Performance of pulmonary embolism severity index in predicting long-term mortality after acute pulmonary embolism

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Abstract

Objective: In this study, we aimed to evaluate the accuracy of the original and simplified pulmonary embolism (PE) severity index (PESI) to predict all-cause mortality after 30 days of acute PE diagnosis up to five years within consecutive sub-periods.

Methods: Adult patients diagnosed with acute PE between January 1, 2003, and June 30, 2013, were retrospectively included. Data on baseline characteristics and mortality during a five-year follow-up were collected.

Results: The study included 414 patients (Male/Female=192/222). The median age at diagnosis was 61.5 (minimum–maximum, 18–93) years. Mortality rates were 13.3% at 30 days, 21.8% at 90 days, 32.6% at one year, and 51.0% at five years. Both stratification into risk classes according to the original PESI and low vs. high-risk classification of original and simplified PESI were significantly correlated with the 30-day, 31-90-day, 91-day-one-year, and one-five-year mortality. Significant PESI predictors for mortality were history of cancer [hazard ratio (HR): 3.31, 95% confidence interval (CI): 1.64-6.68; p=0.001] and heart failure (HR: 2.35, 95% CI: 1.04-5.32, p=0.041) at 31-90-day, history of cancer (HR: 5.45, 95% CI: 2.86-10.40, p<0.001) at 91-day-one-year, advancing age (HR: 1.04, 95% CI: 1.02-1.06, p<0.001) and history of cancer (HR: 5.53, 95% CI: 3.41-8.98, p<0.001) at one-five-year after acute PE diagnosis.

Conclusion: All-cause long-term mortality in high-risk patients with acute PE according to original or simplified PESI significantly increased up to five years of follow-up. This survival disadvantage was mainly related to cancer and comorbidities rather than acute clinical manifestations. Future prospective studies are needed to demonstrate the effect of various comorbidities on long-term mortality in these patients.

Keywords: pulmonary embolism, mortality, prognosis

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Introduction

Acute pulmonary embolism (PE) is a fatal disease. Recent guidelines for acute PE management include assessing clinical status on the basis of an evaluation of the short-term prognosis, including the risk of mortality within 30 days after an acute PE diagnosis (1). Such assessment includes risk prediction indices. Guideline-suggested risk indices include the pulmonary embolism severity index (PESI) and its simplified version (1). The original PESI score calculation is based on age, sex, systolic blood pressure, pulse rate, body temperature, respiratory rate, presence of hypoxemia, change in mental status, history of cancer, heart failure, and chronic lung disease (2). The simplified PESI excludes some of these parameters, namely sex, body temperature, and respiratory rate and combines heart failure and lung disease as a single variable (3).

Although the evaluation for the risk of early mortality is well-defined by the guidelines, late mortality in patients with acute PE is an important issue that remains to be fully elucidated owing to limited available data (4). Several studies have investigated

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HIGHLIGHTS

- All-cause long-term mortality in patients with high-risk acute pulmonary embolism (PE) according to original or simplified PE severity index is significantly high up to five years of follow-up.
- The long-term survival disadvantage in patients with high-risk acute PE is mainly related to cancer and comorbidities rather than acute clinical manifestations.
- The history of cancer is significantly related to the mortality within all sub-periods of long-term follow-up.

parameters and risk classification indices, including the original and simplified PESI, related to long-term mortality in patients with acute PE (5, 6). However, investigating late mortality without excluding early follow-up may lead to a false generalization of the factors affecting early mortality for the entire follow-up, depending on the early mortality rate and the association's strength. Therefore, we aimed to evaluate the accuracy of the original and simplified PESI to predict all-cause mortality within consecutive sub-periods after 30 days of acute PE diagnosis.

Methods

Patients and design

Patients diagnosed with acute PE at a university hospital were retrospectively identified based on inpatient hospital archive records from January 1, 2003, to June 30, 2013. As a standardized diagnostic classification system with diagnostic codes was not used during the entire study period, Turkish keywords for pulmonary embolism and its abbreviation (PE) were used to search for data sources.

