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Emergency department cardiovascular disease encounters and associated mortality in patients with cancer: A study of 20.6 million records from the USA

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ABSTRACT

Background: there is limited data on Emergency department (ED) cardiovascular disease (CVD) presentations and outcomes amongst cancer patients.
Objectives: The present study aimed to describe the clinical characteristics, prevalence, and clinical outcomes of the most common cardiovascular ED admissions in patients with cancer.
Methods: All ED encounters with a primary CVD diagnosis from the US Nationwide Emergency Department Sample between January 2016 to December 2018 were stratified by cancer type as well as metastatic status. Multivariable logistic regression was performed to determine the adjusted odds ratios of in-hospital mortality in different groups.
Results: From a total of 20,737,247 ED encounters with a primary CVD diagnosis, cancer was present in 3.4%. In patients with cancer the most common CVDs were DVT/PE (20%), hypertensive heart or kidney disease (14.7%), and AF/flutter (11.2%). The distribution of CVDs varied by cancer type, with AF/flutter most common in patients with lung cancer, AMI most common in patients with prostate cancer, heart failure most common in those with haematological malignancies, and patients with colorectal cancer having the greatest frequency of DVT/PE. Cancer status was independently associated with significantly higher risk of mortality in almost all CVD categories, consistent across all the cancer types, amongst which lung cancer patients had the highest risk of mortality across all CVD categories, except intracranial haemorrhage and hypertensive crisis.
Conclusions: Cardiovascular presentations to the ED varied by cancer subtype. Across all cancer subtypes, patients presenting with cardiovascular presentations carried a significantly increased risk of mortality compared to patients with no cancer.

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1. Introduction

Cancer and cardiovascular diseases (CVD) are the leading causes of morbidity and mortality worldwide [1,2]. Patients with cancer are at high cardiovascular risk, due to shared risk factors, chemo-radiotherapy related cardiotoxicity, and pathophysiologic processes associated with the underlying malignancy itself [3]. Therapeutic advances have improved the life expectancy of cancer patients through reducing the risk of death from malignancy. As patients with cancer survive to older ages, CVDs are increasingly recognised as an important cause of morbidity and mortality [4].

Up to 10% of in-hospital stays in patients with cancer are attributed to CVD, with significant variations in the CVD admission diagnoses across different cancer sites [5].

The emergency department (ED) is the first point of contact for potentially serious and life-threatening CVDs. Although patients may be hospitalised from the ED, some may be treated and discharged, whilst others may not survive beyond the initial ED encounter. As such, hospital inpatient statistics alone do not provide a complete picture of cardiovascular presentations. To understand the full spectrum of cardiovascular healthcare needs of patients with cancer, it is essential that we consider the type, frequency, and outcomes from ED encounters. The present study aimed to describe the clinical characteristics, prevalence, and outcomes of the most common cardiovascular ED admissions in patients with cancer.

2. Methods

2.1. Data source

We used the Nationwide Emergency Department Sample (NEDS), developed by the Healthcare Cost and Utilisation Project (HCUP) and sponsored by the Agency for Healthcare Research and Quality (AHRQ) [6]. The NEDS produces probabilistically accurate national estimates of hospital-owned ED encounters in the United States (US). Weighted, NEDS data estimate roughly 145 million nationally representative ED visits, comprised of discharge data from 989 hospitals located in 40 states and the District of Columbia. ED diagnoses are recorded using standardised International Classification of Disease (ICD) codes, which from 2016 onwards are based on the tenth revision (ICD-10). Patient demographics, mortality outcomes, discharge status, and charges for all patients are also captured for each encounter.

2.2. Study population

We analysed all ED encounters in adults (≥18 years) with any CVD listed as the primary diagnosis from the NEDS survey between January 2016 to December 2018. CVDs were grouped into the following categories: hypertensive heart or chronic kidney disease, essential hypertension, AF or atrial flutter, AMI, ischemic stroke, heart failure(HF), deep vein thrombosis(DVT) or pulmonary embolism(PE), hypertensive crisis, cardiac arrest, intracranial haemorrhage, supraventricular tachycardia(SVT). We identified patients with record of any cancer, which we then stratified by cancer type (haematological, lung, colorectal, prostate, breast, other). CVD categories and cancer types were assigned using ICD-10 codes provided in Table S1. Information on patient demographics was extracted for each encounter including age, sex, admission day (weekday or weekend), expected primary payer, and median household income according to ZIP code. Encounters with missing data for age, sex, weekend admission, or mortality status were excluded (Supplementary Fig. 1).

2.3. Statistical analysis

Statistical analysis was performed on IBM SPSS version 26. Continuous variables are presented as median (25th percentile, 75th percentile), due to skewed data. Categorical data are presented as frequencies and percentages. Categorical variables were compared using Pearson's chi square test, while continuous variables were compared using Kruskal-Wallis test. Sampling weights were used to calculate the estimated total discharges using methods specified by AHRQ [6].

