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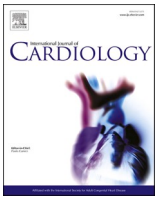

Baseline characteristics, management patterns and outcome in patients with pulmonary embolism and malignancy: Insights from a single-centre study

Aykun Hakgor [a,*], Barkın Kultursay [b], Berhan Keskin [c], Ahmet Sekban [b], Hacer Ceren Tokgoz [b], Seda Tanyeri [c], Ali Karagoz [b], Cihangir Kaymaz [b]

[a] Istanbul Medipol University, Medipol Mega University Hospital, Dept. of Cardiology, Istanbul, Turkey
[b] University of Health Sciences Kosuyolu Training and Research Hospital Dept. of Cardiology, Istanbul, Turkey
[c] Kocaeli City Hospital, Dept. of Cardiology, Kocaeli, Turkey

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ABSTRACT

Background and aim: Acute pulmonary embolism (PE) is one of the main causes of death in patients with active cancer. In this study, we evaluated the impact of malignancy on the treatment choices, and short- and long-term clinical outcomes in patients with acute PE.
Methods: In this study, 872 acute PE patients (age 61.6 ± 16.8 years, female 57.5 %) from different risk and treatment categories were retrospectively analyzed and divided into two groups according to the presence of active malignancy.
Results: Active malignancy was documented in 129 (14.8 %) out of the 872 patients. Ultrasound-assisted-thrombolysis (USAT), rheolytic-thrombectomy (RT), systemic-thrombolysis (ST) and anticoagulation-alone therapies were noted in 27.3 %, 6.4 %, 16.6 % and 49.7 % of overall PE patients. RT and anticoagulation therapies were more frequent in patients with malignancy whereas ST and USAT were more frequently used in the other group. Regardless of the presence of malignancy and the treatment modality chosen, significant improvements were achieved in all treatment targets ($p < 0.001$ for all). Bleeding rates were similar in both groups, while in-hospital and long-term mortality was higher in the malignancy cohort. Active malignancy was found to be an independent predictor for composite of 60-day mortality and PE-related rehospitalization (adjusted OR: 2.43; 95 % CI: 1.32–4.47, $p = 0.04$) and long-term mortality (adjusted HR: 2.25, 95 % CI: 1.29–3.91, $p = 0.004$).
Conclusion: Concomitant malignancy adversely affects both short- and long-term outcomes in patients with acute PE. Although these patients are more vulnerable, it is possible to achieve satisfactory treatment success with acceptable bleeding rates with the inclusion of catheter-based methods as treatment option.

1. Introduction

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most frequent acute cardiovascular syndrome worldwide, further, it is one of the leading causes of morbidity and mortality in patients diagnosed with cancer [1,2]. There is a seven-fold increased risk of VTE in patients with cancer, moreover, among hospitalized patients with cancer, one out of every seven deaths is associated with acute PE [3]. Patients with both cancer and PE present unique challenges in terms of diagnosis, risk assessment, treatment decisions, and the long-term prognosis of PE may be influenced by this specific provoking factor. In a large cohort of incident PE cases, 19.9 % of patients had cancer associated thrombosis (CAT) and survival rates in cancer patients were significantly lower compared to patients with unprovoked PE [4]. In addition to mortality, VTE in this particular patient group is linked with various conditions that significantly impact patients' quality of life, including recurrent VTE, increased risk of bleeding and pulmonary hypertension. Our objective was to evaluate the impact of cancer on PE related in-hospital and long-term mortality, rehospitalization and treatment efficiency.

* Corresponding author at: Istanbul Medipol University, Medipol Mega University Hospital, Dept. of Cardiology, TEM Avrupa Otoyolu Göztepe Çıkışı No:1, 34214, Bağcılar, Istanbul, Turkey.
E-mail addresses: aykunhakgor@gmail.com, aykun.hakgor@medipol.edu.tr (A. Hakgor).

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2. Methods

2.1. Design

This single-center study comprised retrospectively evaluated 872 patients (mean age of 61.6 years ±16.8, 57.5 % female) referred to our tertiary cardiovascular center with confirmed acute PE from August 2012 to November 2023. The systematic work-up for an initial diagnosis of acute PE, and risk stratification including multidetector contrast-enhanced computed tomographic pulmonary angiography (CTPA), transthoracic echocardiography (TTE) assessments, PE severity indexes, and biomarker evaluation have been based on the criteria recommended by the European Society of Cardiology (ESC) / European Respiratory Society (ERS) Guidelines for the diagnosis and management of acute PE [5]. The presence of active cancer is defined as clinical signs and symptoms confirmed with imaging and pathology, or any cancer treatment in the past 6 months (other than non-melanoma skin cancer). Survival status was obtained from the national health database records system, clinic visits and telephone visits. The main clinical endpoints of the study were in-hospital PE-related mortality, composite of 60-day all-cause mortality and PE-related rehospitalization and long-term all-cause mortality. PE-related readmission was defined as a hospital admission occurring within 14 days after discharge and associated with the exacerbation of PE symptoms (such as dyspnea or hemodynamic deterioration), as determined by the physician's discretion. A 14-day monitoring duration was selected, guided by the prior evidence that deaths within this timeframe were associated with PE, while deaths occurring beyond the 14 days were primarily attributed to the ongoing cancer [6]. Patients admitted to the hospital because of the cardiopulmonary arrest before recording their initial data were excluded from the study. Major bleeding was characterized as evident bleeding accompanied by a decrease in the hemoglobin level of at least 2 g/dL, transfusion of 2 units of packed red blood cells, or involvement of a critical site. Bleeding not fulfilling the major bleeding criteria was defined as minor bleeding [7]. Local Ethics Committee approval was obtained for the study and the study complied with the Declaration of Helsinki.