The inclusion criterion was acute PE diagnosis according to the following diagnostic tests: computed tomography pulmonary angiography (CTPA), high probability perfusion or ventilation-perfusion scintigraphy, lower extremity deep venous Doppler ultrasonography (US), echocardiography, or pulmonary angiography. Exclusion criteria were age <18 years at the time of diagnosis, diagnosis of chronic pulmonary embolism, or chronic thromboembolic pulmonary hypertension (CTEPH) without an acute thromboembolic episode between January 1, 2003, and June 30, 2013, and incomplete follow-up data for at least one month.

The study protocol was approved by the Non-Interventional Clinical Research Ethics Board of the university hospital on December 13, 2013 (Application number, GO 13/561-20). The board was subsequently informed about a revision to the data source for mortality and the follow-up duration, and approval for the final protocol was received on June 10, 2015.

Outcomes and variables

The primary study outcome was all-cause mortality. The mortality data were obtained from hospital archive records specifying mortality and a search of the death information system of the public health agency of Turkey for mortality or survival using patient ID numbers. The ID information of patients was strictly protected.

The baseline characteristics, including the variables used in calculating the original and simplified PESI scores, were obtained via a review of the hospital archive records. Other variables, including cancer types, modifiable risk factors other than cancer (i.e., history of surgery or immobilization for ≥72 h within one month, being pregnant or postpartum, and use of oral contraceptive or hormone replacement therapy), type of diagnostic test, concomitant deep venous thrombosis (DVT), treatment for acute PE, history of previous DVT, previous PE, diabetes mellitus (DM), hypertension (HT), coronary artery disease (CAD), and atrial fibrillation (AF) were also recorded.

The patients were categorized into three etiological subgroups:

1. Patients with comorbid active cancer
2. Patients with provoked PE, including those with modifiable risk factors other than cancer
3. Patients with unprovoked (idiopathic) PE, including those without any identifiable risk factors.

The PESI scores were calculated (2), and the patients were divided into five PESI classes and low (risk classes I and II) vs. high (risk classes III-V) risk groups. A dichotomous low- vs. high-risk classification was also performed according to simplified PESI scores (3). As used in the original study for PESI, missing values were accepted as normal (2). The accuracy of both indices was evaluated for mortality within consecutive sub-periods (i.e., 30-day, 31-90-day, 91-day-one-year, and one-five-year) to avoid effects of the mortality in the preceding periods.

Statistical analysis

Descriptive statistics were shown as mean plus or minus the standard deviation or median and minimum–maximum for continuous variables and as number and percentage for categorical variables. The categorical variables were compared using Pearson chi-squared or Fisher's exact test as appropriate.

The mortality at 30-day, 31-90-day, 91-day-one-year, and one-five-year was compared among the risk classes and between low and high-risk groups. We estimated sensitivity, specificity, positive and negative predictive values, and likelihood ratios with 95% confidence intervals (CI) (7) for low vs. high-risk patients according to the original and simplified PESI. The discriminatory power of both indices to predict mortality was also assessed by measuring the area under the receiver operating characteristic (ROC) curves (AUC).

The PESI predictors were analyzed using Cox regression analysis for mortality in 31-90-day, 91-day-one-year, and one-five-year following acute PE diagnosis. Furthermore, variables, namely the PESI predictors together with concomitant deep venous thrombosis, the anticoagulant used in the acute phase treatment, history of previous DVT, previous PE, DM, HT, CAD, and AF were also evaluated for 31-90-day, 91-day-one-year, and one-five-year mortality using multiple regression analysis with stepwise backward elimination and inclusion and exclusion