We first calculated the proportion of admissions attributed to each CVD category by cancer type (any malignancy, haematological, lung, colorectal, prostate, breast, 'other' malignancy). We examined overall ED and in-hospital mortality rates stratified by primary CVD diagnosis and cancer type (haematological, lung, colorectal, prostate, breast, or 'other' malignancy). Then, we estimated the association of cancer diagnosis with mortality (in ED or in-hospital) using fully adjusted multivariable logistic regression models, separately by CVD category and cancer type. Each cancer type (haematological, breast, prostate, lung, colon, other) was entered separately as the exposure of interest with the comparator cohort being encounters without any record of cancer; mortality was set as the model outcome. Modelled covariates included: region of hospital, location/teaching status of hospital, age, sex, weekend admission, primary expected payer, smoking status, previous AMI, valvular heart disease, previous cerebrovascular accident, dementia, hypertension, dyslipidaemia, obesity, thrombocytopenia, anaemia, chronic lung disease, coagulopathy, diabetes mellitus, liver disease, peripheral vascular disorders, chronic renal failure. In secondary analyses, we considered destination of discharge from ED, stratified by CVD category and cancer type.

3. Results

3.1. Baseline characteristics

A total of 20,737,247 primary cardiovascular ED encounters were included in the study; of these, 707,585 (3.4%) had a recorded cancer diagnosis (Table 1). Haematological malignancy was the most common cancer type (178,987, 0.9%), followed by lung (119,263, 0.6%), colorectal (103,224, 0.5%), prostate (69,703, 0.3%) and breast (56,471, 0.3%) malignancies.

Compared with individuals without cancer, patients with cancer were older (median age 72 years vs. 76 years), more commonly males, had Medicare insurance, and presented to metropolitan teaching hospitals. They tended to be multimorbid with increased frequency of HF, AF, chronic lung and liver diseases, anaemia, thrombocytopenia, and coagulopathy, but with a lower prevalence of obesity.

Amongst the specific cancer types, patients with prostate cancer were, the oldest (median 77 years) and had the highest prevalence of previous AMI (12.3%) cerebrovascular disease (7.2%), hypertension (80.5%), and dementia (8.9%). Patients with haematological malignancies had the greatest burden of pre-existing HF (46.6%), valvular heart disease (15.6%), and chronic renal failure (33.8%). Patients with colorectal cancer were the youngest (median 69 years), with a lower prevalence of HF (27.1%), cerebrovascular disease (5.0%), hypertension (68%), dyslipidaemia (36.9%) compared to the other cancer groups (Table 1).

3.2. Primary CVD diagnoses by cancer status and cancer type

Baseline characteristics of patients with specific causes of admission are presented in supplementary Tables 2–8. The distribution of primary CVD diagnoses by cancer status and type is summarised in Table 2, Fig. 1, and Supplementary fig. 2. The most common cardiovascular cause of ED admission amongst patients without cancer was hypertensive heart or kidney disease (14.4%), followed by essential hypertension (13.7%), and AF/flutter (9.9%). Amongst patients with cancer the most common CVD diagnosis was DVT/PE (20%), followed by hypertensive heart or kidney disease (14.7%), and AF/flutter (11.2%).

The proportion of CVD admission attributed to DVT/PE was greater amongst individuals with any cancer compared to those without cancer

(20% vs 6.3%). This was consistent across all the cancer types, and most notable amongst those with colorectal (28.1%), breast (22.7%), and lung (21.9%) cancer.

Attendance for primary diagnosis of hypertensive heart disease or chronic kidney disease featured prominently for both patients with (14.7%) and without (14.4%) cancer, being most common in patients with haematological (20.6%) and prostate (17.2%), and breast (14.5%) cancers. The proportion of attendances attributed to "hypertensive crisis" was slightly more common amongst those with (2.8%) than those without (1.2%) cancer.

AF/flutter appeared more commonly amongst those with cancer (11.2%) compared with those without cancer (9.9%), being most common in patients with lung cancer (14.1%).

Intracranial haemorrhage and ischaemic strokes occurred more

Table 1
Patient characteristic.

