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Catheter-based therapy for intermediate or high-risk pulmonary embolism is associated with lower in-hospital mortality in patients with cancer: Insights from the National Inpatient Sample

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Abstract

Background: Pulmonary embolism (PE) is a common complication among patients with cancer and is a significant contributor to morbidity and mortality. Catheter-based therapies (CBT), including catheter-directed thrombolysis (CDT) and mechanical thrombectomy, have been developed and are used in patients with intermediate or high-risk PE. However, there is a paucity of data on outcomes in patients with cancer as most clinical studies exclude this group of patients.

Aims: To characterize outcomes of patients with cancer admitted with intermediate or high-risk PE treated with CBT compared with no CBT.

Methods: Patients with an admission diagnosis of intermediate or high-risk PE and a history of cancer from October 2015 to December 2018 were identified using the National Inpatient Sample. Outcomes of interest were in-hospital death or cardiac arrest (CA) and major bleeding. Inverse probability treatment weighting (IPTW) was utilized to compare outcomes between patients treated with and without CBT. Variables that remained unbalanced after IPTW were adjusted using multivariable logistic regression.

Results: A total of 2084 unweighted admissions (10,420 weighted) for intermediate or high-risk PE and cancer were included, of which 136 (6.5%) were treated with CBT. After IPTW, CBT was associated with lower death or CA (aOR 0.54, 95% CI 0.46–0.64) but higher major bleeding (aOR 1.41, 95% CI 1.21–1.65). After stratifying by PE risk type, patients treated with CBT had lower risk of death or CA in both intermediate (aOR 0.52, 95% CI 0.36–0.75) and high-risk PE (aOR 0.48, 95% CI 0.33–0.53). However, patients with CBT were associated with increased risk of major bleeding in intermediate-risk PE (aOR 2.12, 95% CI 1.67–2.69) but not in those with high-risk PE (aOR 0.84, 95% CI 0.66–1.07).

Conclusions: Among patients with cancer hospitalized with intermediate or high-risk PE, treatment with CBT was associated with lower risk of in-hospital death or CA but

higher risk of bleeding. Prospective studies and inclusion of patients with cancer in randomized trials are warranted to confirm our findings.

KEYWORDS
cancer-associated VTE, catheter-based therapy, catheter-directed thrombolysis, mechanical thrombectomy, pulmonary embolism

1 | INTRODUCTION

Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), is a common complication in patients with cancer and accounts for a significant burden of morbidity and mortality. Patients with cancer account for approximately 15% of VTE cases and 10% of patients with cancer will develop VTE (which is associated with a four-fold increased risk in death).[1–4] PE in particular has high risk of morbidity and mortality in patients with cancer.[5] In one autopsy series of patients with cancer, 12% of patients had PE at the time of death with 66% of PE being considered fatal.[5]

Anticoagulation is the mainstay therapy among patients with PE with thrombolytic therapy reserved for those demonstrating hemodynamic instability.[6,7] However, bleeding risk is increased among patients with cancer receiving anticoagulants or thrombolytics.[8,9] In acute PE, catheter-based therapies (CBT) including catheter-directed thrombolysis (CDT) and percutaneous mechanical thrombectomy (MT), have been developed as an option for reperfusion and have been shown to improve surrogate outcomes in single-armed trials and registry studies.[10] Both CDT and MT have been studied mainly in single-armed trials and registry studies and have been shown to improve RV dysfunction, hemodynamic parameters, and RV/LV ratio in patients with intermediate and high-risk PE.[11–15]

Trials and registry studies of CDT and MT have not included patients with cancer. Furthermore, patients with cancer have historically been less likely to undergo invasive procedures, for example, percutaneous coronary intervention (PCI) in acute myocardial infarction (AMI), despite potential benefit.[16,17] Therefore, CBT use and outcomes in patients with cancer and PE have not been thoroughly investigated and remain an unanswered question. We used the National Inpatient Sample (NIS), a large inpatient database, to explore outcomes of patients with cancer and intermediate or high-risk PE who underwent CBT compared with those that did not. We hypothesized that patients with cancer and intermediate or high-risk PE who undergo CBT have improved in-hospital outcomes compared with patients who did not.

2 | METHODS

2.1 | Study design and population

This was a retrospective cohort study using the NIS. The NIS is part of the Healthcare Cost and Utilization Project (HCUP) and sponsored by the Agency for Healthcare Research and Quality (AHRQ). The NIS is the largest inpatient database in the United States, capturing approximately 20% of hospitalizations nationwide. We identified admissions with PE as the primary or secondary diagnosis using International Classification of Diseases, tenth editions (ICD-10) codes and who had at least one ICD-10 code for cancer from October 1, 2015 to December 31, 2018 (ICD-10 codes used summarized in Supporting Information: Table 1). Patients with shock or vasopressor use were classified as high-risk PE and patients with cor pulmonale or type 2 myocardial infarction (MI) without shock or vasopressor use were classified as intermediate-risk PE. Patients less than 18 years of age or with unknown vital status were excluded (Figure 1). The study period was selected given the ICD-10 procedure codes for mechanical pulmonary thrombectomy were introduced starting October 1, 2015. CBT, including CDT and MT, were identified using ICD-10 procedure codes (Supporting Information: Table 1). Administration of systemic thrombolysis, mechanical ventilation, and transfusion of blood products were also identified using ICD-10 procedure codes. Cancer types were identified using ICD-10 (Supporting Information: Table 2). This study was deemed exempt by the NYU Grossman School of Medicine Institutional Review Board given that the data used is publicly available and deidentified.