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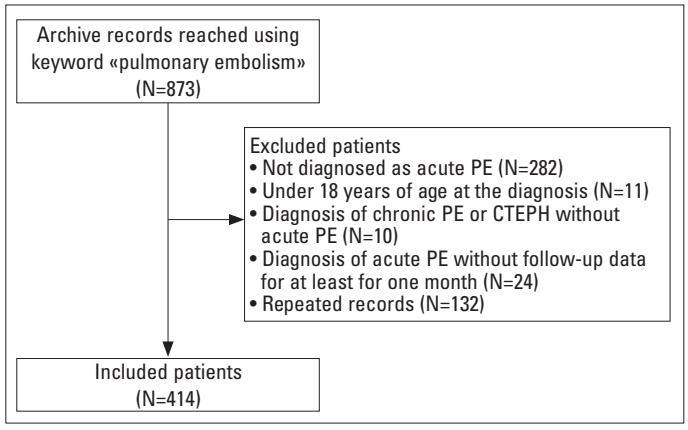

Figure 1. Flow chart of the study

probabilities of 0.05 and 0.10, respectively. The significant parameters in each sub-period's model were further analyzed by replacing the cancer variable with the cancer type and accepting the patients without any cancer as reference. The hazard ratios (HR) for Cox regression analysis were defined in model outputs with a 95% CI.

The overall mortality of low vs. high-risk patients according to the original and simplified PESI was compared using Kaplan–Meier analysis and the log-rank test. A similar analysis was also performed according to the increasing age gradient and etiological subgroups.

All statistical analyses were performed using IBM Statistical Package for Social Sciences for Windows version 22.0 (IBM Corp., Armonk, NY, USA). For all comparisons, the level of statistical significance was set at $p<0.05$.

Results

Baseline patient characteristics

According to the inclusion and exclusion criteria, the study included 414 patients (Fig. 1). The characteristics of patients at the time of acute PE diagnosis are shown in Table 1. Among the 414 patients, there were slightly more women (53.6%) than men (46.4%). The median age at the time of diagnosis was 61.5 (minimum–maximum, 18–93) years. In 95.7% of the patients, acute PE was diagnosed via CTPA. The diagnostic test was ventilation/perfusion or perfusion scintigraphy in 12 patients, lower extremity venous Doppler US in four patients, and transthoracic echocardiography in two patients. Concurrent DVT diagnosed via deep venous Doppler US or CT venography was noted in 33.1% of patients. According to etiological classification, 43.0% of the patients were in the unprovoked acute PE subgroup, 31.9% in the cancer-related, and 25.1% in the provoked acute PE subgroups. Of patients with cancer, 14 patients with other types of cancers included four with carcinoma of unknown primary, three with bladder cancer, one with malignant melanoma, one with squamous cell skin cancer, one with larynx cancer, one with nasopharyngeal cancer, one with adrenal gland tumor, one with esophagus cancer, and one with neuroendocrine tumor. In terms of treatment, systemic thrombolytic treatment was administered to 10.4% of the patients. In all, five patients had pulmonary embolectomy. During the acute phase of PE, 61.8% of the patients were treated with low molecular weight heparin and 37.2% with unfractionated heparin. Four patients were untreated because of complications. Because data on long-term anticoagulation could be reached only for 370 patients, further evaluation for that parameter was not performed.

Table 1. Baseline characteristics of patients and distribution according to risk classification

