4	0.2	0.2	<0.001
Do-not-resuscitate status, %	9.0	19.6	28.3	18.4	17.7	15.1	23.8	<0.001
Metastatic disease, %	<0.1*	59.6	58.4	54.6	46.3	7.5	64.5	<0.001
Comorbidities, %								
Atrial fibrillation	12.2	10.7	15.8	7.5	15.3	14.9	10.2	<0.001
Dyslipidemia	33.8	28.5	34.0	28.1	41.6	32.9	30.1	<0.001
Thrombocytopenia	6.5	7.9	9.2	8.5	7.6	15.8	10.4	<0.001
Dementia	6.8	3.0	2.9	3.4	7.1	3.9	2.7	<0.001
Smoking	1.3	0.6	1.4	0.5	0.8	0.6	0.7	<0.001
Previous AMI	5.2	3.8	5.0	3.1	6.7	4.1	3.7	<0.001
History of IHD	17.8	12.0	17.8	8.4	23.2	15.1	11.6	<0.001
Previous PCI	0.5	0.6	0.5	0.2	0.8	0.4	0.4	<0.001
Previous CABG	3.6	2.0	3.3	1.1	5.6	2.8	2.2	<0.001
Previous CVA	5.6	3.5	5.4	3.7	5.5	4.5	3.8	<0.001
Anemias	22.0	42.0	31.9	32.1	31.7	32.6	36.7	<0.001
Congestive heart failure	20.6	11.9	14.8	12.0	17.9	18.0	10.9	<0.001
Valvular disease	4.5	2.9	2.5	3.0	4.5	3.9	2.4	<0.001
Hypertension	40.5	41.4	43.4	43.2	46.1	38.2	42.7	<0.001
Peripheral vascular disorders	4.0	2.5	5.3	1.9	3.8	3.3	2.3	<0.001
Chronic pulmonary disease	26.3	16.9	49.9	21.0	18.3	21.5	17.8	<0.001
Coagulopathy	12.6	15.6	15.7	15.1	13.9	23.7	18.4	<0.001
Diabetes Mellitus	24.5	22.9	19.9	21.3	25.0	23.3	24.3	<0.001
Liver disease	4.4	5.1	2.7	3.2	3.6	4.2	6.5	<0.001
Chronic renal failure	14.7	9.9	9.0	9.1	19.2	16.8	11.0	<0.001
Hospital factors								
Bed size of hospital, %								<0.001
Small	19.3	17.2	16.5	18.7	19.2	16.2	14.7	
Medium	28.9	28.9	27.0	27.4	27.4	24.2	24.8	
Large	51.7	53.9	56.5	53.9	53.4	59.6	60.5	
Hospital Region, %								<0.001
Northeast	19.8	22.3	22.9	23.3	20.3	22.8	24.2	
Midwest	26.6	26.3	27.7	25.8	27.9	28.2	25.6	
South	39.9	37.5	37.9	37.9	36.2	34.7	35.4	
West	13.8	13.8	11.6	12.9	15.6	14.3	14.7	
Location/teaching status of hospital, %								<0.001
Rural	9.4	7.7	7.1	7.5	9.1	6.8	5.5	
Urban non-teaching	23.6	20.5	21.8	21.1	21.4	17.8	17.1	
Urban teaching	67.0	71.7	71.2	71.5	69.4	75.4	77.4	

Abbreviations: AIDS—acquired immunodeficiency syndrome; AMI—acute myocardial infarction; CABG—coronary artery bypass graft; CAD—coronary artery disease; CVA—cerebrovascular accident; IHD—ischemic heart disease; IQR—interquartile range; PCI—percutaneous coronary intervention.

* Exact reporting of small numbers is discouraged by Agency for Healthcare Research and Quality/Healthcare Cost and Utilization Project.

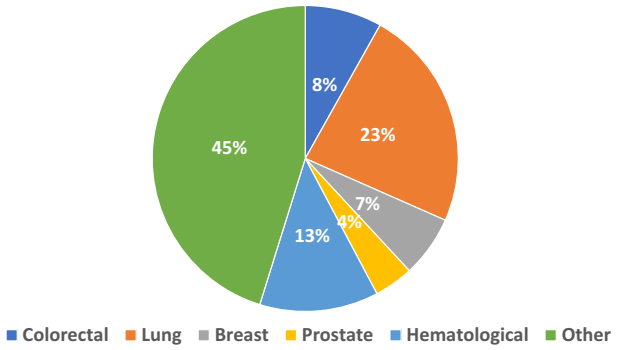

Fig. 1. Overview of malignancy types.

catheter-directed therapy, at 2.7% and 1.1%, respectively ($P < 0.001$). Patients with cancer were generally hospitalized for a longer duration (4–6 vs. 4 days, $P < 0.001$), with colorectal cancer patients having the longest length of stay at a median of 6 days (IQR 3–12).

After multivariable adjustment, cancer patients were consistently less likely to receive any of the advanced management strategies compared to their non-cancer counterparts ($P < 0.001$), with the exception of systemic thrombolysis (aOR 0.96, 95% CI 0.85–1.09, $P = 0.553$) and catheter-directed therapy (aOR 0.82, 95% CI 0.67–1.00, $P = 0.053$) in prostate cancer, with adjusted odds that were no different than in non-cancer patients (Table 3 and Fig. 3).

3.3. Clinical outcomes

Relative to patients without cancer, the unadjusted rates of mortality for all cancer types were higher (7.4–13.8% vs. 5.2%, $P < 0.001$), major bleeding was more frequently observed in all cancer types (5.0–10.8% vs. 4.0%, $P < 0.001$) except for breast cancer (3.5%), while the rates of hemorrhagic stroke were varied greatly depending on the type of cancer, with the highest rates in lung (4.2% and 1.2%, respectively) and 'other' cancer types (2.8% and 1.4%, respectively) (Table 2 and Fig. 2B).