2.2. Chest CT pulmonary angiography

CT images were acquired by using 64-slice helical CT angiography (Toshiba Aquilion 64™, Toshiba Medical Systems Corp., Tokyo, Japan). A validated CTPA score for pulmonary arterial occlusion proposed by Qanadli et al. [8] [Qanadli Score (QS)], right to left ventricle and atrial diameter ratio, main, left, and right pulmonary arterial diameters were measured from CTPA images.

2.3. Echocardiography

Echocardiography was performed to all patients on the first day of admission using a Vivid-7 echocardiography device (GE Vingmed Ultrasound AS, Horten, Norway). Patients were excluded if image quality is too poor. Tricuspid annular plane systolic excursion (TAPSE) measured on M-mode and tricuspid lateral annulus systolic tissue velocity (St) were utilized as indicators of right ventricular (RV) systolic function The maximal tricuspid regurgitation velocity by continuous-wave Doppler was used in conjunction with estimated right atrial pressure measured using inferior vena cava diameter to estimate systolic pulmonary artery pressure (sPAP).

2.4. Treatment strategies

Following the current consensus statements and ESC / ERS PE Guidelines [5,9], patients in high risk (HR) and intermediate-high risk (IHR) categories exhibiting clinical and hemodynamic deterioration received treatment with either systemic thrombolysis (ST) or ultrasound-assisted thrombolysis (USAT), with varying doses and durations of alteplase, a recombinant tissue-type plasminogen activator (t-PA). Patients classified as HR or IHR and having absolute or relative contraindications for ST or those with inadequate response to USAT or ST, underwent treatment with rheolytic thrombectomy (RT). The predominant modality for catheter-directed thrombolysis (CDT) was USAT using EKOS (EkoSonic® Endovascular System, EKOS Corporation; Bothell, WA, USA) and RT with Angiojet (AngioJet™ Peripheral Thrombectomy System-Boston Scientific, USA) system. The dose and duration of catheter-directed or systemic thrombolytic administration were decided individually for each patient, taking into consideration the patients' acute PE risk category, individual clinical characteristics and bleeding tendency. The low risk (LR) and intermediate-low risk (ILR) PE groups primarily treated with anticoagulation alone, as intravenous heparin or subcutaneous low molecular weight heparin (LMWH). For long-term anticoagulation after discharge, LMWH, vitamin-K antagonists or novel oral anticoagulants (NOACs) were preferred on the basis of individual patient characteristics.

2.5. Statistical analysis

Normally distributed continuous research data and data without normal distribution were expressed as mean ± standard deviation and median (25–75 quartile) values respectively, whereas categorical data were expressed as absolute and percentage values. Independent samples *t*-test and Mann–Whitney *U* test were used for the comparisons of independent continuous data groups, and Pearson's chi-squared or Fisher's exact test was used for the comparisons of categorical data groups. Paired sample *t*-test was conducted for the analysis of dependent continuous variables. Predictors of 60-day mortality and PE-related rehospitalization in both the overall patient population and the malignancy subgroup were investigated with binary logistic regression analysis. First, an univariate analysis of clinically significant variables was performed and a multivariate analysis was established with the variables that reached statistical significance ($p < 0.05$). The determinants of long-term mortality were analyzed with similar steps however using Cox-regression method. Long-term survival curves according to the presence of malignancy were obtained with the Kaplan-Meier method. We performed statistical analyses using IBM SPSS Statistics, version 26 (IBM Corporation, NY, USA). A two-sided *p*-value <0.05 was considered statistically significant.

3. Results

3.1. Evaluation of study population

In this study, we evaluated a cohort of 872 patients, 501 (57.5 %) of whom were female, diagnosed with acute PE, mainly from the IHR and HR groups. The comparison of the patients included in the study in terms of various characteristics according to the presence of malignancy is given in Table 1. There was no difference in baseline demographic characteristics except that patients with malignancy were older and more frequently diabetic, whereas those without malignancy had a higher frequency of previous stroke history. In the study population, 129 (14.8 %) patients had concomitant malignancy and the largest proportion of cancer subtypes in these patients were gastrointestinal system (GIS) and lung cancers (Table 2). Upon initial evaluation, the subgroup with malignancy demonstrated compromised vital signs, including lower systolic blood pressure, increased heart rate, and decreased oxygen saturation, alongside higher clinical scores indicative of PE severity (e.g., shock index, Pulmonary Embolism Severity Index [PESI], and simplified PESI [sPESI]). When stratified into risk categories according to the current PE guidelines, it was observed that patients with malignancy were more frequently in the HR category (Fig. 1). Moreover, this group exhibited a significantly higher frequency of contraindications to thrombolytic therapy, a critical consideration in tailoring treatment approaches. When initial TTE and CTPA measurements were compared,

Table 1
General baseline features, treatment strategies and clinical outcomes of the population in terms of malignancy.