Patients, n	**414**
Original and simplified PESI predictors	
Age (years), mean ± SD	59.57±16.18
Median (minimum-maximum)	61.5 (18-93)
Age >80 years, n (%)	31 (7.5)
Male sex, n (%)	192 (46.4)
Pulse rate ≥110 beats per minute, n (%)	54 (13.0)
Systolic blood pressure <100 mm Hg, n (%)	48 (11.6)
Respiratory rate ≥30 per minute, n (%)	24 (5.8)
Body temperature <36°C, n (%)	4 (1.0)
Altered mental status, n (%)	52 (12.6)
Arterial oxygen saturation <90%, n (%)	117 (28.3)
History of heart failure, n (%)	69 (16.7)
History of chronic lung disease, n (%)	90 (21.7)
History of cancer, n (%)	132 (31.9)
Lung	24 (5.8)
Gynecological	19 (4.6)
CNS	15 (3.6)
Hematological	13 (3.1)
Stomach	11 (2.7)
Colorectal	10 (2.4)
Breast	9 (2.2)
Prostate	5 (1.2)
Kidney	5 (1.2)
Other*	14 (3.4)
Other characteristics, n (%)	
History of previous DVT	32 (7.7)
History of previous pulmonary embolism	15 (3.6)
History of diabetes mellitus	64 (15.5)
History of hypertension	161 (38.9)
History of coronary artery disease	58 (14)
History of atrial fibrillation	23 (5.6)
Anticoagulant used in the acute phase treatment, n (%)	
Low-molecular-weight heparin	256 (61.8)
Unfractionated heparin	154 (37.2)
Untreated	4 (1.0)

*Fourteen patients with other types of cancers include four with carcinoma of unknown primary, three with bladder cancer, one with malignant melanoma, one with squamous cell skin cancer, one with larynx cancer, one with nasopharyngeal cancer, one with adrenal gland tumor, one with esophagus cancer, and one with neuroendocrine tumor.
CNS - central nervous system; DVT - deep venous thrombosis; PESI - pulmonary embolism severity index; SD - standard deviation

Table 2. Comparison of risk-class-specific mortality according to original and simplified PESI scores

	30-day mortality *n/N* (%, 95% CI)	31-90-day mortality* *n/N* (%, 95% CI)	91-day-1-year mortality* *n/N* (%, 95% CI)	1-5-year mortality* *n/N* (%, 95% CI)
Overall	55/414 (13.3, 10.1-16.7)	34/354 (9.6, 6.8-12.7)	43/316 (13.6, 10.1-17.4)	71/266 (26.7, 21.4-32.0)
Original PESI				
Low risk	6/173 (3.5, 1.2-6.4)	4/163 (2.5, 0.6-4.9)	11/156 (7.1, 3.2-11.5)	17/142 (12.0, 7.0-17.6)
Class I	1/90 (1.1, 0-3.3)	2/87 (2.3, 0-5.7)	1/84 (1.2, 0-3.6)	3/80 (3.8, 0-8.8)
Class II	5/83 (6.0, 1.2-12.0)	2/76 (2.6, 0-6.6)	10/72 (13.9, 6.9-22.2)	14/62 (22.6, 12.9-33.9)
High risk	49/241 (20.3, 15.4-25.7)	30/191 (15.7, 11.0-21.5)	32/160 (20.0, 14.4-26.9)	54/124 (43.5, 34.7-53.2)
Class III	3/87 (3.4, 0-8.0)	12/83 (14.5, 7.2-21.7)	16/70 (22.9, 14.3-32.9)	21/53 (39.6, 26.4-52.8)
Class IV	10/57 (14.9, 7.5-23.9)	10/57 (17.5, 8.8-28.1)	10/47 (21.3, 10.6-34.0)	18/35 (51.4, 34.3-68.6)
Class V	36/87 (41.4, 32.2-51.7)	8/51 (15.7, 5.9-25.5)	6/43 (14.0, 4.7-25.6)	15/36 (41.7, 25.0-58.3)
P for trend**	<0.001	0.001	0.001	<0.001
P for low- vs. high-risk	<0 .001	<0.001	0.001	<0.001
Simplified PESI				
Low risk	0/104 (0, -)	2/103 (1.9, 0-4.9)	3/100 (3.0, 0-7.0)	6/94 (6.4, 2.1-11.7)
High risk	55/310 (17.7, 13.5-21.6)	32/251 (12.7, 8.8-16.7)	40/216 (18.5, 13.0-24.1)	65/172 (37.8, 30.2-45.3)
P for low- vs. high-risk	<0.001	0.002	<0.001	<0.001