	Malignancy type							
	Haematological	Lung	Colorectal	Prostate	Breast	Other malignancy	Any Malignancy	No malignancy
Number of weighted records, %	178,987 0.9%	119,263 0.6%	103,224 0.5%	69,703 0.3%	56,471 0.3%	179,937 0.9%	707,585 3.4%	19,929,661 96.6%
Age (years), median (IQR) [1,2]	74 (65,82)	71 (63,78)	69 (61, 78)	77 (70,84)	71 (61,80)	71 (62,80)	72 (63,81)	67 (54,78)
Females, % [1,2]	43.0%	46.2%	40.4%	0%	98.5%	49.0%	44.9%	48.8%
Hospital Location [1,2]								
Northeast	21.0%	20.5%	21%	21%	20.7%	20.3%	20.7%	16.9%
Midwest	23.7%	25.6%	22.8%	23.2%	23.3%	22.9%	23.6%	22.6%
South	37.6%	39.6%	37.9%	35.1%	37.9%	37.5%	37.8%	42.6%
West	17.6%	14.3%	18.2%	20.7%	18.2%	19.2%	17.9%	17.9%
Hospital Location/ teaching Status [1,2]								
Metropolitan non-teaching	24.0%	24.4%	23.5%	24.4%	23.4%	22.6%	23.6%	26.1%
Metropolitan teaching	65.5%	63.1%	65.9%	64.6%	65.9%	67.5%	65.6%	58.6%
Non-metropolitan	10.5%	12.5%	10.5%	11.1%	10.7%	9.9%	10.8%	15.2%
Weekend Admission [1,2]	23.7%	22.6%	22.8%	23.6%	22.9%	23%	23.1%	24.6%
Median ZIP income [1,2]								
1st quartile	25.5%	29.9%	28.7%	27.8%	28.4%	26.8%	27.5%	33.3%
2nd quartile	24.9%	27.3%	25.7%	25.1%	25.3%	25.5%	25.6%	27.2%
3rd quartile	24.5%	23.4%	23.4%	24%	23.2%	24.3%	23.9%	21.6%
4th quartile	25%	19.4%	22.2%	23.1%	23.2%	23.5%	23.0%	17.9%
Expected Primary Payer [1,2]								
Medicare	75.9%	70.9%	64.6%	81.2%	67.2%	67.1%	71.0%	56.2%
Medicaid	5.2%	8.5%	9.5%	3/6%	9%	8.2%	7.3%	12.1%
Private	15.7%	16.9%	21.5%	12%	23.1%	20.7%	18.1%	22.3%
Uninsured	1.4%	1.5%	1.9%	1%	1.3%	1.9%	1.6%	6.6%
No charge	0.1%	0.1	0.1%	0.1%	0.1%	0.1%	0.1%	0.4%
Other	1.6%	2.1%	2.3%	2.1%	1.2%	1.9%	1.9%	2.5%
Comorbidities								
Previous MI [1,2]	10.3%	9.8%	8.2%	12.3%	6.1%	8.6%	9.3%	8.9%
Cerebrovascular disease [1,2]	5.9%	5.9%	5%	7.2%	5.3%	6.5%	6%	5.7%
Heart failure [1,2]	46.6%	32.1%	27.1%	40%	34.4%	30.8%	35.7%	30.9%
Valvular disease [1,2]	15.6%	9%	8.6%	14.1%	11.8%	10.5%	11.7%	8.8%
Atrial fibrillation/flutter [1,2]	40%	35.8%	27.1%	37.2%	28.9%	29.3%	33.5%	26%
Hypertension [1,2]	76.5%	68.7%	68%	80.5%	71.8%	71.1%	72.6%	75.6%
Dyslipidaemia [1,2]	45.7%	42%	36.9%	51.2%	39%	40.5%	42.5%	37.4%
Diabetes Mellitus [1,2]	31.7%	26.1%	34%	31.9%	29.7%	28.8%	30.2%	30.2%
Smoking [1,2]	36.5%	66.5%	40.3%	42.2%	29.7%	39.5%	42.9%	34.9%
Peripheral vascular disease [1,2]	7.7%	9.3%	5.7%	8.8%	5.4%	6.5%	7.3%	5.6%
Chronic lung disease [1,2]	23.9%	50.6%	19.3%	20.9%	20.8%	21.3%	26.5%	18.7%
Chronic renal failure [1,2]	33.8%	17.7%	18.5%	30.9%	18.9%	25%	25.1%	20.7%
Obesity [1,2]	11.5%	7.6%	9.2%	9.8%	14.8%	11.6%	10.6%	12.6%
Anaemia [1,2]	39.9%	21.7%	41%	32.7%	28.9%	34%	35.8%	15.1%
Thrombocytopenia [1,2]	13.4%	7.2%	10.1%	6.7%	5%	7.1%	8.9%	2.5%
Coagulopathy [1,2]	2.9%	4.1%	5.9%	2.6%	2.9%	3.7%	3.7%	1.2%
Dementia [1,2]	6%	4.4%	3.7%	8.9%	5.6%	5%	5.4%	5.1%
Chronic Liver Disease [1,2]	1.2%	0.8%	5.6%	0.9%	0.9%	1%	1.7%	0.7%
ED and In-hospital outcomes								
Total ED and inpatient charge, median (IQR) [1,2]	37,440 (20,898, 70,862)	37,860 (21,568, 70,195)	38,080 (21,510, 72,254)	37,560 (20,860, 71,536)	34,041 (19,532, 61,603)	38,482 (21,342, 72,446)	37,571 (21,085, 70,658)	37,398 (20,723, 71,004)
LOS (days), median, (IQR)* [1,2]	4 (2,6)	4 (2,7)	4 (2,7)	3 (2,6)	3 (2,6)	4 (2,7)	4 (2,6)	3 (2,5)
Overall Mortality^ [1,2]	5.2%	8.9%	8.1%	4.9%	4.4%	6.2%	6.4%	3.7%

^ ED and in-hospital mortality.

1 p value for any malignancy vs no malignancy <0.0001; 2 p value differences between cancer types <0.0001.

* For patients admitted to hospital.

commonly amongst cancer patients, however these differences were small. The proportion of admissions attributed to AMI and cardiac arrests were comparable amongst those with and without cancer; however, within the cancer subtypes, those with prostate cancer had the greatest proportion of AMI (10.7% vs 8.9% amongst those without cancer). HF was most common in patients with haematological cancers (11%), appearing more commonly than in those without cancer (7.4%) and in the cancer cohorts combined (7.8%).