	Malignancy (+) (n = 129, 14.8 %)	Malignancy (−) (n = 743, 85.2 %)	Overall group (n = 872)	p value
Clinical characteristics and initial vital signs				
Age (years)	65.4 ± 13.6	60.9 ± 17.2	61.6 ± 16.8	0.018
Female gender	78 (60.5 %)	423 (56.9 %)	501 (57.5 %)	0.454
Symptom duration (days)	3 (1–7)	3 (2–7)	3 (2–7)	0.406
Presence of syncope	41 (31.8 %)	190 (25.6 %)	231 (26.5 %)	0.140
Hypertension	45 (34.9 %)	283 (38.1 %)	328 (37.6 %)	0.488
Coronary artery disease	17 (13.2 %)	88 (11.8 %)	105 (12 %)	0.667
Dyslipidemia	5 (3.9 %)	62 (8.3 %)	67 (7.7 %)	0.079
Diabetes mellitus	29 (22.5 %)	114 (15.3 %)	143 (16.4 %)	0.043
Heart failure	4 (3.1 %)	20 (2.7 %)	24 (2.8 %)	0.793
Current smoker	15 (11.6 %)	91 (12.4 %)	107 (12.3 %)	0.810
COPD	12 (9.3 %)	51 (6.9 %)	63 (7.2 %)	0.323
Permanent or temporary immobility	17 (13.2 %)	149 (20.1 %)	166 (19 %)	0.066
Previous stroke	2 (1.6 %)	56 (7.5 %)	58 (6.7 %)	0.012
OC/HRT usage	0 (0 %)	20 (2.7 %)	20 (2.3 %)	0.059
Atrial fibrillation	8 (6.2 %)	49 (6.6 %)	57 (6.5 %)	0.867
Recent prolonged travel	1 (0.8 %)	52 (7 %)	53 (6.1 %)	0.006
Acute DVT	62 (48.1 %)	384 (51.7 %)	446 (51.1 %)	0.448
Previous VTE	9 (7 %)	72 (9.7 %)	81 (9.3 %)	0.327
Recent major surgery	39 (30.2 %)	192 (25.8 %)	231 (26.5 %)	0.297
Recent bone fracture	3 (2.3 %)	45 (6.1 %)	48 (5.5 %)	0.086
Hereditary trombophilia	0 (0 %)	7 (0.9 %)	7 (0.8 %)	0.268
Systolic BP (mmHg)	115 ± 23.7	124.4 ± 24.3	123.1 ± 24.4	<0.001
Diastolic BP (mmHg)	72.2 ± 16.1	76.1 ± 17.7	75.4 ± 17.5	0.046
Heart rate (bpm)	112.3 ± 19.3	105.6 ± 20.2	106.6 ± 20.2	<0.001
Pulse O_2 saturation (%)	88.2 ± 5.8	89.5 ± 6.3	89.3 ± 6.3	0.002
Shock index	1.1 ± 0.35	0.9 ± 0.37	0.9 ± 0.37	<0.001
PESI score	133.5 ± 33.5	95.4 ± 34.7	101 ± 37.1	<0.001
sPESI	2 (2–3)	1 (0–2)	1 (1–2)	<0.001
Acute PE risk status	LR: 4 (3.1 %) ILR: 23 (17.8 %) IHR: 78 (60.5 %) HR: 24 (18.6 %)	LR: 116 (15.6 %) ILR: 124 (16.7 %) IHR: 446 (60 %) HR: 57 (7.7 %)	LR: 120 (13.8 %) ILR: 147 (16.9 %) IHR: 524 (60.1 %) HR: 81 (9.3 %)	<0.001
Contraindication for thrombolysis	29 (22.5 %)	81 (10.9 %)	110 (12.6 %)	<0.001
Echocardiographyc, CTPA and laboratory measures				
sPAP (mmHg)	51.4 ± 14	50.3 ± 14.3	50.5 ± 14.3	0.346
TAPSE (mm)	17.5 ± 4.3	18.9 ± 4.4	18.7 ± 4.4	0.002
St (cm/s)	10.8 ± 3.1	11.7 ± 2.9	11.6 ± 3	0.028
Qanadli Score	20.4 ± 7.2	20.2 ± 7.4	20.3 ± 7.3	0.842
RV/LVd ratio	1.19 ± 0.25	1.16 ± 0.24	1.16 ± 0.24	0.294
RA/LAd ratio	1.25 ± 0.29	1.25 ± 0.28	1.25 ± 0.28	0.771
MPA diameter (mm)	29.7 ± 3.6	22.9 ± 4.2	29.9 ± 4.1	0.991
LPA diameter (mm)	22.4 ± 3.1	22.5 ± 3.1	22.5 ± 3.1	0.759
RPA diameter (mm)	23.6 ± 3.4	23.2 ± 3.4	23.3 ± 3.4	0.329
D-dimer (U/mL)	8.2 (3.7–15.7)	7 (3.6–13.7)	7.1 (3.6–14.1)	0.295
Hs- Troponine I (ng/mL)	0.1 (0.03–0.27)	0.07 (0.02–0.2)	0.07 (0.03–0.21)	0.049
Hs- CRP (mg/L)	6.8 (2.5–15.5)	4.5 (1.9–11.6)	4.8 (2.1–12.3)	0.057
Treatment Strategy				
USAT	25 (19.4 %)	213 (28.7 %)	238 (27.3 %)	0.029
ST	12 (9.3 %)	133 (17.9 %)	145 (16.6 %)	0.015
RT	14 (10.9 %)	42 (5.7 %)	56 (6.4 %)	0.026
Anticoagulation alone	78 (60.5 %)	355 (47.8 %)	433 (49.7 %)	0.008
Mean t-PA dose in USAT (mg)	35.1 ± 14.3	36.3 ± 13.6	36.1 ± 13.7	0.592
Mean t-PA duration in USAT (hour)	25.9 ± 7.2	25.1 ± 6.7	25.2 ± 6.8	0.604
Mean t-PA dose in ST (mg)	57 ± 34.2	54 ± 28.3	54.3 ± 28.7	0.876
Mean t-PA duration in ST (hour)	4.5 ± 3	6.4 ± 5.3	6.2 ± 5.1	0.263
Mean bolus t-PA dose in RT (mg)	15 ± 0.01	23.3 ± 9.3	21.2 ± 8.7	0.429
Hospital stay (days)	9 (6–13)	9 (7–13)	9 (7–13)	0.528
Clinical Outcomes				
Median survival (years)	1.4 (0.2–5.1)	4.5 (2.2–5.8)	4.2 (1.9–5.7)	<0.001
In-hospital mortality	22 (17.1 %)	38 (5.1 %)	60 (6.9 %)	<0.001
60-day mortality and PE-related rehospitalization	41 (31.8 %)	62 (8.3 %)	103 (11.8 %)	<0.001
Mortality during FU	48 (37.2 %)	90 (12.1 %)	138 (15.8 %)	<0.001
Anticoagulant in FU				
• NOACs	76 (71 %)	579 (82.1 %)	655 (80.6 %)	
• VKAs	0 (0 %)	98 (13.9 %)	98 (12.1 %)	<0.001
• LMWH	31 (29 %)	28 (4 %)	59 (7.3 %)	
Overall long-term mortality	70 (54.3 %)	128 (17.2 %)	198 (22.7 %)	<0.001
Major bleeding	7 (5.5 %)	34 (4.6 %)	41 (4.7 %)	0.660
Minor bleeding	6 (4.7 %)	35 (4.7 %)	41 (4.7 %)	0.991