*Of 414 patients, five without follow-up data after 30 days, four without follow-up data after 90 days, and seven without follow-up data after one year were only included in mortality analysis of the periods with available follow-up data.
**Five PESI classes were compared.
n - number of deaths; *N* - number of patients with available follow-up information; CI - confidence interval; PESI - pulmonary embolism severity index

The distribution of patients according to PESI risk classes was 90 (21.7%) in class I, 83 (20.0%) in class II, 87 (21.0%) in class III, 67 (16.2%) in class IV, and 87 (21.0%) in class V. According to the simplified PESI, 104 patients (25.1%) were at low risk and 310 (74.9%) patients at high risk.

Mortality and evaluation of the original and simplified PESI

The number of patients with complete follow-up data was 398 (96.1%). Five patients without follow-up data after 30 days, four patients without follow-up data after 90 days, and seven patients without follow-up data after one year were only included in the mortality analysis of the periods with available follow-up data. Mortality rates were 13.3% (95% CI: 10.1-16.7) at 30 days, 21.8% (95% CI: 17.8-25.9) at 90 days, 32.6% (95% CI: 28.1-37.0) at one year, and 51.0% (95% CI: 46.0-55.8) at five years. The analysis of mortality according to the original and simplified PESI risk classes at 30-day, 31-90-day, 91-day-one-year, and one-five-year is shown in Table 2. Both stratification into five risk classes according to the PESI score and low vs. high-risk classification of the original and simplified PESI were significantly correlated with the 30-day, 31-90-day, 91-day-one-year, and one-five-year mortality. The sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, and AUC for low and high-risk classification of both indices in each follow-up period are given in Table 3.

The distribution of long-term mortality according to PESI predictors and comorbidities, including concomitant deep venous thrombosis, the anticoagulant used in the acute phase treatment, history of previous DVT, previous PE, DM, HT, CAD, and AF was analyzed (Table 4). A significant difference in 91-day-one-year and one-five-year mortality was observed among age groups (p values were 0.030 and <0.001, respectively). A higher 31-90-day mortality was observed with a history of heart failure (8.2% vs. 18.0%, p=0.039) and chronic lung disease (7.5% vs. 17.6%, p=0.009). History of DM was also related to higher one-five-year mortality (23.8% vs. 45.7%, p=0.006). History of cancer was significantly associated with higher long-term mortality in all sub-periods (6.5% vs. 16.5%, p=0.003 for 31-90-day, 6.6% vs. 31.5%, p<0.001 for 91-day-one-year, and 16.4% vs. 62.7%, p<0.001 for one-five-year mortality). According to the cancer type, the distribution of long-term mortality revealed significantly higher one-five-year mortality in most cancer types, and long-term mortality in patients with gynecological and stomach cancer was significantly higher in all sub-periods (the mortality and p values are given in Table 5).

Parameters used in the calculation of PESI score were analyzed with univariate and multiple Cox regression analyses. Because any mortality was not observed in patients meeting the body temperature criterion and surviving after 30 days, that parameter could not be evaluated for long-term mortality. The significant PESI predictors for long-term mortality were history of cancer (HR: 3.31, 95% CI: 1.64-6.68, p=0.001) and history of heart failure (HR: 2.35, 95% CI: 1.04-5.32, p=0.041) for 31-90-day, history of cancer (HR: 5.45, 95% CI: 2.86-10.40, p<0.001) for 91-day-one-year, advancing age (HR: 1.04, 95% CI: 1.02-1.06, p<0.001) and history of cancer (HR: 5.53, 95% CI: 3.41-8.98, p<0.001) for one-five-year after the diagnosis of acute PE (Table 6).