3.3. Mortality

Patients with cancer had higher unadjusted rates of all-cause mortality compared with the no-cancer group (6.4% vs. 3.7%, $p < 0.001$) Amongst the cancer subgroups, lung cancer carried the highest rate of all-cause mortality (8.9%), followed by colorectal cancer (8.1%), cancer of other causes (6.2%), haematological (5.2%), prostate (4.9%) and breast (4.4%) cancer (Table 1).

When accounting for the specific principal diagnoses, the unadjusted rates of all-cause mortality were higher in patients with cancer across all selected cardiovascular admission diagnoses ($P < 0.001$), except in patients with haematological malignancies who had the lowest mortality following presentation with hypertensive crisis (<0.1% vs 0.1%–1.1%) and cardiac arrest (87.2% vs 87.8%–90.8%). As expected, admission with cardiac arrest was associated with the highest mortality rate across all cancers (87.2%–90.8%), followed by intracranial haemorrhage (13.2%–24.9%). Table 2.

Amongst the cancer subtypes, patients with lung cancer had the highest in hospital (in ED and during admission as inpatient) mortality for acute MI (11.7%), ischemic stroke (9.3%), DVT/PE (5.5%) hypertensive heart or kidney disease (5%), atrial fibrillation/flutter (3.2%), SVT (2.3%), and hypertensive crisis (1.1%). The highest mortality of patients presenting with intracranial haemorrhage was observed in patients with haematological cancers. The lowest mortality of AMI (5.8%) and ischemic stroke (3.6%), DVT/PE (2.2%) atrial fibrillation/ flutter (1.6%) was observed in patients with prostate cancer. Finally, the lowest mortality rates associated with the primary diagnoses of intracranial haemorrhage (13.8%) and HF (2.9%) were observed in the breast cancer group (Table 2).

Following adjustment for differences in baseline covariates, the adjusted odds of in hospital mortality were significantly increased for most of the acute CV causes for ED presentation in all cancers. Presentation with AF/flutter (aOR 2.22–5.23), hypertensive heart or kidney disease (aOR 1.33–2.57), HF (aOR1.5–2.55), and DVT/PE (aOR 1.58–4.53) were associated with an increased odds of all-cause mortality in all cancer groups. SVT was associated with highest aOR for mortality amongst patients with lung (aOR 8.17, 95% CI 5,88–11.34) and haematological malignancies (aOR 3.9, 95% CI 2.76–5.52).

Cardiac arrest, AMI, ischemic, and haemorrhagic stroke, were associated with increased odds of mortality amongst most cancer types. The exceptions are prostate cancer which was associated with lower odds of mortality after cardiac arrest (aOR 0.83, 95%CI 0.7–0.99), and similar odds of mortality after AMI (aOR 0.94, 95% CI 0.85–1.03) and ischemic stroke (aOR 0.9, 95% CI 0.79–1.02); and breast cancer which was associated with similar odds of mortality after intracranial haemorrhage (aOR 0.93, 95% CI (0.78–1.09) Table 3.

Table 2
Prevalence of the cardiovascular admission diagnoses and associated total ED and in-hospital mortality based on malignancy.