Abbreviations; BP: blood pressure, COPD: chronic obstructive pulmonary disease, CTPA: computed tomographic pulmonary angiography, CRP: C-reactive protein, DVT: deep vein thrombosis, FU: follow-up, Hs: high sensitive, LMWH: low molecular weight heparin, LPA: left pulmonary artery, MPA: main pulmonary artery, NOACs: novel oral anticoagulants, OC/HRT: oral contraceptive / hormone replacement therapy, PE: pulmonary embolism, PESI: pulmonary embolism severity index, RPA: right pulmonary artery, RT: rheolytic thrombectomy RV/LVd: right to left ventricle diameter, RA/LAd: right to left atrial diameter, sPAP: systolic pulmonary artery pressure, sPESI: simplified PESI, St: tricuspid lateral annulus systolic tissue velocity, ST: systemic thrombolysis, TAPSE: tricuspid annular plane systolic excursion, t-PA: tissue-type plasminogen activator, USAT: ultrasound-assisted thrombolysis, VKAs: vitamin-K antagonists, VTE: venous thromboembolism.

Table 2
Distribution of cancer types in the patient population.

Active area of cancer	Count (n = 129)
Lung	26 (20.2 %)
Gastrointestinal system	37 (28.7 %)
Breast	16 (12.4 %)
Urogenital system	17 (13.2 %)
Central nervous system	9 (7 %)
Hematological	15 (11.6 %)
Other	9 (7 %)

sPAP was similar in both groups, whereas parameters expressing RV systolic function such as TAPSE and St were lower in the malignancy population. CTPA findings were similar in both groups.

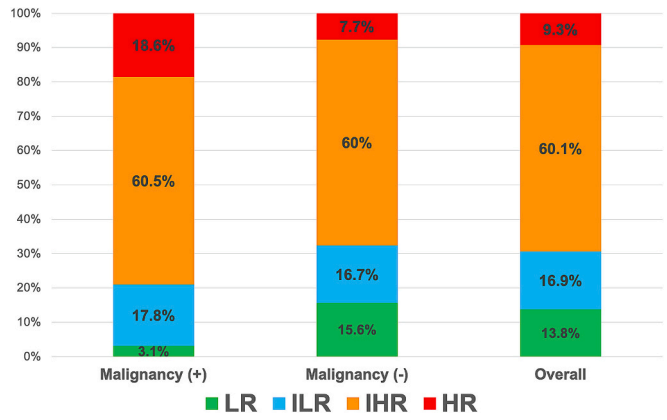

Fig. 1. Classification of the study population according to acute pulmonary embolism risk categories for the presence of malignancy. (HR: high-risk, IHR: intermediate-high risk, ILR: intermediate-low risk, LR: low-risk).

3.2. Comparison of therapeutic approaches

In this study, patients were stratified and treated based on acute PE risk categories, individual clinical features and estimated bleeding risk using USAT ($n = 238$, 27.3 %), ST ($n = 145$, 16.6 %), RT ($n = 56$, 6.4 %), or anticoagulation alone ($n = 433$, 49.7 %). The analysis revealed that the presence of malignancy significantly influenced treatment decisions. Non-malignant patients more frequently received t-PA-based therapies (USAT and ST), whereas in patients with malignancy the RT method was applied more often, where the use of t-PA was limited or only anticoagulant therapy was given (Fig. 2). Notably, t-PA dosages and treatment durations in USAT and ST protocols did not differ significantly between malignant and non-malignant cohorts. Although malignancy affected treatment approach, it did not influence median hospitalization duration. Distinct preferences in long-term anticoagulation were also evident between both patient groups (Table 1).