Following multivariable adjustment, odds of mortality were significantly increased among all cancer types ($P < 0.05$); lung cancer patients had the highest aOR at 2.68 (95% CI 2.61–2.76, $P < 0.001$), while prostate cancer was associated with the lowest aOR at 1.11 (95% CI 1.02–1.21, $P = 0.011$), compared to patients without cancer. Patients with breast cancer had significantly lower odds of major bleeding (aOR 0.76, 95% CI 0.70–0.84, $P < 0.001$), while patients with colorectal (aOR 2.04, 95% CI 1.94–2.15, $P < 0.001$) and 'other' cancers (aOR 1.39, 95% CI 1.35–1.43, $P < 0.001$) had increased odds compared to their non-cancer counterparts, the remaining cancers were not significantly associated with major bleeding (Table 3 and Fig. 4).

Compared to non-cancer patients, both patients with lung (aOR 1.75, 95% CI 1.61–1.90, $P < 0.001$) and 'other' cancers (aOR 1.65, 95% CI 1.55–1.75, $P < 0.001$) had increased odds of acute hemorrhagic stroke, while the remaining cancer patients (except for breast cancer) had significantly lower odds of an incident hemorrhagic stroke (Table 3 and Fig. 4).

3.4. Sensitivity analysis by metastatic status

When considering metastatic status, patients with non-metastatic cancer were consistently less likely to receive systemic thrombolysis, catheter-directed therapy, and surgical thrombectomy/embolectomy compared to non-cancer patients ($P < 0.05$), except for prostate cancer. Patients with prostate cancer but no metastases did not show any difference, when compared with the non-cancer cohort, in the utilization of systemic thrombolysis (aOR 1.13, 95% CI 0.96–1.34, $P = 0.134$) and surgical thrombectomy/embolectomy (aOR 1.07, 95% CI 0.57–2.01, $P = 0.833$) (Supplementary Table 2 and Supplementary Fig. 2A).

The aOR for patients with metastatic cancers for all three interventions were significantly lower relative to cancer-free patients across all cancer types (Supplementary Table 3 and Supplementary Fig. 3A).

Patients with non-metastatic cancer generally had increased odds of all-cause mortality compared with the non-cancer group, except for breast (aOR 0.75, 95% CI 0.66–0.85, $P < 0.001$) and prostate cancers (aOR 0.63, 95% CI 0.55–0.72, $P < 0.001$) that had lower odds of mortality (Supplementary Table 2 and Supplementary Fig. 2B).

Upon assessing patients with metastatic malignancies, the direction of effects for all four clinical outcomes was consistent with those obtained in all cancer patients. However, the strength of association between all-cause mortality and all cancer types were increased (Supplementary Table 3 and Supplementary Fig. 3B).

3.5. Sensitivity analysis by hemodynamic stability

An additional sensitivity analysis was conducted in hemodynamically unstable patients, which were assessed as having cardiogenic shock (Supplementary Table 4). Significantly reduced odds in the utilization of systemic thrombolysis was observed in patients with lung cancer (aOR 0.49, 95% CI 0.35–0.68, $P < 0.001$), and 'other' cancers (aOR 0.61, 95% CI 0.50–0.75, $P < 0.001$), compared to non-cancer group. The utilization of catheter-directed therapy was lower only in 'other' cancer patients (aOR 0.62, 95% CI 0.44–0.88, $P = 0.008$), while surgical embolectomy/thrombectomy was less frequently used in lung (aOR 0.20, 95% CI 0.08–0.49, $P < 0.001$), hematological (aOR 0.25, 95% CI 0.10–0.61, $P = 0.002$), and 'other' cancer patients (aOR 0.69, 95% CI 0.50–0.97, $P =$

Table 2
In-hospital management and clinical outcomes based on malignancy.

Characteristics	No malignancy ($N = 873,305$)	Malignancy type						*P*-Value
		Colorectal (N = 17,635)	Lung (N = 50,905)	Breast (N = 14,075)	Prostate (N = 8980)	Hematological (N = 27,245)	Other ($N = 97,985$)	
Management, %								
Systemic thrombolysis	2.9	1.5	0.9	1.3	2.7	1.5	1.7	<0.001
Catheter-directed therapy	1.2	0.6	0.3	0.7	1.1	0.7	0.5	<0.001
Surgical embolectomy/ thrombectomy	0.2	<0.1*	<0.1*	<0.1*	0.1	0.1	0.1	<0.001
Clinical outcomes, %								
All-cause mortality	5.2	8.9	13.8	7.8	7.4	9.2	11.4	<0.001
Major bleeding	4.0	10.8	5.0	3.5	5.6	5.6	7.4	<0.001
Hemorrhagic stroke	0.7	0.3	1.2	0.6	0.3	0.7	1.4	<0.001
Length of stay, median (IQR)	4 (2–8)	6 (3–12)	5 (3–9)	4 (2–7)	5 (2–8)	5 (3–11)	5 (3–10)	<0.001
Total charges (USD1,000), median (IQR)	37.5 (20.1–78.9)	50.6 (24.4–112.3)	46.5 (24.3–89.3)	36.1 (20.0–70.7)	40.7 (21.1–80.3)	52.0 (25.5–119.1)	46.8 (24.3–95.4)	<0.001

Abbreviations: IQR—interquartile range; USD – United States Dollar.
* Exact reporting of small numbers is discouraged by Agency for Healthcare Research and Quality/Healthcare Cost and Utilization Project.