Co-morbidities including thrombocytopenia, prior VTE, prior stroke, prior MI, coronary artery disease (CAD) were captured using ICD-10 codes and Elixhauser comorbidities included as variables in the NIS database.[18] The Charlson Comorbidity Index (CCI) was calculated for each patients.[19]

2.2 | Outcomes

Primary outcomes were in-hospital death or cardiac arrest (CA) and major bleeding. Major bleeding was a composite outcome of in-hospital gastrointestinal (GI), intracranial (IC) bleeding, other bleeding (retroperitoneal bleeding, hemoperitoneum, epistaxis, and hemoptysis), and procedure-related bleeding. Exploratory outcomes included components of primary outcomes and transfusion of blood products. To assess for residual confounding we tested the association between CBT and the outcome of acute kidney injury (AKI) used as a falsification endpoint. Outcomes were identified using ICD-10 codes (Supporting Information: Table 1).

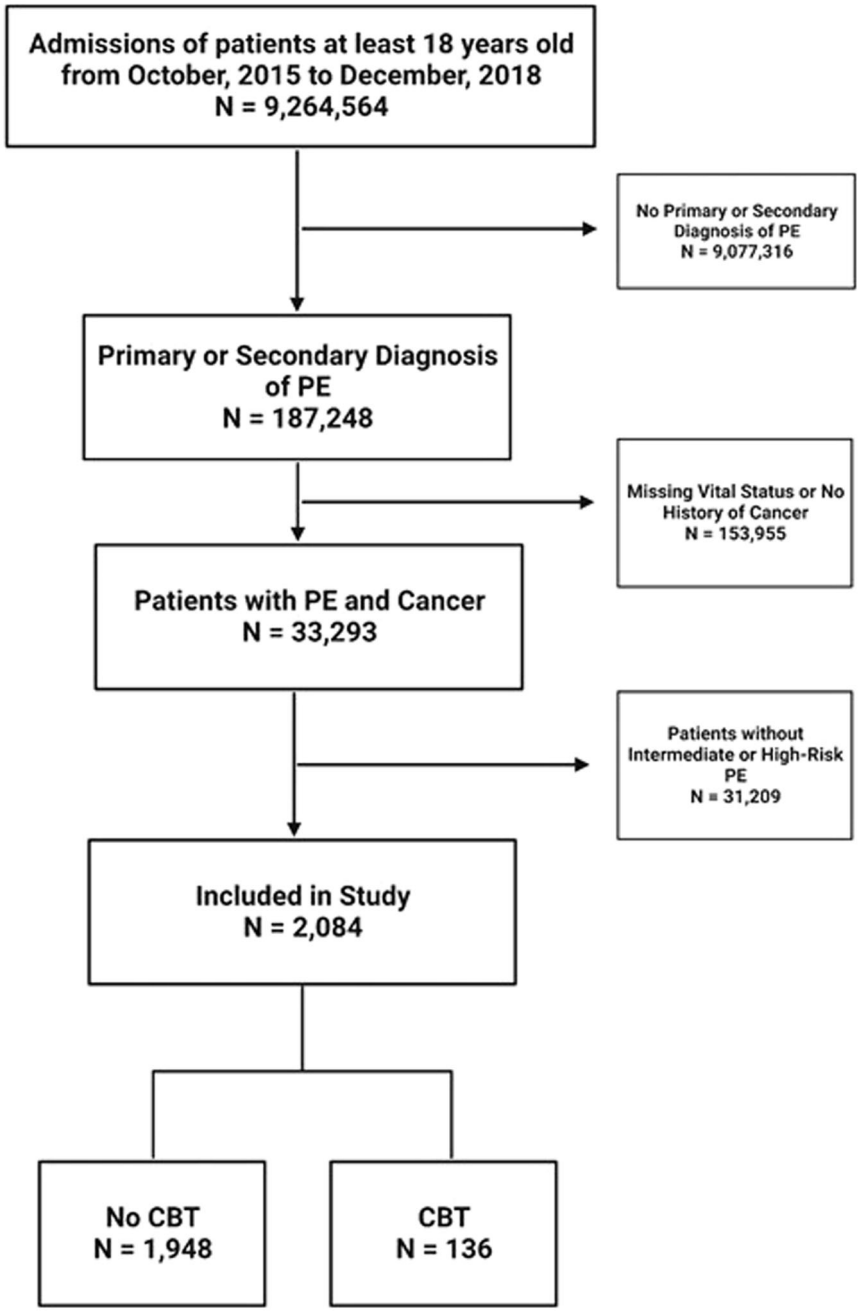

FIGURE 1 Study flowchart of patients included.

2.3 | Statistical analysis

Categorical variables were presented as frequency and percentages and comparisons between groups was performed using Fisher's exact or χ^2 tests, as appropriate. Continuous variables were presented as means and standard deviations and compared using the Wilcoxon-Rank sum test.

Primary analysis compared outcomes of CBT use versus no CBT use in patients with intermediate or high-risk PE. For secondary analyses, we compared outcomes between CBT use versus no CBT use separately in patients with intermediate-risk PE and in those with high-risk PE. We also compared outcomes between patients with intermediate or high-risk PE who underwent CBT compared with patients treated with systemic thrombolysis alone.