3.3. Short- and long-term clinical outcomes

The study initially identified that patients with malignancy exhibit significantly higher in-hospital mortality rates (17.1 % vs. 5.1 %) compared to those without. Univariate logistic regression analysis investigating the association of all clinically relevant variables on the composite endpoint is given in Supplementary Table 1. Multivariate analysis including age, presence of malignancy, PESI score, sPAP, TAPSE and QS revealed that PESI score (adjusted odds ratio [OR]: 1.02, 95 % confidence interval [CI] [1.01–1.03], $p < 0.001$) and the presence of malignancy (adjusted OR: 2.43, 95 % CI [1.32–4.47], $p = 0.04$) as independent predictors of composite 60-day mortality and PE-related rehospitalization (Table 3). As expected, long-term outcomes showed reduced median survival in cancer patients (1.4 vs. 4.5 years). Mortality during follow-up and overall long-term mortality rates were markedly higher in the cancer group (37.2 % and 54.3 %, respectively) compared to non-cancer patients (12.1 % and 17.2 %). In addition, the presence of malignancy does not seem to have impact on major and minor bleeding rates in this series. Independent from treatment modality or presence of malignancy, significant improvements were noted across post-treatment clinical, hemodynamic, echocardiographic, and CTPA parameters (Table 4). When the median 4.2-year follow-up outcomes of patients who achieved in-hospital survive was evaluated, it was observed that variables such as age, heart failure, chronic obstructive pulmonary disease (COPD), atrial fibrillation, malignancy, PESI, post-treatment sPAP and TAPSE influenced mortality during the follow-up period. Multivariate Cox regression analysis highlighted COPD (adjusted hazard ratio [HR]: 2.26, 95 % CI [1.21–4.19], $p = 0.010$), malignancy (adjusted HR: 2.25, 95 % CI [1.29–3.91], $p = 0.004$), post-treatment sPAP (adjusted HR: 1.01, 95 % CI [1.00–1.03], $p = 0.049$), and PESI (adjusted HR: 1.01, 95 % CI [1.00–1.01], $p < 0.001$) as independent predictors (Table 5). Finally, in the Kaplan-Meier survival curves constructed according to the presence of malignancy, there was a significant difference between the two groups, especially in the first 2 years (HR: 4.07, CI 95 % [3.04–5.46], p (log-rank) <0.001) (Fig. 3).

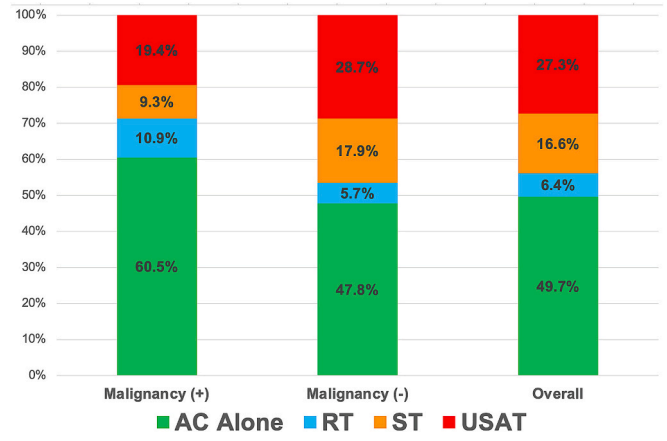

Fig. 2. Classification of the study population for the presence of malignancy according to treatment strategies. (AC: anticoagulation, RT: rheolytic thrombectomy, ST: systemic thrombolysis, USAT: ultrasound-assisted thrombolysis).

3.4. Clinical outcomes of the malignancy subgroup

In addition to the total patient population, short- and long-term clinical outcomes were also evaluated in the acute PE subgroup with active malignancy. In this subgroup, PESI, baseline sPAP and TAPSE were associated with 60-day mortality and PE-related rehospitalization. According to the multivariate analysis including these three variables, only PESI emerged as an independent predictor (adjusted OR: 1.02, 95 % CI [1.01–1.03], $p = 0.035$). Long-term prognosis in cancer patients treated with acute PE depends on the ongoing malignancy process rather than age and comorbid diseases, as predicted. Thus, in the Cox-regression analysis, post-treatment TAPSE (adjusted HR: 0.83, 95 % CI [0.72–0.96], $p = 0.020$) and the presence of lung cancer (adjusted HR: 3.06, 95 % CI [1.19–7.88], $p = 0.046$) were found to be independent predictors of long-term mortality in the malignancy subgroup (Table 6).

3.5. Evaluation of the IHR and HR PE subgroup

The prognostic impact of the presence of malignancy was further investigated in the IHR and HR PE subgroups, which comprised 60.1 %

Table 3
Predictors of composite end-point including all-cause mortality and pulmonary embolism related rehospitalization in first 60 days.

	60-day mortality and PE related rehospitalization			
	Univariate		Multivariate	
	Unadjusted OR (95 %CI)	p value	Adjusted OR (95 % CI)	*p* value
Age (years)	1.03 (1.01–1.04)	<0.001	1.00 (0.98–1.02)	0.966
Malignancy	5.11 (3.25–8.01)	<0.001	2.43 (1.32–4.47)	0.004
PESI	1.03 (1.02–1.04)	<0.001	1.02 (1.01–1.03)	<0.001
sPAP (mmHg)	1.03 (1.01–1.04)	<0.001	1.01 (0.99–1.03)	0.143
TAPSE (mm)	0.88 (0.83–0.93)	<0.001	0.96 (0.91–1.03)	0.342
Qanadli Score	1.06 (1.03–1.09)	<0.001	1.00 (0.95–1.04)	0.986

Abbreviations; CI: confidence interval, OR: odds ratio, PE: pulmonary embolism, PESI: pulmonary embolism severity index, sPAP: systolic pulmonary artery pressure, TAPSE: tricuspid annular plane systolic excursion.

Table 4
Treatment efficacy on clinical, hemodynamic, echocardiographic and CTPA measures.