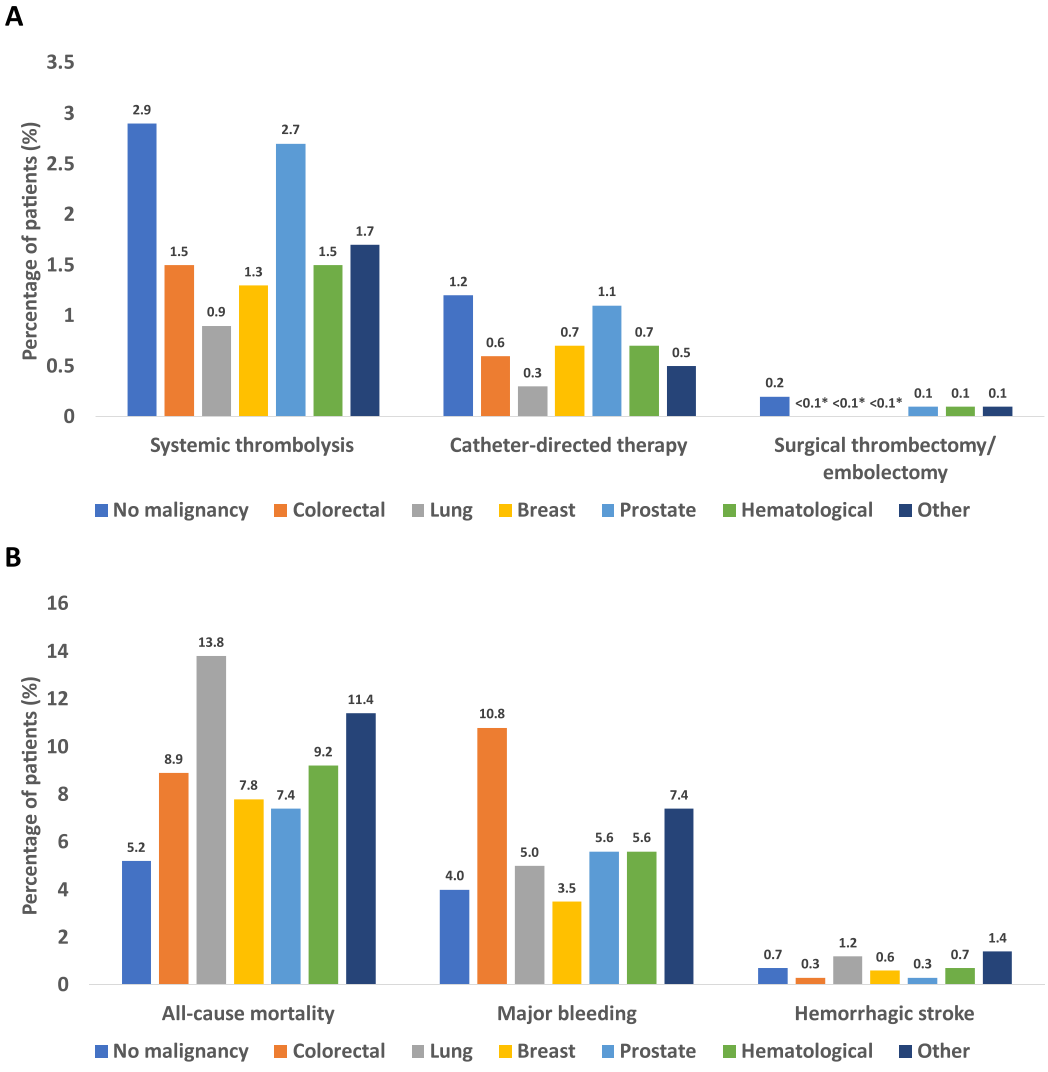

Fig. 2. (A) In-hospital management and (B) clinical outcomes.

0.032), compared with non-cancer patients.

We also assessed management outcomes in patients requiring mechanical ventilation and vasopressors (Supplementary Table 5). Our findings are consistent, with the utilization of all 3 advanced therapies significantly decreased in most cancer patients relative to non-cancer patients. However, the use of catheter-directed therapy ($P = 0.534$) and surgical embolectomy ($P = 0.082$) were not significantly different when comparing colorectal and non-cancer patients. As for prostate cancer patients, there were also no significant difference compared with non-cancer patients ($P = 0.143$).

3.6. Sensitivity analysis by do-not-resuscitate (DNR) status

An additional sensitivity analysis was conducted by restricting the analysis to patients without a DNR order (Supplementary Table 6). The findings of this analysis were generally consistent with the main analysis. However, the mortality odds in lung cancer patients without DNR (aOR 2.38, 95% CI 2.28–2.48, $P < 0.001$) was lower than in the main analysis (aOR 2.68, 95% CI 2.61–2.76, $P < 0.001$). The odds of hemorrhagic stroke was interestingly higher in patients without DNR (aOR 2.08, 95% CI 1.88–2.30, $P < 0.001$) compared to the overall analysis (aOR 1.75, 95% CI 1.61–1.90, $P < 0.001$).

When compared with the main analysis (aOR 1.49, 95% CI 1.42–1.55, $P < 0.001$), the odds for mortality in hematological cancer patients without DNR were markedly reduced (aOR 1.29, 95% CI 1.21–1.37, $P < 0.001$). 'Other' cancer patients also experience lower odds of mortality following the exclusion of patients with DNR status (aOR 1.75, 95% CI 1.69–1.81, $P < 0.001$) as compared with the main analysis (aOR 2.07, 95% CI 2.03–2.12, $P < 0.001$).