For all analyses, variables were compared between patients treated with CBT and without CBT, and standardized mean differences (SMD) were calculated. Imbalances between groups were considered significant if the SMD for a given co-variable was 0.10 or greater. We estimated propensity scores (PS) using a nonparsimonious multivariable logistic regression using age, sex, race, type of malignancy (solid or hematologic), metastatic cancer, if multiple cancers were present, hypertension, prior VTE, heart failure, diabetes, CAD, peripheral vascular disease (PVD), liver disease, thrombocytopenia, anemia, CCI, high-risk PE, concomitant DVT, respiratory failure, mechanical ventilation, large or medium hospital

size, and insurance type as co-variables. We utilized the PS to perform an inverse probability treatment weighting (IPTW) analysis.[20] Weights were created using the PS with 1/PS being assigned to patients treated with CBT and 1/(1-PS) for patients not treated with CBT. The relative odds of outcomes of patients treated with CBT compared with patients without CBT were estimated using IPTW logistic regression. Variables with residual imbalance (SMD ≥ 0.10) after IPTW were adjusted using an IPTW multivariable logistic regression. All tests were two-tailed and a p value of <0.05 was considered significant.

A sensitivity analysis was performed for the primary outcome which included do-not resuscitate (DNR) or palliative care, brain tumor, or metastasis as additional variables in logistic regression modeling to estimate PS in addition to the previously mentioned variables and analyzed in a similar manner to potentially account for residual confounding. Statistical analyses were performed using SPSS version 27.0 (IBM) and STATA version 15 (STATA).

3 | RESULTS

3.1 | Baseline characteristics and outcomes of cancer patients with intermediate or high-risk PE

A total of 2084 patients with intermediate or high-risk PE and cancer were included with 136 (6.5%) patients treated with CBT. Of patients treated with CBT, 94 (69.1%) were treated with CDT alone, 35 (25.7%) with MT alone and 7 (5.1%) with both. The mean age was 66.4 years, 1024 (49.1%) were female and 660 (31.7%) were non-White race. Solid malignancies were present in 1718 (82.4%), hematologic malignancies in 402 (19.3%), and metastatic disease in 799 (38.3%) of patients. There were 861 (41.3%) patients with high-risk PE. The overall mortality in both groups was 27.3%. Thrombocytopenia was present in 297 (14.2%), respiratory failure in 1178 (56.5%), and mechanical ventilation used in 363 (17.4%) of patients. Patients treated with CBT had lower rates of respiratory failure (46.3% vs. 57.2%, SMD = 0.220), mechanical ventilation (11.8% vs. 17.8%, SMD = 0.171), and lower CCI (mean 6.0 vs. 6.5, SMD = 0.194) compared with patients not treated with CBT. Patient characteristics are described in Table 1.

Before IPTW, patients treated with CBT had lower rates of death or CA (13.2% vs. 28.3%, $p < 0.001$) and no difference in major bleeding (22.8% vs. 19.2%, $p = 0.314$) compared with patients not treated with CBT. After IPTW, patients treated with CBT had lower rates of death or CA (16.9% vs. 27.9%, $p < 0.001$) and higher rates of major bleeding compared with patients without CBT (22.6% vs. 19.1%, $p = 0.006$) including postprocedure bleeding (16.8% vs. 11.9%, $p < 0.001$) and other bleeding (7.4% vs. 4.6%, $p < 0.001$). Patients treated with CBT also had lower rates of AKI (29.7% vs. 33.3%, $p = 0.014$) (Table 2).

After IPTW, hypertension (59.7% vs. 52.0%, SMD = 0.156), anemia (29.5% vs. 21.8%, SMD = 0.177), and vasopressor use (7.1% vs. 12.1%, SMD = 0.170) were not balanced between the CBT and non-CBT groups. After adjusting for unbalanced variables and IPTW, patients with CBT had lower odds of in-hospital death or CA compared with patients without CBT (adjusted OR 0.54, 95% CI 0.46–0.64) and higher odds of major bleeding (adjusted OR 1.41, 95% CI 1.21–1.65). Patients treated with CBT also had lower risk of in-hospital death (adjusted OR 0.49, 95% CI 0.41–0.59) and IC bleeding (adjusted OR 0.22 95% CI 0.09–0.53) but higher risk of postprocedure bleeding (adjusted OR 1.78, 95% CI 1.48–2.14), other bleeding (adjusted OR 1.86, 95% CI 1.42–2.44), and transfusion of blood products (adjusted OR 4.64, 95% CI 3.90–5.51) compared with patients without CBT. Treatment with CBT was not associated with AKI (adjusted OR 0.90, 95% CI 0.78–1.03) (Table 3).

Sensitivity analysis with the inclusion of DNR or palliative care, brain tumor, or metastasis variables showed similar associations of decreased odds of death or CA (adjusted OR 0.44, 95% CI 0.38–0.52) and increased odds of major bleeding (adjusted OR 1.23, 95% CI 1.05–1.43) among patients treated with CBT compared with those without CBT (Supporting Information: Table 5 and 6).

3.2 | Characteristics and outcomes of patients with intermediate-risk PE

A total of 1231 patients had intermediate-risk PE, of which 86 (7.0%) underwent CBT. Patient characteristics summarized in Supporting Information: Table 3. After IPTW, patients with CBT had lower rates of death or CA (3.9% vs. 9.0%, $p < 0.001$), in-hospital death (2.1% vs. 8.3%, $p < 0.001$), GI bleeding (2.7% vs. 4.4%, $p = 0.035$) but higher rates of major bleeding (21.9% vs. 11.3%, $p < 0.001$), postprocedure bleeding (16.3% vs. 5.1%, $p < 0.001$), other bleeding (9.0% vs. 3.2%, $p < 0.001$), and transfusion (22.2% vs. 5.4%, $p < 0.001$) (Supporting Information: Table 4). After IPTW multivariable logistic regression adjusted for unbalanced variables (age, hematologic malignancy, heart failure, DVT, mechanical ventilation, and insurance type), patients treated with CBT had lower odds of death or CA (adjusted OR 0.52, 95% CI 0.36–0.75), in-hospital death (adjusted OR 0.27, 95% CI 0.17–0.44), and GI bleeding (adjusted OR 0.57, 95% CI 0.36–0.92) but higher odds of major bleeding (adjusted OR 2.12, 95% CI 1.67–2.69), postprocedure bleeding (adjusted OR 3.67, 95% CI 2.65–5.06), other bleeding (adjusted OR 3.11, 95% CI 2.07–4.68), and transfusion (adjusted OR 6.43, 95% CI 4.72–8.74). Patients treated with CBT had similar odds of AKI compared with patients not treated with CBT (adjusted OR 0.98, 95% CI 0.80–1.20) (Table 4).