	Malignancy group			Overall population		
	Pretreatment	Posttreatment	p value	Pretreatment	Posttreatment	p value
Heart rate (bpm)	112.3 ± 19.3	87.1 ± 11.9	<0.001	105.4 ± 19.7	83.4 ± 11.5	<0.001
Systolic BP (mmHg)	115.1 ± 23.7	121.7 ± 14.8	0.074	125.1 ± 23.1	124.7 ± 15.4	0.711
Diastolic BP (mmHg)	72.2 ± 16.1	74.1 ± 10.8	0.613	79.6 ± 15.1	76.1 ± 10.1	<0.001
Pulse O_2 saturation (%)	88.2 ± 5.8	93.8 ± 3.5	<0.001	89.8 ± 5.6	94.9 ± 5.6	<0.001
Shock index	1.03 ± 0.35	0.72 ± 0.14	<0.001	0.88 ± 0.29	0.68 ± 0.13	<0.001
sPAP (mmHg)	51.4 ± 14	38.9 ± 12	<0.001	51.5 ± 14.2	36.7 ± 11.9	<0.001
TAPSE (mm)	17.5 ± 4.3	21.6 ± 3.3	<0.001	18.7 ± 4.1	22.6 ± 4	<0.001
St (cm/s)	10.8 ± 3.1	13.4 ± 2.5	<0.001	11.4 ± 2.8	13.9 ± 2.3	<0.001
RV/LVd ratio	1.19 ± 0.25	0.91 ± 0.15	<0.001	1.19 ± 0.23	0.91 ± 0.13	<0.001
RA/LAd ratio	1.25 ± 0.29	1.02 ± 0.19	<0.001	1.27 ± 0.27	1.11 ± 0.21	<0.001
Qanadli score	20.4 ± 7.2	11.1 ± 5.8	<0.001	21.5 ± 6.5	10.4 ± 5.8	<0.001
MPA diameter (mm)	29.7 ± 3.6	27.9 ± 3.8	<0.001	30.1 ± 4.1	27.8 ± 4.2	<0.001
LPA diameter (mm)	22.4 ± 3.1	21.6 ± 2.9	0.001	22.5 ± 3.1	21.1 ± 3.1	<0.001
RPA diameter (mm)	23.6 ± 3.4	22.2 ± 2.9	0.002	23.2 ± 3.4	21.8 ± 3.4	<0.001

Abbreviations; BP: blood pressure, CTPA: computed tomographic pulmonary angiography, LPA: left pulmonary artery, MPA: main pulmonary artery, RA/LAd: right to left atrial diameter, RPA: right pulmonary artery, RV/LVd: right to left ventricle diameter, sPAP: systolic pulmonary artery pressure, St: tricuspid lateral annulus systolic tissue velocity, TAPSE: tricuspid annular plane systolic excursion.

Table 5
Cox regression analyses for predictors of mortality during follow-up.

	Long-term Mortality			
	Univariate		Multivariate	
	Unadjusted HR (95 %CI)	*p* value	Adjusted HR (95 % CI)	p value
Age (years)	1.03 (1.02–1.04)	<0001	1.01 (0.98–1.02)	0.545
Heart failure	2.22 (1.09–4.54)	0.028	1.21 (0.37–4.02)	0.745
COPD	2.91 (1.84–4.58)	<0.001	2.26 (1.21–4.19)	0.010
Atrial fibrillation	2.21 (1.31–3.72)	0.003	0.97 (0.42–2.26)	0.960
Malignancy	4.36 (3.07–6.21)	<0.001	2.25 (1.29–3.91)	0.004
Posttreatment sPAP (mmHg)	1.02 (1.01–1.03)	0.001	1.01 (1.00–1.03)	0.049
Posttreatment TAPSE (mm)	0.91 (0.86–0.96)	0.002	0.94 (0.89–1.01)	0.075
PESI	1.02 (1.01–1.03)	<0.001	1.01 (1.00–1.02)	<0.001

Abbreviations; CI: confidence interval, COPD: chronic obstructive pulmonary disease, HR: hazard ratio, PESI: pulmonary embolism severity index, sPAP: systolic pulmonary artery pressure, TAPSE: tricuspid annular plane systolic excursion.

and 9.3 % of the study cohort, respectively. The impact of all clinically relevant variables on 60-day all-cause mortality and PE-related rehospitalization is given in Supplementary Table 2. The presence of malignancy and PESI remained independent predictors of this composite endpoint in the IHR and HR subgroups (Table 7). The presence of malignancy, COPD, and PESI were also found to be independent predictors of long-term mortality in these subgroups (Table 8).

4. Discussion

This large single-center study with a median follow-up of 4.2 years included 872 acute PE patients from different risk categories treated with both medical and interventional therapies, of whom 14.8 % had a diagnosis of cancer within the last 6 months. Both short- and long-term effects of the presence of malignancy on the diagnosis and management of acute PE have been demonstrated.

The presence of malignancy is a factor that directly increases the risk of acute PE and DVT, furthermore it is associated with increased mortality, bleeding and recurrence rates in these patients, as VTE is the second most common cause of death in cancer patients, although it varies according to the type of underlying malignancy [10]. In this series, the most common cancer subtype was GIS cancers, followed by lung, urogenital system and breast cancers, respectively. In the Contemporary management of pulmonary embolism (COPE) registry, urogenital system, GIS and lung cancers took the first three places, with approximately half of them being metastatic [11]. In the large observational-prospective The Global Anticoagulant Registry in the FIELD (GARFIELD)-VTE registry, which included more than 10,000 patients, lung, colorectal and breast cancers were the most common cancers in active cancer patients diagnosed with VTE [12].

According to the results of the COPE registry, in-hospital vs. 30-day mortality rates were reported as 7.9 % vs. 13.8 %, 4.3 % vs. 5.2 % and 2.2 % vs. 2.6 %, respectively, in acute PE patients with active cancer clinic, patients with a history of cancer and patients who had never had cancer [11]. In the present study, like the COPE registry, in-hospital mortality rate was significantly higher in patients with active malignancy compared to those without (17.1 % vs. 5.1 %). Moreover, the presence of malignancy was found to be an independent predictor of composite endpoint including 60-day mortality and PE-related rehospitalization (adjusted OR: 2.43, CI 95 % [1.32–4.47], $p = 0.04$). According to the COPE series, approximately 60 % of the first 30-day deaths in acute PE patients with active malignancy were related to cancer and only 16.5 % were related to PE, which supports our study results. In addition, when cancer subtypes were analyzed, the highest 30-day mortality was observed in lung cancer patients with 22.4 % [11].