		Malignancy type							
		Haematological	Lung	Colorectal	Prostate	Breast	Other Malignancy	Any Malignancy	No Malignancy
Number of weighted records, %		178,987	119,263	103,224	69,703	56,471	179,937	707,585	19,929,661
		0.9%	0.6%	0.5%	0.3%	0.3%	0.9%	3.4%	96.6%
Hypertensive heart or chronic kidney disease, 14.4%	Prevalence [1,2]	20.6%	11.1%	10.5%	17.2%	14.5%	13%	14.7%	14.4%
(N = 2,978,453)	Mortality [1,2]	3.8%	5%	4.1%	3.5%	3%	3.9%	3.9%	1.7%
Essential (primary) hypertension, 13.3% (N = 2,750,217)	Prevalence [1,2]	1.9%	1.2%	2%	3%	4%	2.7%	2.3%	13.7%
	Mortality	<0.1%	<0.1%	<0.1%	<0.1%	<0.1%	0.2%	0.1%	<0.1%
Atrial Fibrillation/ Flutter, 10% (*N* = 2,056,294)	Prevalence [1,2]	12.7%	14.1%	9.1%	10.6%	11.1%	9.3%	11.2%	9.9%
	Mortality [1,2]	1.7%	3.2%	3.0%	1.6%	1.8%	1.9%	2.2%	0.4%
Acute Myocardial infarction, 8.9% (N = 1,829,582)	Prevalence [1,2]	8.2%	8.1%	6.8%	10.7%	6.1%	7.3%	7.8%	8.9%
	Mortality [1,2]	6.7%	11.7%	11.2%	5.8%	6%	7.9%	8.3%	4.1%
Ischemic stroke, 8.1% (*N* = 1,662,442)	Prevalence [1,2]	7.7%	10.7%	9.6%	10%	8.1%	9.5%	9.2%	8%
	Mortality [1,2]	4.7%	9.3%	8.9%	3.6%	4.7%	6.4%	6.6%	2.7%
Heart Failure, 7.4% (N = 1,524,789)	Prevalence [1,2]	11%	6.7%	5.2%	8.4%	8.4%	6.3%	7.8%	7.4%
	Mortality [1,2]	4.8%	4.7%	3.5%	3.7%	2.9%	3.9%	4.2%	1.7%
DVT/PE, 6.7% (N = 1,387,342)	Prevalence [1,2]	11.8%	21.9%	28.1%	12.2%	22.7%	24.3%	20%	6.3%
	Mortality [1,2]	2.9%	5.5%	3.9%	2.2%	2.5%	3.4%	3.6%	1%
Hypertensive Crisis, 2.8% (*N* = 573,542)	Prevalence [1,2]	1.2%	0.6%	1.1%	1.3%	1.7%	1.4%	1.2%	2.8%
	Mortality [1,2]	<0.1%	1.1%	1%	0.8%	0.5%	0.6%	0.5%	0.1%
Cardiac Arrest, 2.4% (*N* = 495,406)	Prevalence [1,2]	1.5%	3.3%	3.3%	1.5%	1.6%	2.1%	2.2%	2.4%
	Mortality [1,2]	87.2%	90.5%	90.8%	85.7%	88.8%	88.9%	89.2%	87.8%
Intracranial Haemorrhage, 2.2% (*N* = 460,816)	Prevalence [1,2]	2.7%	2.6%	2.1%	3%	2.1%	4.7%	3.1%	2.2%
	Mortality [1,2]	24.9%	17.1%	23.4%	22.7%	13.8%	16.5%	19.6%	13.2%
Supraventricular Tachycardia, 1.9% (*N* = 395,098)	Prevalence [1,2]	1.3%	1.8%	1.6%	1.6%	2%	1.4%	1.5%	1.9%
	Mortality [1,2]	1.8%	2.3%	0.7%	0.5%	0.4%	0.8%	1.2%	0.1%

1 p value for any malignancy vs no malignancy <0.0001; 2 p value differences between cancer types <0.0001.

3.4. Destination of discharge from ED

supplementary fig. 3 and supplementary table 9 presents the destination of discharge of patients from ED. Compared to patients without cancer, those with cancer were more likely to be admitted to the hospital (76.7% vs 49.8%), and less likely to be discharged home (16.4% vs 39.4%). Amongst different cancer types, patients with lung cancer were most likely to be admitted to the hospital (79%) and patients with breast cancer were least likely to be admitted (71.6%). Only 12.9% of lung cancer patients were discharged home. While the ED mortality rate was higher amongst patients with colorectal (3.1%) or lung (2.8%) compared to patients with no cancer (2.2%) it was lower amongst patients in other cancer groups (1.2%–1.8%).

4. Discussion

We evaluated over 20 million ED encounters with a primary CVD diagnosis and considered the distribution of CVDs and subsequent mortality outcomes by cancer status and cancer type. A total of 3.4% of ED encounters were in patients with cancer. The most common CVDs in patients without cancer were hypertensive heart or kidney disease (14.4%), essential hypertension (13.7%), and AF/flutter (9.9%). Whilst, in patients with cancer the most common CVDs were DVT/PE (20%), hypertensive heart or kidney disease (14.7%), AF/flutter (11.2%), and ischemic stroke (9.2%). The distribution of CVDs varied by cancer type, with AF/flutter most common in patients with lung cancer, AMI most common in patients with prostate cancer, HF most common in those with haematological malignancies, and DVT/PE in patients with colorectal cancer. Patients with cancer presenting with an emergency CVD encounter were at higher risk of adverse outcomes compared with those without cancer. Cancer status was independently associated with significantly higher risk of mortality in almost all CVD categories, consistent across all the cancer types, amongst which lung cancer patients had the highest risk of mortality across all CVD categories, except intracranial haemorrhage and hypertensive crisis.

Previous epidemiologic studies have characterised the rates and utilisation patterns of EDs by patients with cancer [7–14] However, these studies have not specifically looked in granular detail at cardiovascular data. Whilst those that have systematically examined CVD diagnoses have focussed on in-hospital admissions [15] or mortality data. Thus, there is limited data on ED CVD presentations and outcomes amongst cancer patients. Our study presents a dedicated analysis of primary CVD ED encounters, extending existing literature and providing novel insights into the full spectrum of cardiovascular healthcare needs of patients with cancer.