The parameters including PESI predictors, concomitant deep venous thrombosis, the anticoagulant used in the acute phase

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Table 3. Ability of original and simplified PESI scores to predict mortality according to low- vs. high-risk classification

		30-day mortality (*N*=414)	31-90-day mortality* (*N*=354)	91-day-1-year mortality* (*N*=316)	1-5-year mortality* (*N*=266)
Original PESI	Sensitivity, % (95% CI)	89.1 (77.1-95.5)	88.2 (71.6-96.2)	74.4 (58.5-86.0)	76.1 (64.2-85.1)
	Specificity, % (95% CI)	46.5 (41.3-51.8)	49.7 (44.1-55.3)	53.1 (47.0-59.1)	64.1 (56.9-70.7)
	Positive predictive value, % (95% CI)	20.3 (15.5-26.1)	15.7 (11.0-21.8)	20.0 (14.3-27.2)	43.5 (34.8-52.7)
	Negative predictive value, % (95% CI)	96.5 (92.3-98.6)	97.5 (93.4-99.2)	92.9 (87.4-96.3)	88.0 (81.3-92.7)
	Positive likelihood ratio (95% CI)	1.67 (1.46-1.90)	1.75 (1.49-2.07)	1.59 (1.28-1.97)	2.12 (1.69-2.66)
	Negative likelihood ratio (95% CI)	0.23 (0.11-0.50)	0.24 (0.09-0.60)	0.48 (0.29-0.81)	0.37 (0.25-0.57)
	AUC (95% CI)	0.68 (0.61-0.74)	0.69 (0.61-0.77)	0.64 (0.55-0.72)	0.70 (0.63-0.77)
Simplified PESI	Sensitivity, % (95% CI)	100.0 (91.9-100.0)	94.1 (78.9-99.0)	93.0 (79.9-98.2)	91.5 (81.9-96.5)
	Specificity, % (95% CI)	29.0 (24.4-34.0)	31.6 (26.6-37.0)	35.5 (29.9-41.6)	45.1 (38.1-52.4)
	Positive predictive value, % (95% CI)	17.7 (13.7-22.6)	12.7 (9.0-17.7)	18.,5 (13.7-24.5)	37.8 (30.6-45.5)
	Negative predictive value, % (95% CI)	100.0 (95.6-100.0)	98.1 (92.5-99.7)	97.0 (90.8-99.2)	93.6 (86.1-97.4)
	Positive likelihood ratio (95% CI)	1.41 (1.32-1.50)	1.38 (1.23-1.54)	1.44 (1.28-1.63)	1.66 (1.44-1.93)
	Negative likelihood ratio (95% CI)	NA	0.19 (0.05-0.72)	0.20 (0.07-0.59)	0.18 (0.09-0.41)
	AUC (95% CI)	0.65 (0.58-0.71)	0.63 (0.54-0.71)	0.64 (0.57-0.72)	0.68 (0.62-0.75)

*Of 414 patients, five without follow-up data after 30 days, four without follow-up data after 90 days, and seven without follow-up data after one year were only included in mortality analysis of the periods with available follow-up data.
N - number of patients with available follow-up information; AUC - area under the curve; CI - confidence interval; PESI - pulmonary embolism severity index