3.3 | Characteristics and outcomes of patients with high-risk PE

There were 861 patients with high-risk PE, of which 50 (5.8%) underwent CBT. Patient characteristics summarized in Supporting Information: Table 3. After IPTW, patients with CBT had lower rates of death or CA (36.6% vs. 55.0%, $p < 0.001$), in-hospital death (27.2% vs. 48.7%, $p < 0.001$), IC bleeding (0% vs. 1.9%, $p < 0.001$) but higher rates of GI bleeding (13.1% vs. 8.6%, $p = 0.004$), other bleeding (9.2% vs. 6.4%, $p = 0.037$), and transfusion (44.7% vs.

TABLE 1 Baseline unweighted and inverse probability treatment weighted characteristics of patients with intermediate or high-risk pulmonary embolism treat with and without CBT.

	Unweighted			Inverse-probability treatment weighted			
	All patients *N* = 2084	No CBT *N* = 1948	CBT *N* = 136	SMD	No CBT	CBT	SMD
Age, years (SD)	66.4 (12.7)	66.6 (12.7)	64.2 (12.4)	0.190	66.4 (12.7)	65.9 (12.4)	0.041
Female sex, *N* (%)	1024 (49.1)	955 (49.0)	69 (50.7)	0.034	49.1%	48.2%	0.018
Non-White race, *N* (%)	660 (31.7)	613 (31.5)	47 (34.6)	0.066	31.7%	33.1%	0.03
Solid malignancies, *N* (%)	1718 (82.4)	1617 (83.0)	101 (74.3)	0.215	17.6%	15.4%	0.059
Metastatic disease, *N* (%)	799 (38.3)	750 (38.5)	49 (36.0)	0.051	61.7%	63.8%	0.043
Hematologic malignancies, *N* (%)	402 (19.3)	366 (18.8)	36 (26.5)	0.184	19.3%	16.5%	0.073
Multiple cancers, *N* (%)	94 (4.5)	90 (4.6)	4 (2.9)	0.088	4.5%	3.4%	0.056
Co-morbidities, *N* (%)							
Hypertension	1083 (52.0)	1002 (51.4)	81 (59.6)	0.164	52.0%	59.7%	0.156
Prior VTE	213 (10.2)	199 (10.2)	14 (10.3)	0.003	10.2%	11.3%	0.036
Heart failure	402 (19.3)	377 (19.4)	25 (18.4)	0.025	19.3%	22.9%	0.088
Diabetes	465 (22.3)	428 (22.0)	37 (27.2)	0.122	22.3%	22.5%	0.005
CAD	348 (16.7)	337 (17.3)	11 (8.1)	0.279	16.7%	14.2%	0.069
Peripheral vascular disease	111 (5.3)	105 (5.4)	6 (4.4)	0.045	5.3%	5.3%	0
Chronic kidney disease	222 (10.6)	207 (10.6)	15 (11.0)	0.013	10.6%	10.3%	0.010
Liver disease	79 (3.8)	72 (3.7)	7 (5.1)	0.071	3.8%	3.1%	0.038
Anemia	454 (21.8)	419 (21.5)	35 (25.7)	0.100	21.8%	29.5%	0.177
Thrombocytopenia	297 (14.2)	269 (13.8)	28 (20.6)	0.180	14.3%	14.0%	0.009
Respiratory failure	1178 (56.5)	1115 (57.2)	63 (46.3)	0.220	56.5%	58.0%	0.030
Mechanical ventilation	363 (17.4)	347 (17.8)	16 (11.8)	0.171	17.4%	16.8%	0.016
Systemic thrombolysis	165 (7.9)	153 (7.9)	12 (8.8)	0.035	7.9%	9.4%	0.053
Vasopressor use	252 (12.1)	244 (12.5)	8 (5.9)	0.231	12.1%	7.1%	0.170
ECMO	10 (0.5)	8 (0.4)	2 (1.5)	0.110	0.5%	0.6%	0.014
Shock	696 (33.4)	649 (33.3)	47 (34.6)	0.026	33.4%	34.3%	0.019
Type 2 MI	205 (9.8)	197 (10.1)	8 (5.9)	0.156	9.8%	11.1%	0.043
Cor pulmonale	1183 (56.8)	1087 (55.8)	96 (70.6)	0.310	56.8%	58.3%	0.030
Charlson Comorbidity Index, mean (SD)	6.5 (2.5)	6.5 (2.5)	6.0 (2.4)	0.194	6.5 (2.5)	6.4 (2.3)	0.045
Large or medium hospital, *N* (%)	1789 (85.8)	1669 (85.7)	120 (88.2)	0.076	85.8%	85.0%	0.023
Urban teaching hospital, *N* (%)	1623 (77.9)	1513 (77.7)	110 (80.9)	0.079	77.9%	79.7%	0.044
Medicare or medicaid, *N* (%)	1387 (66.5)	1302 (66.8)	85 (62.5)	0.091	66.6%	66.0%	0.013
Private insurance, *N* (%)	604 (29.0)	561 (28.8)	43 (31.6)	0.061	29.0%	30.7%	0.037

Abbreviations: CAD, coronary artery disease; CBT, catheter-based therapy; IPTW, inverse probability treatment weighting; MI, myocardial infarction; PE, pulmonary embolism; SD, standard deviation; SMD, standard mean difference; VTE, venous thromboembolism.