Our findings indicate that patients with haematologic, lung, and colorectal cancers are the top three cancer types attending ED with a primary CVD diagnosis, whilst patients with breast and prostate cancer were less frequently encountered. Previous studies examining ED attendances without specificity to CVD have reported a slightly different distribution of cancer types. In an analysis of 37,760 ED visits by patient with cancer in North Carolina, Mayer et al. identified patients with lung, breast, prostate, and colorectal cancers as the most common cancer types encountered [13]. Consistent with these findings, Gallaway et al. [12] also showed that lung, breast, colorectal, and prostate are the most commonly encountered cancer types in ED. Lee et al. [14] presented a nationwide analysis of ED use amongst cancer patients in Korea. They identified lung, liver, and colorectal cancer as the most common cancers. Thus, it appears that lung and colorectal cancers are frequent attenders of the ED for both CVD and non-CVD diagnoses. However, whilst breast cancer patients were featured highly in unselected analyses of ED presentations [12,13] they were less commonly encountered in our analysis. This suggests that breast cancer patients are high users of ED services, but that this is most often for non-CVD illnesses. Indeed, in an earlier analysis of unselected ED visits by cancer patients using the NEDS database, Rivera et al. [8] reported breast [14.9%], prostate [11.3%], and lung [10.3%] cancer as the most common cancer presenting to ED. The most common primary reasons for visits were pneumonia (4.5%), nonspecific chest pain (3.7%), and urinary tract infection (3.2%). These observations indicate differential ED usage for CVD diagnoses by cancer type, which is distinct from patterns of unselected ED utilisation.

We found that 76.4% of cancer patients presenting to ED with a CVD required hospitalisation, which was significantly greater than individuals without cancer. Rivera et al. [8] report association of cancer-related ED visits with significantly higher inpatient admission rate than non–cancer-related ED visits (59.7% vs 16.3%). These admission rates for cancer patients presenting to ED are reasonably consistent across the literature, with Mayer et al. [13] reporting a rate of 63.2%, Lee et al. [14] a rate of 54.8%, and in a nationwide study from France, Peyroni et al. [11] report a hospitalisation rate of 64.9%. Thus, overall cancer patients presenting to the ED have high likelihood of requiring hospitalisation; however, our findings suggest that this risk is greatly increased in patients presenting with a primary CVD diagnosis.

In our study of ED CVD visits, a greater proportion of cancer patients

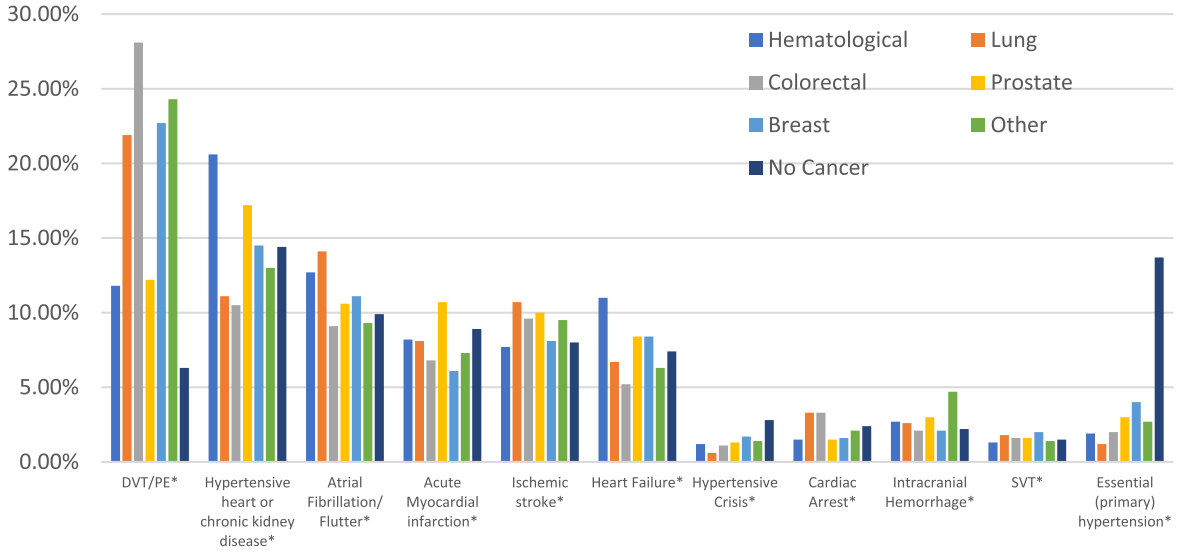

Fig. 1. Overview of the cardiovascular ED admission diagnoses for patients with malignancy, by malignancy type.
DVT: deep vein thrombosis, PE: pulmonary embolism, SVT: supraventricular tachycardia. *p Value <0.001.

Table 3
Adjusted odds of total (ED and inpatient) mortality in different malignancy types and selected cardiovascular admission diagnoses*