In daily clinical practice, the majority of low and intermediate-risk acute PE patients are primarily treated with parenteral anticoagulants in the hospital, followed by a transition to long-term anticoagulation with NOACs after discharge [13–15]. Recent evidence on the efficacy and safety of NOACs in the treatment of CAT has begun to mature, although conflicting outcomes have been reported across various studies and meta-analyses [16–18]. It should be considered that the bleeding risk of NOACs may be high, particularly in VTE patients with GIS cancer. Therefore, in the current PE guideline, it was stated that rivaroxaban and edoxaban may be preferred as an alternative to LMWH in patients with non-GIS malignancy [5].

Indeed, the treatment approach for acute PE is more diverse and complex, especially for IHR and HR PE patients. For HR acute PE patients presenting with significant hemodynamic instability or shock, ST demonstrates marked superiority over anticoagulant therapy by rapidly resolving thrombotic vascular obstruction, decreasing pulmonary vascular resistance and pulmonary arterial pressure, and ultimately improving RV dysfunction, though it carries a substantial risk of serious bleeding [19,20]. While the presence of malignancy increases the

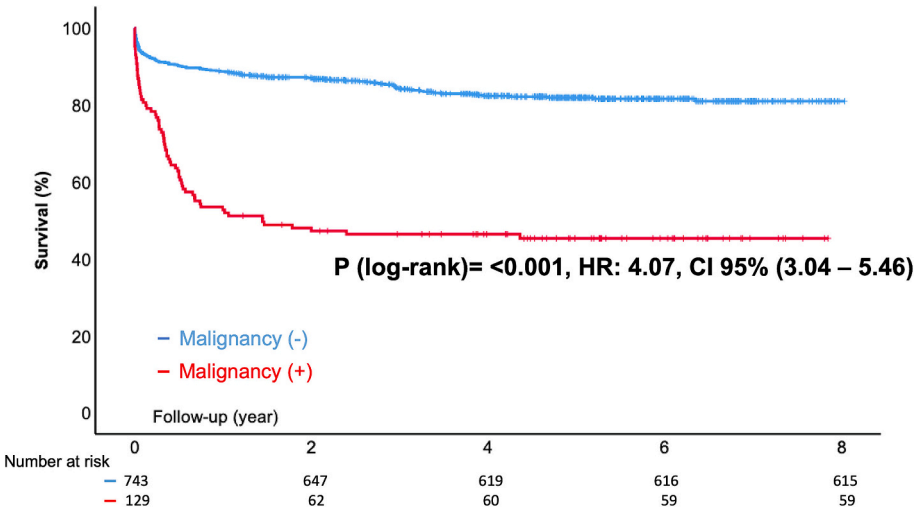

Fig. 3. Kaplan-Meier survival curves based on the presence of malignancy.

Table 6
Predictors of composite end-point including all-cause mortality and pulmonary embolism related rehospitalization in first 60 days and long-term mortality in patients with malignancy.

	60-day mortality and PE related rehospitalization			
	Univariate		Multivariate	
	Unadjusted OR (95 %CI)	*p* value	Adjusted OR (95 % CI)	p value
PESI	1.02 (1.01–1.03)	0.002	1.02 (1.01–1.03)	0.035
sPAP (mmHg)	1.03 (1.01–1.06)	0.027	1.02 (0.98–1.05)	0.239
TAPSE (mm)	0.89 (0.81–0.99)	0.041	0.93 (0.83–1.04)	0.211
	Long-term Mortality			
	Univariate		**Multivariate**	
	Unadjusted HR (95 %CI)	**p value**	**Adjusted HR (95 % CI)**	**p value**
Posttreatment TAPSE (mm)	0.84 (0.73–0.96)	0.015	0.83 (0.72–0.96)	0.020
Lung cancer	2.41 (1.28–4.51)	0.006	3.06 (1.19–7.88)	0.046

Abbreviations; CI: confidence interval, HR: hazard ratio, OR: odds ratio, PE: pulmonary embolism, PESI: pulmonary embolism severity index, sPAP: systolic pulmonary artery pressure, TAPSE: tricuspid annular plane systolic excursion.

Table 7
Multivariate logistic regression analysis investigating the independent predictors of 60-day all-cause mortality and PE-related rehospitalization in the IHR and HR acute PE subgroup.

	Adjusted OR	CI 95 %	*p* value
Age (years)	1.01	0.98–1.02	0.811
PESI	1.02	1.01–1.03	<0.001
Malignancy	2.67	1.45–4.91	0.002
TAPSE (mm)	0.96	0.89–1.03	0.324
sPAP (mmHg)	1.01	0.99–1.03	0.244

Abbreviations; CI: confidence interval, HR: high risk, IHR: intermediate-high risk, OR: odds ratio, PE: pulmonary embolism, PESI: pulmonary embolism severity index, sPAP: systolic pulmonary artery pressure, TAPSE: tricuspid annular plane systolic excursion.

bleeding risk, it does not constitute an absolute contraindication to thrombolytic therapy, except in cases of intracranial cancers [21]. Yet, clinical data on ST application in this patient group are notably limited, and evidence on percutaneous interventions is even scarcer. In the Registro Informatizado de la Enfermedad Trombo Embólica (RIETE) registry, only 118 of 17,271 CAT patients were treated with thrombolytic drugs and 31 patients received mechanical thrombolysis [22]. In

Table 8
Cox regression analyses for predictors of mortality during follow-up in IHR and HR PE subgroup.