17.4%, $p < 0.001$) (Supporting Information: Table 4). After IPTW multivariable logistic regression adjusting for unbalanced variables (non-White race, solid malignancy, anemia, shock, CCI, and insurance), patients treated with CBT had lower odds of death or CA (adjusted OR 0.48, 95% CI 0.33–0.53) and in-hospital death (adjusted OR 0.42, 95% CI 0.33–0.53). There was no difference in odds of major bleeding (adjusted OR 0.84, 95% CI 0.66–1.07) but higher rates of GI bleeding (adjusted OR 1.68, 95% CI 1.17–2.43) and transfusion (adjusted OR 4.02, 95% CI 3.12–5.17). Patients treated with CBT had similar odds of AKI compared with patients not treated with CBT (adjusted OR 0.86, 95% CI 0.69–1.07) (Table 4).

TABLE 2 Outcomes of unweighted and IPTW patients with intermediate or high-risk PE.

		Unweighted			Inverse-probability treatment weighted		
	All patients *N* = 2084	No CBT *N* = 1948	CBT *N* = 136	*p* Value	No CBT	CBT	*p* Value
Primary outcomes							
Death or cardiac arrest	570 (27.3)	552 (28.3)	18 (13.2)	<0.001	27.9%	16.9%	<0.001
Major bleeding	406 (19.5)	375 (19.2)	31 (22.8)	0.314	19.1%	22.6%	0.006
Secondary outcomes							
Death	507 (24.3)	494 (25.4)	13 (9.6)	<0.001	25.0%	13.6%	<0.001
Cardiac arrest	183 (8.8)	175 (9.0)	8 (5.9)	0.272	8.8%	9.8%	0.306
GI bleeding	127 (6.1)	120 (6.2)	7 (5.1)	0.852	6.1%	5.6%	0.506
Intracranial bleeding	29 (1.4)	28 (1.4)	1 (0.7)	1.00	1.4%	0.3%	<0.001
Postprocedure bleeding	254 (12.2)	233 (12.0)	21 (15.4)	0.224	11.9%	16.8%	<0.001
Other bleeding[a]	100 (4.8)	89 (4.6)	11 (8.1)	0.092	4.6%	7.4%	<0.001
Transfusion	249 (11.9)	205 (10.5)	44 (32.3)	<0.001	10.5%	34.5%	<0.001
Acute kidney injury	691 (33.2)	649 (33.3)	42 (30.9)	0.64	33.3%	29.7%	0.014

Abbreviations: CBT, catheter-based therapy; GI, gastrointestinal; IPTW, inverse probability treatment weighting; PE, pulmonary embolism.

[a]Includes retroperitoneal bleeding, hemoperitoneum, and epistaxis.

TABLE 3 Logistic regression modeling of outcomes of patients with intermediate or high-risk PE treated with CBT compared with patients without CBT.

	Unweighted OR (95% CI)	IPTW OR (95% CI)	Adjusted IPTW OR (95% CI)[a]
Primary outcomes			
Death or cardiac arrest	0.39 (0.23–0.64)	0.52 (0.45–0.61)	0.54 (0.46–0.64)
Major bleeding	1.24 (0.82–1.88)	1.23 (1.06–1.44)	1.41 (1.21–1.65)
Secondary outcomes			
Death	0.31 (0.17–0.56)	0.47 (0.40–0.56)	0.49 (0.41–0.59)
Cardiac arrest	0.63 (0.30–1.32)	1.12 (0.91–1.39)	1.07 (0.85–1.34)
GI bleeding	0.83 (0.38–1.81)	0.91 (0.70–1.18)	0.95 (0.73–1.24)
Intracranial bleeding	0.51 (0.07–3.76)	0.22 (0.09–0.51)	0.22 (0.09–0.53)
Postprocedure bleeding	1.34 (0.83–2.18)	1.50 (1.26–1.79)	1.78 (1.48–2.14)
Other bleeding	1.84 (0.96–3.53)	1.68 (1.29–2.18)	1.86 (1.42–2.44)
Transfusion	4.07 (2.76–5.99)	4.50 (3.81–5.32)	4.67 (3.93–5.55)
Acute kidney injury	0.89 (0.61–1.30)	0.85 (0.74–0.97)	0.90 (0.78–1.03)

Abbreviations: CBT, catheter-based therapy; CI, confidence interval; GI, gastrointestinal; IPTW, inverse probability treatment weighting; OR, odds ratio; PE, pulmonary embolism.

[a]Adjusted for vasopressor use and anemia.

3.4 | Characteristics and outcomes of patients treated with CBT alone compared with systemic thrombolysis alone

A total of 289 patients with PE underwent either CBT alone (*N* = 124) or systemic thrombolysis alone (*N* = 165). Patient characteristics summarized in Supporting Information: Table 7. Patients treated with CBT alone had lower rates of high-risk PE (36.3% vs. 62.4%, SMD = 0.541), mechanical ventilation (10.5% vs. 36.4%, SMD = 0.642), and respiratory failure (44.4% vs. 73.3%, SMD = 0.616) compared with patients treated with systemic thrombolysis alone. After adjusting for unbalanced variables IPTW logistic regression (solid malignancy, metastatic malignancy, hypertension, CCI, large or medium hospital), patients treated with CBT alone had lower odds of

TABLE 4 Logistic regression modeling of outcomes of patients treated with CBT compared with without CBT among patients with PE stratified by risk category.