4. Discussion

In this large-scale nation-wide study, we systematically evaluated data on patients hospitalized for acute PE according to the presence and type of cancer in the US. There are several key findings of the present study. First, cancer is highly prevalent among patients hospitalized for PE. Second, we demonstrate that cancer patients are significantly less likely to be treated with systemic thrombolysis, catheter-directed therapy and surgical thrombectomy/embolectomy compared to patients without cancer, with patients with hematological malignancies the least likely to receive these treatments, even among those with evidence of hemodynamic instability. Third, the presence of cancer, regardless of type, is associated with an increased risk of mortality following admission for an acute PE, with the greatest risk observed in patients with lung cancer. Fourth, metastatic status in cancer patients is a key determinant of adverse clinical outcomes following admission for PE.

VTE, including acute PE, is the second most common cause of mortality in outpatient cancer patients [19]. Compared with patients

Table 3
Adjusted odds ratios of in-hospital management and clinical outcomes in different malignancy types.*

Characteristics	aOR (95% CI)					
	Malignancy type					
	Colorectal	Lung	Breast	Prostate	Hematological	Other
Management						
Systemic thrombolysis	0.45 (0.40–0.51)	0.31 (0.28–0.34)	0.43 (0.38–0.50)	0.96 (0.85–1.09)	0.44 (0.39–0.48)	0.48 (0.45–0.50)
	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P = 0.553$	$P < 0.001$	$P < 0.001$
Catheter-directed therapy	0.46 (0.38–0.56)	0.23 (0.20–0.27)	0.59 (0.49–0.72)	0.82 (0.67–1.00)	0.47 (0.41–0.54)	0.38 (0.34–0.41)
	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P = 0.053$	$P < 0.001$	$P < 0.001$
Surgical thrombectomy/ embolectomy	0.08 (0.03–0.20)	0.11 (0.06–0.17)	NA†	0.47 (0.25–0.87)	0.14 (0.08–0.23)	0.28 (0.23–0.34)
	$P < 0.001$	$P < 0.001$		$P < 0.001$	$P < 0.001$	$P < 0.001$
Clinical outcomes						
All-cause mortality	1.58 (1.50–1.67)	2.68 (2.61–2.76)	1.55 (1.45–1.65)	1.11 (1.02–1.21)	1.49 (1.42–1.55)	2.07 (2.03–2.12)
	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P = 0.011$	$P < 0.001$	$P < 0.001$
Major bleeding	2.04 (1.94–2.15)	1.00 (0.96–1.04)	0.76 (0.70–0.84)	0.95 (0.87–1.05)	1.04 (0.98–1.09)	1.39 (1.35–1.43)
	$P < 0.001$	$P = 0.998$	$P < 0.001$	$P = 0.316$	$P = 0.202$	$P < 0.001$
Hemorrhagic stroke	0.36 (0.27–0.47)	1.75 (1.61–1.90)	0.92 (0.75–1.14)	0.40 (0.28–0.57)	0.80 (0.69–0.92)	1.65 (1.55–1.75)
	$P < 0.001$	$P < 0.001$	$P = 0.439$	$P < 0.001$	$P = 0.003$	$P < 0.001$

Note: Binomial multivariable logistic regression analysis.
Multivariable model: Multivariable logistic regression model adjusted for: bed size of hospital, region of hospital, location/teaching status of hospital, age, sex, weekend admission, primary expected payer, smoking status, previous myocardial infarction, previous coronary artery bypass graft surgery, previous percutaneous coronary intervention, previous cerebrovascular accident, dementia, dyslipidemia, thrombocytopenia, and other comorbidities (anemias, chronic pulmonary disease, coagulopathy, diabetes mellitus, hypertension, liver disease, peripheral vascular disorders, chronic renal failure).
Abbreviations: aOR—adjusted odds ratios; CI—confidence interval.
* Reference group is the group without any malignancy.
† Unable to be evaluated due to zero cases.