	Long-term Mortality			
	Univariate		Multivariate	
	Unadjusted HR (95 %CI)	p value	Adjusted HR (95 % CI)	p value
Age (years)	1.02 (1.01–1.03)	0.001	0.99 (0.97–1.01)	0.782
COPD	2.76 (1.58–4.81)	<0.001	2.12 (1.01–4.45)	0.045
Atrial fibrillation	2.39 (1.31–4.41)	0.005	0.93 (0.35–2.47)	0.890
Malignancy	3.94 (2.57–6.03)	<0.001	2.18 (1.17–4.04)	0.013
Posttreatment sPAP (mmHg)	1.02 (1.01–1.04)	0.004	1.01 (0.99–1.04)	0.079
Posttreatment TAPSE (mm)	0.91 (0.85–0.97)	0.004	0.93 (0.87–1.00)	0.051
PESI	1.01 (1.01–1.02)	<0.001	1.01 (1.02–1.02)	<0.001

Abbreviations; CI: confidence interval, COPD: chronic obstructive pulmonary disease, HR: hazard ratio, HR PE: high-risk pulmonary embolism, IHR: intermediate-high risk, PESI: pulmonary embolism severity index, sPAP: systolic pulmonary artery pressure, TAPSE: tricuspid annular plane systolic excursion.

this context, the findings of this study for patients in the IHR and HR PE categories who received ST- or catheter-directed therapies at various doses and durations are extremely important. The utilization of percutaneous treatments in acute PE has been increasingly widespread in recent years [23–25]. Percutaneous treatment options emerge as an ideal method especially in HR patients in whom ST is contraindicated or does not yield successful results or in the IHR group in whom hemodynamic deterioration occurs [26]. A significant contraindication rate to ST in the cancer group was observed at 22.5 %, leading to a notably lower utilization rate compared to the non-cancer group (9.3 % vs 17.9 %). The USAT method, which allows prolonged catheter-mediated infusion of a lower dose of t-PA over a longer period of time compared to ST, was applied in 25 patients in the malignancy group. Both groups received similar total doses and durations of t-PA. Another preferred percutaneous method for PE patients with high bleeding risk, particularly those with malignancies, is RT, used significantly more in the cancer group (10.9 % vs 5.7 %). While COPE results indicated higher in-hospital and 30-day major bleeding rates in the active cancer group, this study revealed similar rates of major and minor bleeding between the

two groups. This discrepancy might be due to higher rates of ST utilization in the COPE series, whereas in this study catheter-directed treatments were applied with a substantially higher frequency. Thus, percutaneous treatments could be promising for CAT patients with anticipated high bleeding risk. This study's results demonstrate that satisfactory treatment outcomes can be achieved in acute PE patients across all risk categories with malignancies when appropriate treatment strategies, including percutaneous methods, are employed.

Finally, the study's follow-up data, extending up to 8 years, provide significant insights into the long-term prognosis of patients treated for acute PE, showing about 2.3-fold increased long-term mortality risk in patients with active malignancies. Although malignancy was the main determinant of mortality in long-term follow-up, post-treatment sPAP and TAPSE were also found to be associated with prognosis. These results may suggest that more rigorous hemodynamic and echocardiographic targets should be established when determining the treatment strategy in the acute setting. While the divergence in survival between the two groups was more pronounced in the first 2 years after the index event, the survival plots were almost parallel after the second year.

5. Conclusion

In a large population of patients from different risk and treatment categories with a diagnosis of acute PE and a long follow-up period, malignancy was found in 14.8 %. In the presence of active cancer, acute PE patients are more frequently classified as IHR and HR and have higher in-hospital mortality rates. Malignancy in acute PE patients is associated with a 2.4-fold increase in composite endpoint of 60-day mortality and PE-related rehospitalization and a 2.3-fold increase in long-term mortality. Given the heightened bleeding risk in patients with malignancy, percutaneous treatments capable of direct thrombus aspiration may be more beneficial, particularly in massive and submassive PE cases. The presence of malignancy complicates the treatment and worsens prognosis in acute PE patients, yet effective treatment outcomes can be achieved with precise risk stratification and appropriate treatment selection. To provide more reliable recommendations for managing this patient group, especially regarding interventional treatments like mechanical thrombectomy, further randomized studies are needed.

5.1. Study limitations

This study, which provides comprehensive short- and long-term data on the treatment of patients with cancer-related PE, has some limitations. The first limitation is its single-center and retrospective nature. Although the population is heterogeneous from different risk categories, IHR and HR PE groups are predominant since the center where the study was conducted is a tertiary center with high patient referrals. The fact that treatment decisions were based on individual patient-based risk assessment, the lack of randomization between treatment arms and the absence of a control group are also significant limitations. In addition, doses and durations of systemic or catheter-directed thrombolytic administration were determined according to physician preference. The presence of end-stage cancer patients on palliative care in the study population may not accurately reflect the efficacy of acute PE treatments. Finally, since the patient population was not large enough, differences according to cancer subtypes could not be adequately demonstrated.

CRediT authorship contribution statement

Aykun Hakgor: Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Barkın Kultursay:** Writing – original draft, Methodology, Investigation. **Berhan Keskin:** Validation, Resources, Data curation. **Ahmet Sekban:** Validation, Resources. **Hacer Ceren Tokgoz:** Supervision. **Seda Tanyeri:** Project administration, Formal analysis. **Ali Karagoz:** Visualization, Software, Formal analysis, Data curation. **Cihangir Kaymaz:** Supervision.

Declaration of competing interest

Nothing to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2024.132719.

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