	Haematological	Lung	Colorectal	Prostate	Breast	Other Malignancy
Hypertensive heart or chronic kidney disease	1.59	2.57	1.93	1.33	1.68	1.88
aOR (95%CI), p value	(1.5–1.68) P < 0.001[2]	(2.37–2.78) P < 0.001[2]	(1.75–2.13) *P* < 0.001[2]	(1.21–1.47) *P* < 0.001[2]	(1.48–1.92) *P* < 0.001[2]	(1.76–2.01) <0.001[2]
Atrial Fibrillation/Flutter	2.22	5.23 (4.76–5.75)	4.55	2.3	3.42	3.11
aOR (95%CI), p value	(1.99–2.47) P < 0.001[2]	P < 0.001[2]	(4.02–5.16) P < 0.001[2]	(1.91–2.78) P < 0.001[2]	(2.82–4.14) P < 0.001[2]	(2.77–3.48) P < 0.001[2]
Acute Myocardial infarction	1.09	2.65	2.18	0.94	1.13	1.46
aOR (95%CI), p value	(1.01–1.16) *P* = 0.02[2]	(2.49–2.83) P < 0.001[2]	(2.02–2.35) P < 0.001[2]	(0.85–1.03) *P* = 0.2[2]	(0.98–1.3) *P* = 0.1[2]	(1.37–1.56) P < 0.001[2]
Ischemic stroke	1.21 (1.12–1.32)	2.86 (2.69–3.05)	2.36 (2.19–2.54)	0.9 (0.79–1.02)	1.41 (1.23–1.62)	1.88 (1.76–2)
aOR (95%CI), p value	P < 0.001[2]	P < 0.001[2]	P < 0.001[2]	P = 0.1[2]	P < 0.001[2]	P < 0.001[2]
Heart Failure	2.1	2.55	1.69	1.5	1.63	1.88
aOR (95%CI), p value	(1.96–2.25) P < 0.001[2]	(2.29–2.83) P < 0.001[2]	(1.56–1.96) P < 0.001[2]	(1.31–1.72) P < 0.001[2]	(1.37–1.93) P < 0.001[2]	(1.7–2.07) *P* < 0.001[2]
DVT/PE	2.04 (1.88–2.22)	4.53	3.06	1.58	2.1 (1.87–2.36)	2.79
aOR (95%CI), p value	P < 0.001[2]	(4.27–4.81) P < 0.001[2]	(2.86–3.26) P < 0.001[2]	(1.36–1.83) P < 0.001[2]	P < 0.001[2]	(2.64–2.95) P < 0.001[2]
Hypertensive Crisis	N/A[1]	4.41	5.8	2.77	3.74	3.11
aOR (95%CI), p value		(2.03–9.57) P < 0.001[2]	(3.15–10.7) P < 0.001[2]	(1.31–5.8) *P* = 0.008[2]	(1.52–9.23) *P* = 0.004[2]	(1.18–5.33) P < 0.001[2]
Cardiac Arrest	1.1	1.46	1.37	0.83	1.24	1.22
aOR (95%CI), p value	(0.98–1.25) 1.2 *P* = 0.09[2]	(1.31–1.63) P < 0.001[2]	(1.22–1.54) P < 0.001[2]	(0.7–0.99) *P* = 0.04[2]	(1–1.52) *P* = 0.047[2]	(1.01–1.35) P < 0.001[2]
Intracranial Haemorrhage	1.76	1.23	1.7	1.69	0.93	1.28
aOR (95%CI), p value	(1.65–1.88) P < 0.001[2]	(1.11–1.35) P < 0.001[2]	(1.54–1.88) P < 0.001[2]	(1.52–1.8) P < 0.001[2]	(0.78–1.09) *P* = 0.37[2]	(1.2–1.35) P < 0.001[2]
Supraventricular Tachycardia	3.9	8.17	1.73	0.99	3.19	2.14
aOR (95%CI), p value	(2.76–5.52) P < 0.001[2]	(5.88–11.34) P < 0.001[2]	(0.9–3.32) P = 0.1[2]	(0.39–2.49) *P* = 0.98[2]	(1.3–7.83) *P* = 0.01[2]	(1.32–3.46) *P* = 0.002[2]

[1]N/A due to small numbers. 2 Hosmer and Lemeshow test p value>0.05.
Abbreviations: aOR – adjusted Odds Ratios; CI – Confidence Interval.
* Reference group is group without any malignancy.Note: Binomial multivariable logistic regression analysis. adjusted for: region of hospital, location/teaching status of hospital, age, sex, weekend admission, primary expected payer, smoking status, previous myocardial infarction, valvular heart disease, previous cerebrovascular accident, dementia, dyslipidemia, obesity, thrombocytopenia and other comorbidities (anemias, chronic lung disease, coagulopathy, diabetes mellitus, liver disease, peripheral vascular disorders, chronic renal failure).

died (ED and in-hospital) compared with those without cancer (6.4% vs 3.7). Lee et al. [14] and Peyroni et al. [11] report higher mortality rates, than in our study, of 9.5% and 13.4%, respectively. The absence of CVD-specific data in these studies preclude direct comparison with our results, particularly given the great heterogeneity in clinical status of cancer patients and the wide range of illnesses with which they may present.

Our findings suggest that cancer status appeared to be significantly associated with mortality independent of a wide range demographic and clinical factors, this appeared broadly consistently across all cancer types and CVD subtypes. We found that the risk of death to be most augmented in patients with lung cancer. Patients with lung cancer had over 8-fold and over 5-fold greater adjusted risk of death after an ED encounter with SVT and AF/flutter, respectively, and over 4-fold risk of death after encounter with DVT/PE or hypertensive crisis. The association between AF and lung cancer is multifactorial with smoking status, pre-existing chronic lung disease, pulmonary hypertension, mass affect from atrial structures radiotherapy, and subclinical metastatic disease all implicated [16–19]. This is particularly important as AF is challenging from an anticoagulation perspective as patients with cancer are at both an increased risk of VTE and bleeding, both as progression of the disease and medications associated with treatment [20]. Historically, patients with AF or VTE and cancer were managed with low molecular weight heparin (LMWH) or warfarin [21]. More recently, direct oral anticoagulants (DOACs) therapies have been shown to be non-inferior with easier dosing strategies than LMWH or warfarin, even amongst patients with cancer-related VTE [22].