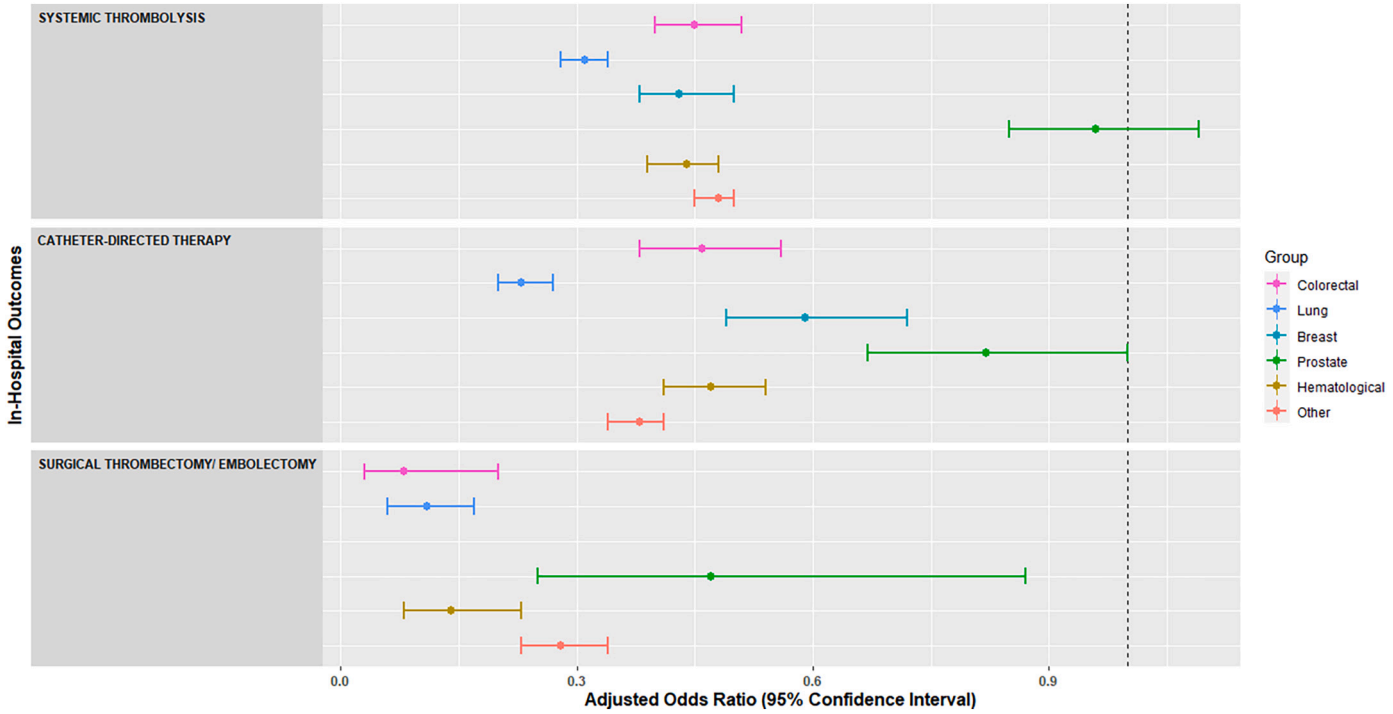

Fig. 3. Forest plot of adjusted odds ratios for in-hospital management.

without cancer, there is a 4-fold increase in VTE risk [20–22]; when considering patients with metastatic cancer, the risk increases up to 58-fold [9,21]. Similarly, while the incidence of PE in the general population is 0.11% [23], a meta-analysis by Reynolds et al. found the incidence of PE in cancer patients to be significantly elevated, ranging from 0.13% to 8.65% [24]. Thromboprophylaxis is also rarely used during treatment, which could potentiate the increased risk of PE in cancer [25]. Nonetheless, the risk of VTE can be reduced significantly through primary thromboprophylaxis with direct oral anticoagulants, as demonstrated by two randomized controlled trials [26–28].

This increased risk can be attributed to the hypercoagulable state and thromboses induced by the presence of malignancy [7]. Progression of cancer, thus, is commonly associated with procoagulant effects, and thromboembolic disease has been known to occur in advanced cancer and is predictive of a poor prognosis [29]. Indeed, patients with active cancer constitute one-fifth of all patients presenting with VTE [30]. The coagulation system, as such, contributes greatly to tumour biology, and may even play a role in tumour angiogenesis and metastasis [31].

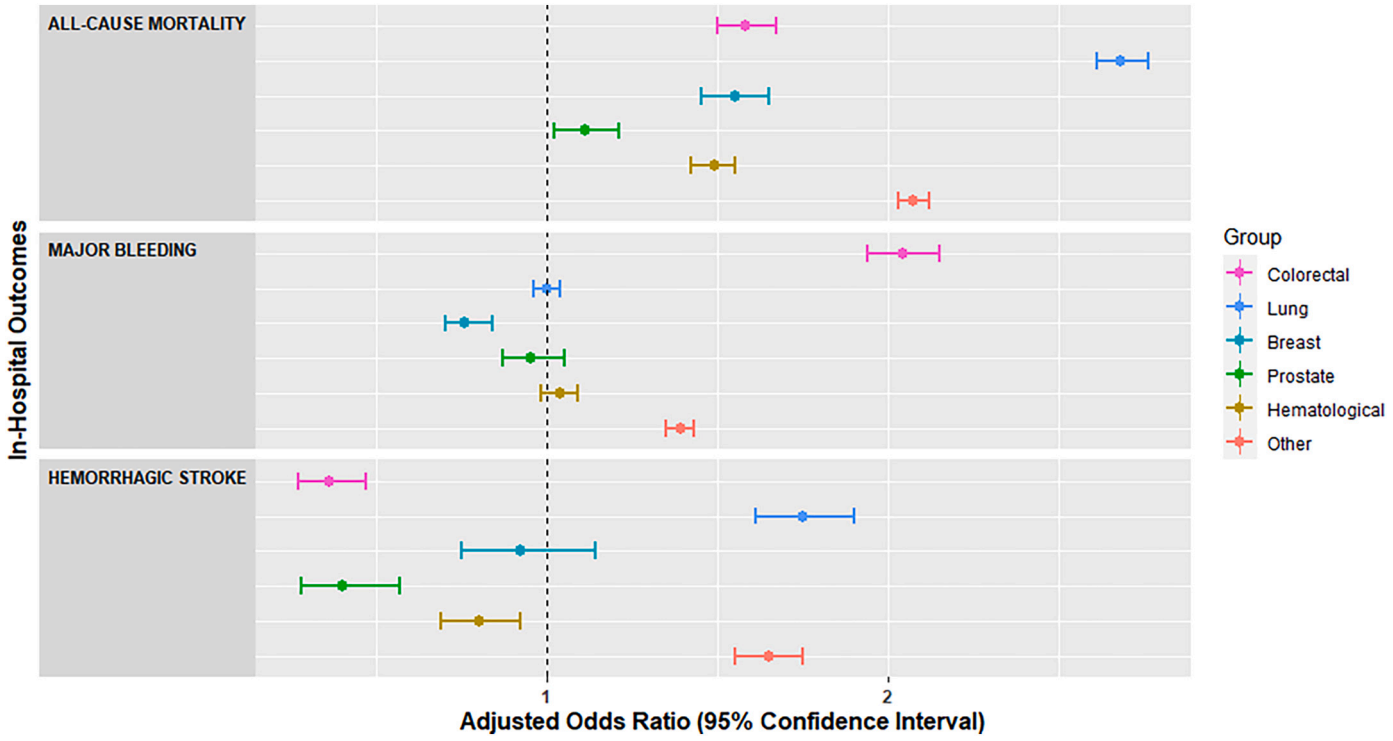

Fig. 4. Forest plot of adjusted odds ratios for in-hospital outcomes.