	Unweighted OR (95% CI)	IPTW OR (95% CI)	Adjusted IPTW OR (95% CI)[a,b]
Intermediate-risk PE			
Primary outcomes			
Death or cardiac arrest	0.48 (0.17–1.33)	0.41 (0.28–0.58)	0.52 (0.36–0.75)
Major bleeding	1.77 (1.00–3.14)	2.19 (1.75–2.74)	2.12 (1.67–2.69)
Secondary outcomes			
Death	0.26 (0.06–1.06)	0.24 (0.15–0.37)	0.27 (0.17–0.44)
Cardiac arrest	1.02 (0.24–4.39)	0.82 (0.46–1.46)	1.47 (0.75–2.88)
GI bleeding	0.51 (0.12–2.13)	0.62 (0.39–0.96)	0.57 (0.36–0.92)
Intracranial bleeding	1.02 (0.13–7.92)	0.51 (0.20–1.31)	0.48 (0.19–1.26)
Postprocedure bleeding	2.15 (1.03–4.50)	3.65 (2.71–4.92)	3.67 (2.65–5.06)
Other bleeding	3.07 (1.38–6.82)	2.95 (2.03–4.29)	3.11 (2.07–4.68)
Transfusion	5.64 (3.24–9.83)	5.01 (3.77–6.65)	6.43 (4.72–8.74)
Acute kidney injury	0.99 (0.58–1.68)	0.91 (0.76–1.12)	0.98 (0.80–1.20)
High-risk PE			
Primary outcomes			
Death or cardiac arrest	0.31 (0.17–0.59)	0.47 (0.39–0.58)	0.48 (0.39–0.60)
Major bleeding	1.00 (0.53–1.86)	0.84 (0.67–1.04)	0.84 (0.66–1.07)
Secondary outcomes			
Death	0.29 (0.15–0.58)	0.39 (0.32–0.49)	0.42 (0.33–0.53)
Cardiac arrest	0.60 (0.25–1.44)	1.04 (0.81–1.34)	0.93 (0.70–1.24)
GI bleeding	1.19 (0.46–3.11)	1.62 (1.18–2.24)	1.68 (1.17–2.43)
Intracranial bleeding	N/A	N/A	N/A
Postprocedure bleeding	1.16 (0.59–2.26)	1.08 (0.85–1.37)	1.08 (0.83–1.41)
Other bleeding	0.93 (0.28–3.09)	1.48 (1.02–2.15)	1.30 (0.85–2.01)
Acute kidney injury	0.89 (0.50–1.57)	0.82 (0.67–1.00)	0.86 (0.69–1.07)

Note: Abbreviations defined in prior tables. Odds ratio not calculated for intracranial bleeding or stroke for high-risk PE patients given 0 events in CBT group.

[a]Intermediate-risk PE analysis adjusted for age, hematologic malignancy, heart failure, CAD, mechanical ventilation, DVT, and insurance.

[b]High-risk PE analysis adjusted for non-White race, malignancy type, metastatic cancer, multiple cancer, heart failure, PVD, anemia, shock, Charlson comorbidity index, private insurance.

in-hospital death or CA (adjusted OR 0.49, 95% CI 0.33–0.74) compared with patients treated with systemic thrombolysis alone. However, there was no difference in odds of major bleeding (adjusted OR 1.12, 95% CI 0.74–1.68), GI or IC bleeding (adjusted OR 0.47, 95% CI 0.18–1.27), and postprocedural or other bleeding (adjusted OR 1.03, 95% CI 0.56–1.89). Patients treated with CBT alone also had lower odds of in-hospital CA (adjusted OR 0.47, 95% CI 0.28–0.81) but no difference in in-hospital death (adjusted OR 0.65, 95% CI 0.41–1.01). Patients with CBT alone were also associated with increased risk of transfusion of blood products (adjusted OR 3.10, 95% CI 2.09–4.59) compared with patients treated with systemic thrombolysis alone after IPTW. There was no difference in odds AKI between patients treated with and without CBT (adjusted OR 0.76, 95% CI 0.55–1.07) (Table 5).

4 | DISCUSSION

PE is a common complication of patients with cancer and is associated with significant morbidity and mortality. In our study of patients with cancer hospitalized with intermediate or high-risk PE, approximately 27.3% of patients had in-hospital death or CA and

TABLE 5 Logistic regression modeling of outcomes of patients with intermediate or high-risk treated with CBT compared with systemic thrombolysis.

	Unweighted OR (95% CI)	IPTW OR (95% CI)	Adjusted IPTW OR (95% CI)
Primary outcomes			
Death or cardiac arrest	0.18 (0.10–0.34)	0.53 (0.35–0.78)	0.49 (0.33–0.74)
Bleeding composite	0.78 (0.45–1.36)	1.10 (0.74–1.63)	1.12 (0.74–1.68)
Secondary outcomes			
Death	0.27 (0.14–0.53)	0.67 (0.43–1.04)	0.65 (0.41–1.01)
Cardiac arrest	0.14 (0.05–0.37)	0.47 (0.28–0.80)	0.47 (0.28–0.81)
GI or intracranial bleeding	0.51 (0.19–1.35)	0.78 (0.42–1.46)	0.47 (0.18–1.27)
Postprocedural or other bleeding	0.95 (0.52–1.72)	1.36 (0.89–2.09)	1.03 (0.56–1.89)
Transfusion	2.24 (1.29–3.91)	3.16 (2.14–4.65)	3.10 (2.09–4.59)
Acute kidney injury	0.73 (0.45–1.19)	0.69 (0.49–0.95)	0.76 (0.55–1.07)

Note: Adjusted for CCI, cancer type, metastatic disease, hypertension, large or medium hospital size.