The most common CVD amongst those with cancer was DVT/PE, being over 3-fold more frequent amongst those with cancer compared with those without (20% vs 6.3%). The greater risk of venous thromboembolism amongst cancer patients is widely reported and our findings are consistent with previous population-based studies [23,24]. Malignancies activate the coagulation cascade and enhance prothrombotic properties of host cells, in addition to known risk factors of thrombosis including chemotherapy and immobilisation [25]. Cancer patients have been shown to have a 5–7 fold increase of developing VTE [26,27], and for those patients who develop VTE with cancer, they have a significantly worse prognosis compared to cancer patients without VTE [28]. In our analysis, DVT/PE was more common in those with colorectal (28.1%), breast (22.7%), and lung cancer (21.9%); these findings are consistent with previous reports [23,29]. The augmented risk of VTE in patients with these cancers is likely complicated with requirement for major surgeries, which as well as further increasing the risk of VTE may also be associated with interruptions to anticoagulation. Such scenarios are challenging and require careful risk balance evaluations. There are also suggestions that distinct pathophysiology of these cancers may further predispose to VTE. For example, in colorectal cancer tissue factor is abnormally expressed on tumour cells [30] and colorectal cancer patients with high serum tissue levels have been shown to have significantly increased risk of recurrent VTE whilst on anticoagulation [31]. Thus, whilst VTE risk is elevated amongst cancer patients, the risk is not uniform across cancer types with a multitude of treatment and cancer-

specific mechanisms playing a role in cancer-associated thrombosis.

Interestingly, we found that attendances for severe manifestations of hypertension (e.g., end-organ damage or crisis) appeared prominent amongst across the whole sample of patients presenting with CVD, with comparable distribution amongst cancer and non-cancer patients. However, many more admissions were attributed to essential hypertension amongst those without cancer (13.7%), than those with cancer (2.3%). This may reflect different referral and service use patterns amongst cancer patients. As patients with cancer have greater healthcare contact through multiple sources, they may be less likely to present to the ED with problems that could be managed in other settings.

Haematological malignancies were most common in patients with HF, with breast cancer the least frequent compared to other cancer subgroups. Breast cancer, specifically with the use of Herceptin has been associated with cardiotoxicity and HF [32], whilst haematological malignancies have been implicated in HF due to the use of anthracyclines which have been shown to be cardiotoxic but are often used to treat both solid and haematological cancers [33]. However, surveillance strategies do differ by cancer subtype with increasingly frequent monitoring by echocardiogram or cardiac magnetic resonance imaging in breast cancer, which may in part reflect the reduced rates of HF in this group [34,35]. The frequency of haematological malignancy was also highest in patients with AMI. This is likely a reflection of their prothrombotic state. Additionally, patients with CLL tended to be male, older and the higher prevalence of AMI increased with age.

4.1. Strengths and limitations

In this study we utilised the NEDS database to evaluate a large sample of nationally representative record of ED visits with diagnoses recorded using ICD-10 codes. Of course, administrative datasets that utilise ICD-10 coding also have several limitations, including risk of misdiagnoses, miscoding, or coding omissions. However, this is an unlikely source of bias in our study as it is unlikely that the rates of such errors are differential across patients. As we were reliant on ICD-10 codes, the granularity of our diagnoses was limited by the predefined disease categories. However, the as ICD-10 codes are used in routine health records internationally, their use permits wider generalisability of our findings and allows for comparison across other cohorts. Additionally, due to limitations of the NEDS dataset, we were unable to evaluate the influence of factors such as chemo-radiotherapy, haematological and blood biochemistry indices, stage of cancer, how long patients have been diagnosed with cancer in relation to the index admission, or whether there are ceilings of care in place that limit the management and therefore determine clinical outcomes. Although we were able to reliably ascertain fact of death, we were unable to consider cause-specific mortality. Finally, the NEDS includes in-hospital events and does not provide long-term outcomes. As with other observational studies of this nature, it is possible that our results could be affected by confounding. We have tried to mitigate for this by adjusting for the appropriate variables in our multivariate models. Finally, our analysis is largely descriptive and is not used to test hypotheses.

5. Conclusions

In this analysis of ED encounters, patients with cancer tended to be older and increasingly multimorbid. Cardiovascular presentations to the ED varied by cancer subtype with lung cancer being increasingly prevalent with AF, colorectal cancer with VTE and haematological malignancies with HF and AMI. Across all cancer subtypes, cancer patients presenting with cardiovascular presentations carried a significantly increased risk of mortality. They were more likely to be admitted to hospital. Recognition of their increased risk factor profile is likely to influence management of this high risk heterogenous group of patients by physicians in the ED.

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Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.06.053.

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