Furthermore, oncological treatments also increase the risk of thromboembolism; suggested mechanisms include the toxicity of these treatments on the vascular endothelium, as well as the reduction in the concentrations of natural anticoagulants [32].

The present study found the prevalence of hospitalized PE patients with a cancer diagnosis to be 19.9%, a finding that is comparable to those of Heit et al. [30] In addition, the most frequently encountered cancers in PE patients were lung and hematological cancers. As for the management of VTE in hemodynamically stable cancer patients, the European Society of Cardiology (ESC) and the American Society of Clinical Oncology recommend the use of low molecular weight heparin or direct oral anticoagulants [33,34]. However, which high-risk cancer patients may benefit from specific treatment in the form of systemic thrombolysis, catheter-based therapy or surgical thrombectomy has not been well established.

The latest ESC guidelines recommend systemic thrombolysis for PE patients who deteriorate hemodynamically, while catheter-based therapy and surgical thrombectomy should be alternatively considered [33]. Yet, it is a matter of debate whether these recommendations are applicable to cancer patients, given the lack of specific data for cancer patients in this setting [35]. Until novel data, systemic and catheter-direct thrombolysis, and surgical embolectomy, continue to be used on a case-by-case basis, mostly for hemodynamically unstable patients with low risk of bleeding [36].

This study confirms that cancer patients are less likely to be offered these treatments, with worse in-hospital mortality. This could be due to different reasons including the increased propensity towards bleeding complications in these patients, medical bias, comorbidity burden, unfavourable short- or long-term prognosis, and patient preference. It is also possible that PE in advanced cancer stages may lead to physician's reluctance to offer invasive management. Bleeding risk, of note, is a major determinant of patients not receiving invasive therapy, as supported by the fact that patients with hematological malignancies are amongst the least likely to receive such treatments. The bleeding diathesis, arising from physiological effects of the underlying cancer type, can be further compounded by the presence of thrombocytopenia, anaemia, and coagulopathy.

Nevertheless, we cannot exclude the possibility that patients with cancer were less likely to have PE that caused hemodynamic compromise (due to smaller PEs) or RV failure, and that lower rates of invasive treatments may have been appropriate. In our sensitivity analyses restricted to patients with hemodynamic instability, some cancer groups such as patients with lung and 'other' cancer, were consistently less likely to receive invasive treatment, though it may have been indicated in this patient subgroup. We similarly could not exclude that the less frequent use of thrombolysis was due to less severe episodes of PE, as the NIS database lacks the data on PE severity. However, given the high mortality and morbidity rates in PE patients with cancer, a more aggressive treatment method may be indicated even in less severe episodes of PE. The decision to utilize more invasive interventions requires a careful evaluation of the risks and benefits, taking into account the risk of mortality, the presence of hemodynamic instability, and other factors.

Our study demonstrated that cancer patients constitute a significant portion of hospitalized PE patients and are at greater risk of adverse in-hospital outcomes. Previous studies also indicate mortality rates following PE were greatly elevated in cancer patients, relative to non-cancer patients [37–39], a finding that is echoed by the present study. Okushi et al., similarly noted an increase in mortality risk across 11 cancer types, including lung, breast, and colon cancer [38]. Prostate cancer patients with acute PE appear to have the lowest risk of death in both our study and that by Okushi et al., compared to patients suffering from other cancer types [38].

An unusual finding of the present study merits discussion. First is that while patients with colorectal cancer had the highest odds of developing major bleeding, they also had the lowest risk of hemorrhagic stroke. While there has been no prior literature describing this observation, we offer a potential hypothesis. Given the increased risk of VTE in patients with cancer, most patients with colorectal cancer would be placed on antiplatelet or anticoagulation therapy, especially post-surgery. Previous studies have also demonstrated that the most common hemorrhagic complication of such therapies is extracranial major bleeding, for which GI bleeding is an important source [40]. Patients with colorectal cancer

are predisposed to GI bleeding owing to tumor biology and other conditions relating to advancing age (diverticulosis, ischemic colitis) [40]. As such, the disproportionate increase in risk of GI bleeding relative to hemorrhagic stroke could have accounted for such a finding.

The differences between the various cancer types could inform our clinical decision-making. For example, patients with breast cancer experienced significantly lower odds of major bleeding, while patients with colorectal and 'other' cancers were at greater odds of developing major hemorrhages. These differences could eventually guide therapy implementation and possibly allow for risk- and cancer type-based recommendations in the management of PE.

This paper, nonetheless, has several limitations. First, as is with all data extracted using the ICD-10 codes, the data presented in this study is subject to over- or under-coding, while the granularity of data was limited by the ICD-10 codes as well. Second, the NIS neither captures the medications prescribed such as anticoagulants, nor does it record if the patients were recently on chemotherapy, which may significantly impact clinical outcomes. Third, the NIS does not have data on the hematologic profiles of the patients, such as platelet and white cell counts, or coagulation biomarkers that are relevant to our analysis. Fourth, data on the stage of cancer, time since diagnosis, ceilings of care that limit the invasiveness of management strategies, and cause of death, are not available as well. Fifthly, a very important factor for the therapeutic approach to PE patients is their hemodynamic status, RV/LV function and underlying coronary disease which could not be directly assessed in this patient group, although we performed a sensitivity analysis in patients with cardiogenic shock with similar findings to our main analysis. Sixth, only in-hospital events are recorded in the NIS, and follow-up data for longer-term outcomes are unavailable. Finally, we could not account for patient preference and informed decision-making around treatment options. Longitudinal analyses, such as survival analysis and competing risk analysis, hence, cannot be undertaken.