Abbreviations: CBT, catheter-based therapy; CI, confidence interval; GI, gastrointestinal; IPTW, inverse probability treatment weighting; OR, odds ratio.

19.5% had a major bleeding event. Our results suggest that CBT was associated with decreased risk of in-hospital death or CA though at the expense of increased risk of major bleeding. Additionally, among patients with intermediate or high-risk PE treated with either CBT alone or systemic thrombolysis alone, treatment with CBT alone was associated with lower risk of in-hospital death or CA but no difference in major bleeding.

Currently, the American College of Chest Physicians (CHEST) and European Society of Cardiology (ECS) guidelines recommend CBT for patients with high-risk PE at high bleeding risk or have contraindications or failed systemic thrombolysis.[21,22] While large, randomized trials are lacking, small single-armed trials suggest hemodynamic improvement after CDT (including RV/LV ratio and mean pulmonary artery pressure) and retrospective studies have suggested possible benefit of CBT in PE.[11–15] In one study of 41,903 patients hospitalized with PE in Germany, CDT was associated with decreased in-hospital mortality in patients with PE and shock or RV dysfunction compared with systemic thrombolysis or no thrombolysis.[23] Our current study also suggests an association between CBT and lower in-hospital mortality in patients with intermediate or high-risk PE and cancer, though these results need to be confirmed in prospective clinical studies.

Though CBT may offer the advantage of lower bleeding given lack of systemic administration of thrombolytics with CDT or no thrombolytics with the use of MT, randomized trials are lacking. This is particularly important in patients with cancer who are at increased risk of bleeding complications. While our study suggested an association of CBT with lower in-hospital death or CA this was at the expense of major bleeding especially postprocedural and other bleeding (including retroperitoneal bleeding and hemoperitoneum) compared with patients without CBT. This increased risk of major bleeding in CBT group was more apparent among patients with intermediate-risk PE while among patients treated with CBT in high-risk PE group there was no significant difference in major bleeding. The increased risk of bleeding in the intermediate-risk PE is likely due: (1) comparison of CDT (with local deliver of thrombolytics) with that of anticoagulation alone; (2) procedural risk associated with big bore cannulas such as those used during MT. The lack of excess bleeding with CBT in high-risk PE is likely due to comparison of CDT with that of systemic thrombolytics. It is no surprise that there was an association with decreased IC bleeding in this cohort of patients. Observational studies have suggested decreased bleeding (particularly IC and GI) with CBT compared with systemic thrombolysis.[24] Further prospective trials are needed to confirm our findings and clarify the risk of bleeding among patients undergoing CBT compared with either anticoagulation alone or systemic thrombolysis, especially in patients with cancer. Our results in the CBT group was driven largely by CDT. Given the MT is a lytic free option, further studies, especially in patients with PE and cancer are needed to evaluate whether MT will be not only associated lower death but also no excess bleeding.

Among patients hospitalized with PE, patients with cancer have higher risk of bleeding and in-hospital mortality compared with patients without cancer.[25,26] Additionally, patients with cancer are less likely to be treated with invasive interventions for thrombosis, including PE, compared with patients without cancer.[25] For instance, while PCI in the setting of AMI is beneficial to patients with and without malignancy alike, those with cancer are less likely to receive this therapy.[16,17] Among patients with PE, those with cancer are less likely to receive thrombolytics despite similar rates of in-hospital mortality.[9] Our study suggests there may be a potential utility of CBT in patients with cancer and intermediate or high-risk PE and this

merits further investigation in this patient population who are often excluded from clinical trials.

There are several limitations to consider when interpreting our results. Limitations of our study arise from the retrospective nature and the limitations of the NIS database itself. The data in the NIS is abstracted from administrative ICD-10 codes and therefore there is a limit to the granularity of the data obtained and may be a source of unmeasured confounding. Our study included a sensitivity and falsification endpoint analyses to account for residual confounding. Despite similar results in our sensitivity analysis and our main analysis and no association between CBT and AKI, it is possible that residual unmeasured confounding exists and our results should be considered hypothesis-generating. Additionally, our classification of intermediate and high-risk PE is based on ICD-10 codes, including for the diagnosis of shock. Given that the NIS does not distinguish temporal relationship of diagnoses, it is possible that patients with PE had shock or required vasopressors due to other etiologies. This lack of temporal relationship of diagnoses also raises the possibility that bleeding events may have occurred before CBT and affected the decision for CBT. Additionally, we identified patients with cancer with ICD-10 codes but lack important variables including prior or active cancer treatment, laboratory values, tumor characteristics, and genetics which may influence both the probability of undergoing CBT and outcomes. The NIS also does not record medications and therefore systemic anticoagulation strategies are unknown in this study. Another limitation is that outcomes, particularly nondeath outcomes (including CA), are encoded via ICD-10 codes thus the temporality of treatment effect of CBT cannot be distinguished and only associations can be reported. The NIS does not distinguish if outcomes and diagnoses occurred during or before hospital admissions. Additionally, we were limited to only investigating in-hospital outcomes and therefore longer-term outcomes remain unanswered in this patient population.