5. Conclusion

This study demonstrated that cancer patients were less likely to receive systemic thrombolysis, catheter-directed therapy, and surgical interventions, with overall significantly higher in-hospital mortality compared with patients without cancer, irrespective of the cancer type. The risk of major bleeding varied according to cancer type, with colorectal cancer having the worst bleeding outcomes and lung cancer having the highest odds of hemorrhagic stroke. The metastatic status of the disease is especially important, as these patients have particularly lower rates of invasive management, higher rates of mortality, and major bleeding. Future treatment pathways should consider cancer type and stage, and future work should focus on the barriers to receipt of invasive treatment strategies in this patient group.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.09.049.

Declarations

Nothing to be declared.

Declaration of Competing Interest

None.

References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2018, CA Cancer J. Clin. 68 (1) (2018) 7–30.
[2] A.J. Sebastian, A.J. Paddon, Clinically unsuspected pulmonary embolism–an important secondary finding in oncology CT, Clin. Radiol. 61 (1) (2006 Jan) 81–85.
[3] A.M. Browne, C.G. Cronin, C. English, J. NiMhuircheartaigh, J.M. Murphy, J. F. Bruzzi, Unsuspected pulmonary emboli in oncology patients undergoing routine computed tomography imaging, J. Thorac. Oncol. Off. Publ. Int. Assoc. Study Lung Cancer. 5 (6) (2010 Jun) 798–803.
[4] S. Tresoldi, N. Flor, A. Luciani, M.A. Lombardi, B. Colombo, G. Cornalba, Contrast enhanced chest-MDCT in oncologic patients. Prospective evaluation of the prevalence of incidental pulmonary embolism and added value of thin reconstructions, Eur. Radiol. 25 (11) (2015 Nov 1) 3200–3206.
[5] J. Bělohlávek, V. Dytrych, A. Linhart, Pulmonary embolism, part I: Epidemiology, risk factors and risk stratification, pathophysiology, clinical presentation, diagnosis and nonthrombotic pulmonary embolism, Exp. Clin. Cardiol. 18 (2) (2013) 129–138.
[6] Y. Yang, L. Liang, Z. Zhai, H. He, W. Xie, X. Peng, et al., Pulmonary embolism incidence and fatality trends in Chinese Hospitals from 1997 to 2008: A Multicenter Registration Study, PLoS One 6 (11) (2011 Nov 1), e26861.
[7] G.J. Caine, P.S. Stonelake, G.Y. Lip, S.T. Kehoe, The hypercoagulable state of malignancy: pathogenesis and current debate, Neoplasia N Y N. 4 (6) (2002 Nov) 465–473.
[8] P.D. Stein, A. Beemath, F.A. Meyers, E. Skaf, J. Sanchez, R.E. Olson, Incidence of venous thromboembolism in patients hospitalized with cancer, Am. J. Med. 119 (1) (2006 Jan 1) 60–68.
[9] A.A. Khorana, C.W. Francis, E. Culakova, N.M. Kuderer, G.H. Lyman, Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer patients, Cancer. 110 (10) (2007) 2339–2346.
[10] H.K. Chew, T. Wun, D. Harvey, H. Zhou, R.H. White, Incidence of venous thromboembolism and its effect on survival among patients with common cancers, Arch. Intern. Med. 166 (4) (2006 Feb 27) 458–464.
[11] C. Font, A. Carmona-Bayonas, C. Beato, Ò. Reig, A. Sáez, P. Jiménez-Fonseca, et al., Clinical features and short-term outcomes of cancer patients with suspected and unsuspected pulmonary embolism: the EPIPHANY study, Eur. Respir. J. 49 (1) (2017 Jan 1) [cited 2021 Dec 18]. Available from, https://erj.ersjournals.com/content/49/1/1600282.
[12] J.L. Zamorano, P. Lancellotti, D. Rodriguez Muñoz, V. Aboyans, R. Asteggiano, M. Galderisi, et al., 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC), Eur. Heart J. 37 (36) (2016 Sep 21) 2768–2801.
[13] F.I. Mulder, E. Horváth-Puhó, N. van Es, H.W.M. van Laarhoven, L. Pedersen, F. Moik, et al., Venous thromboembolism in cancer patients: a population-based cohort study, Blood. 137 (14) (2021 Apr 8) 1959–1969.
[14] M. Levine, J. Hirsh, M. Gent, A. Arnold, D. Warr, A. Falanga, et al., Double-blind randomised trial of a very-low-dose warfarin for prevention of thromboembolism in stage IV breast cancer, Lancet Lond Engl. 343 (8902) (1994 Apr 9) 886–889.
[15] G. Agnelli, G. Gussoni, C. Bianchini, M. Verso, M. Mandalà, L. Cavanna, et al., Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study, Lancet Oncol. 10 (10) (2009 Oct) 943–949.
[16] J.R. Perry, J.A. Julian, N.J. Laperriere, W. Geerts, G. Agnelli, L.R. Rogers, et al., PRODIGE: a randomized placebo-controlled trial of dalteparin low-molecular-weight heparin thromboprophylaxis in patients with newly diagnosed malignant glioma, J. Thromb. Haemost. JTH. 8 (9) (2010 Sep) 1959–1965.
[17] F.I. Mulder, F.T.M. Bosch, N. van Es, Primary thromboprophylaxis in ambulatory cancer patients: where do we stand? Cancers. 12 (2) (2020 Feb) 367.
[18] HCUP National Inpatient Sample (NIS). Healthcare Cost and Utilization Project (HCUP). 2012. Agency for Healthcare Research and Quality, Rockville, MD. www.hcup-us.ahrq.gov/nisoverview.jsp.
[19] A.A. Khorana, Venous thromboembolism and prognosis in cancer, Thromb. Res. 125 (6) (2010 Jun) 490–493.
[20] J.A. Heit, M.D. Silverstein, D.N. Mohr, T.M. Petterson, W.M. O'Fallon, L.J. Melton, Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study, Arch. Intern. Med. 160 (6) (2000 Mar 27) 809–815.
[21] J.W. Blom, C.J.M. Doggen, S. Osanto, F.R. Rosendaal, Malignancies, prothrombotic mutations, and the risk of venous thrombosis, JAMA. 293 (6) (2005 Feb 9) 715–722.
[22] D.P. Cronin-Fenton, F. Søndergaard, L.A. Pedersen, J.P. Fryzek, K. Cetin, J. Acquavella, et al., Hospitalisation for venous thromboembolism in cancer patients and the general population: a population-based cohort study in Denmark, 1997-2006, Br. J. Cancer 103 (7) (2010 Sep 28) 947–953.
[23] P.D. Stein, F. Matta, Epidemiology and incidence: the scope of the problem and risk factors for development of venous thromboembolism, Clin. Chest Med. 31 (4) (2010 Dec) 611–628.
[24] M.W. Reynolds, A. Shibata, S. Zhao, N. Jones, K. Fahrbach, L.T. Goodnough, Impact of clinical trial design and execution-related factors on incidence of thromboembolic events in cancer patients: a systematic review and meta-analysis, Curr. Med. Res. Opin. 24 (2) (2008 Feb) 497–505.
[25] C.C. Kirwan, E. Nath, G.J. Byrne, C.N. McCollum, Prophylaxis for venous thromboembolism during treatment for cancer: questionnaire survey, BMJ. 327 (7415) (2003 Sep 13) 597–598.
[26] A.A. Khorana, M.G. McNamara, A.K. Kakkar, M.B. Streiff, H. Riess, U. Vijapurkar, et al., Assessing full benefit of rivaroxaban prophylaxis in high-risk ambulatory patients with cancer: thromboembolic events in the randomized CASSINI trial, TH Open Comp. J. Thromb. Haemost. 4 (2) (2020 Apr) e107–e112.
[27] A. Li, N.M. Kuderer, D.A. Garcia, A.A. Khorana, P.S. Wells, M. Carrier, et al., Direct oral anticoagulant for the prevention of thrombosis in ambulatory patients with cancer: a systematic review and meta-analysis, J. Thromb. Haemost. JTH. 17 (12) (2019 Dec) 2141–2151.

[28] M. Carrier, K. Abou-Nassar, R. Mallick, V. Tagalakis, S. Shivakumar, A. Schattner, et al., Apixaban to prevent venous thromboembolism in patients with cancer, N. Engl. J. Med. 380 (8) (2019 Feb 21) 711–719.
[29] S.A. Mousa, Anticoagulants in thrombosis and cancer: the missing link, Semin. Thromb. Hemost. 28 (1) (2002 Feb) 45–52.
[30] J.A. Heit, W.M. O'Fallon, T.M. Petterson, C.M. Lohse, M.D. Silverstein, D.N. Mohr, et al., Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study, Arch. Intern. Med. 162 (11) (2002 Jun 10) 1245–1248.
[31] A.Y.Y. Lee, M.N. Levine, R.I. Baker, C. Bowden, A.K. Kakkar, M. Prins, et al., Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer, N. Engl. J. Med. 349 (2) (2003 Jul 10) 146–153.
[32] A.D. Fox, A.P. Banning, K. Channon, L. Hands, Saddle embolus of the carotid bifurcation. A late complication of mediastinal radiotherapy, Eur. J. Vasc. Endovasc. Surg. Off. J. Eur. Soc. Vasc. Surg. 17 (4) (1999 Apr) 360–362.
[33] S.V. Konstantinides, G. Meyer, C. Becattini, H. Bueno, G.J. Geersing, V.P. Harjola, et al., 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS), Eur. Heart J. 41 (4) (2020 Jan 21) 543–603.
[34] N.S. Key, A.A. Khorana, N.M. Kuderer, K. Bohlke, A.Y.Y. Lee, J.I. Arcelus, et al., Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update, J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 38 (5) (2020 Feb 10) 496–520.
[35] Acute Management of Pulmonary Embolism [Internet], American College of Cardiology [cited 2021 Dec 22]. Available from: https://www.acc.org/latest-in-cardiology/articles/2017/10/23/12/12/http%3a%2f%2fwww.acc.org%2flatest-in-cardiology%2farticles%2f2017%2f10%2f23%2f12%2f12%2facute-management-of-pulmonary-embolism.
[36] M.B. Streiff, S.A. Abutalib, D. Farge, M. Murphy, J.M. Connors, G. Piazza, Update on guidelines for the management of cancer-associated thrombosis, Oncologist 26 (1) (2021) e24–e40.
[37] G. Bozas, N. Jeffery, D. Ramanujam-Venkatachala, G. Avery, A. Stephens, H. Moss, et al., Prognostic assessment for patients with cancer and incidental pulmonary embolism, Thromb. J. 16 (1) (2018 Feb 6) 8.
[38] Y. Okushi, K. Kusunose, Y. Okayama, R. Zheng, M. Nakai, Y. Sumita, et al., Acute hospital mortality of venous thromboembolism in patients with cancer from registry data, J. Am. Heart Assoc. 10 (11) (2021 Jun 1) e019373.
[39] G. Alotaibi, C. Wu, A. Senthilselvan, M.S. McMurtry, Short- and long-term mortality after pulmonary embolism in patients with and without cancer, Vasc. Med. Lond. Engl. 23 (3) (2018 Jun) 261–266.
[40] A. Rubboli, C. Becattini, F.W. Verheugt, Incidence, clinical impact and risk of bleeding during oral anticoagulation therapy, World J. Cardiol. 3 (11) (2011 Nov 26) 351–358.