Patients with cancer may have several reasons for not being treated with anticoagulation, systemic lysis or CBT which are not captured in an administrative database. As such, the current analysis cannot rule out unmeasured confounding despite statistical adjustments. However, our results are hypothesis generating suggesting a potential utility of CBT in this high-risk cohort. Our study highlights the importance of studying this high-risk patient population in future clinical trials.

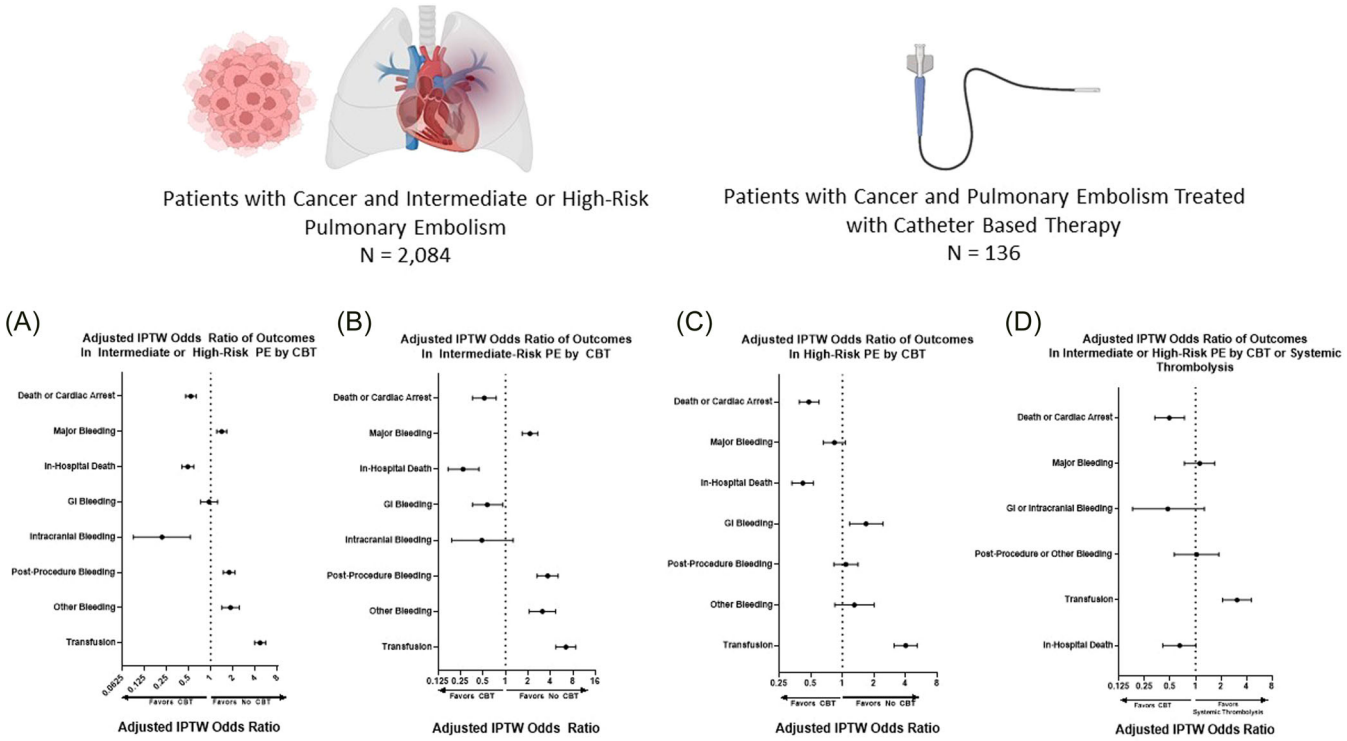

FIGURE 2 Outcomes of patient with cancer and PE by catheter-based therapy treatment. A total of 2084 patients with cancer were admitted with intermediate or high-risk PE, with 136 undergoing CBT. Among patients with either intermediate or high-risk PE, treatment with CBT was associated with lower risk of death or cardiac arrest, in-hospital death, and intracranial bleeding but were at higher risk of major bleeding, postprocedure bleeding, other bleeding, and transfusion (A). Among patients with intermediate-risk PE, CBT was associated with decreased risk of death or cardiac arrest, in-hospital death, and gastrointestinal bleeding but was associated with increased risk of major bleeding, postprocedural bleeding, other bleeding, and transfusion (B). In patients with high-risk PE, CBT was associated with decreased risk of death or cardiac arrest and in-hospital death but increased risk of gastrointestinal bleeding and transfusion (C). Among patients treated with either CBT alone or systemic thrombolysis alone, treatment with CBT was associated with lower risk of death or cardiac arrest but higher risk of transfusion (D). CBT, catheter-based therapy; PE, pulmonary embolism. [Color figure can be viewed at wileyonlinelibrary.com]

5 | CONCLUSIONS

Patients with cancer are at elevated risk of PE, which is of substantial prognostic significance. The advent of CBT for PE provide an additional tool for clinicians treating patients with intermediate or high-risk PE. Our study suggests that in a high-risk population, those with cancer and intermediate or high-risk PE, CBT may be associated with a reduced risk of in-hospital death or CA at the expense of increased risk of major bleeding (Figure 2). Further prospective studies are needed to evaluate the utility of CBT in patients with PE and cancer and to confirm our results.

CONFLICT OF INTEREST STATEMENT

Dr. Eric H. Yang reports nonrelevant consulting fees from Pfizer and Edwards Lifesciences, nonrelevant research grants from CSL Behring, Boehringer Ingelheim and Eli and Lilly. Dr. Sripal Bangalore ad hoc consulting and speaking for Abbott Vascular, Biotronik, Boston Scientific, Amgen, Pfizer, Merck, and Inari. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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