treatment, history of previous DVT, previous PE, DM, HT, CAD, and AF were also evaluated for long-term mortality using multiple regression analysis with stepwise backward elimination. Final models achieved included male sex (HR: 0.40, 95% CI: 0.19-0.84, p=0.016), history of cancer (HR: 3.15, 95% CI: 1.58-6.26, p=0.001), history of heart failure (HR: 2.56, 95% CI: 1.16-5.65, p=0.020), and history of chronic lung disease (HR: 2.28, 95% CI: 1.12-4.64, p=0.023) for 31-90-day, advancing age (HR: 1.02, 95% CI: 1.00-1.05, p=0.035) and history of cancer (HR: 5.45, 95% CI: 2.91-10.21, p<0.001) for 91-day-one-year, advancing age (HR: 1.04, 95% CI: 1.02-1.06, p<0.001), history of cancer (HR: 5.43, 95% CI: 3.39-8.70, p<0.001), and history of DM (HR: 1.83, 95% CI: 1.03-3.24, p=0.040) for one-five-year. The significant parameters in each sub-period's model were further analyzed by replacing the cancer variable with the cancer type and accepting the patients without any cancer as reference. The 31-90-day mortality was significantly higher with gynecological (HR: 4.71, 95% CI: 1.66-13.39, p=0.004), lung (HR: 3.45, 95% CI: 1.01-11.83, p=0.049), hematological (HR: 5.91, 95% CI: 1.25-28.01, p=0.025), stomach cancer (HR: 16.71, 95% CI: 4.91-56.93, p<0.001). The types of cancer which were significantly related to 91-day-one-year mortality were gynecological (HR: 4.53, 95% CI: 1.31-15.67, p=0.017), lung (HR: 11.85, 95% CI: 4.93-28.52, p<0.001), central nervous system (HR: 7.07, 95% CI: 2.00-25.06, p=0.002), breast (HR: 4.91, 95% CI: 1.42-17.01, p=0.012), kidney (HR: 16.30, 95% CI: 2.02-131.39, p=0.009), stomach (HR: 18.15, 95% CI: 5.88-56.02, p<0.001), and other cancers (HR: 7.21, 95% CI: 2.08-24.99, p<0.001). The one-five-year mortality was significantly increased with gynecological (HR: 6.96, 95% CI: 2.67-18.13, p<0.001), lung (HR: 9.41, 95% CI: 3.84-23.08, p<0.001), central nervous system (HR: 8.07, 95% CI: 2.77-23.45, p<0.001), colorectal (HR: 6.17, 95% CI: 2.46-15.49, p<0.001), pancreas (HR: 12.82, 95% CI: 3.86-42.57, p<0.001), hematological (HR: 3.61, 95% CI: 1.27-10.29, p=0.016), breast (HR: 5.25, 95% CI: 1.84-14.96, p=0.002), and stomach cancers (HR: 18.53, 95% CI: 4.31-79.55, p<0.001).

The survival analysis of the patients was performed using Kaplan-Meier statistics according to dichotomized original and simplified PESI as low vs. high-risk, and survival curves are shown in Figures 2a and 2b, respectively. Statistical significance was observed (log-rank test p<0.001) for both indices. A significant survival difference (log-rank test p<0.001) was also observed according to advancing age (Fig. 2c). According to classification into etiological groups (i.e., provoked, unprovoked, and cancer), significantly lower survival in patients with cancer (log-rank test p<0.001) was observed in the survival analysis (Fig. 2d). The survival was similar in patients with provoked and unprovoked acute PE (log-rank test p=0.693).

Discussion

In this study, we reviewed the performance of the original and simplified PESI in predicting the long-term mortality in patients with acute PE. To our knowledge, this is the first study to investigate the performances of both indices in predicting long-term mortality within five years after acute PE. Our results indicated a significant difference in long-term mortality between low- vs. high-risk groups according to both indices up to five years, despite the analysis of mortality within sub-periods of the follow-up to exclude mortality in preceding periods. Depending on the sub-period, significant PESI predictors for long-term mortality included advancing age, a history of cancer, and a history of heart failure. Final models achieved using the multiple

Table 4. Distribution of long-term mortality after acute PE according to PESI predictors and comorbidities

	31-90-day mortality* *n/N* (%, 95% CI)	91-day-1-year mortality* *n/N* (%, 95% CI)	1-5-year mortality* *n/N* (%, 95% CI)
Overall	34/354 (9.6, 6.8-12.7)	43/316 (13.6, 1.1-17.4)	71/266 (26.7, 21.4-32.0)
Age (years)			
<50	5/102 (4.9, 1.0-8.8)	6/95 (6.3, 2.1-11.6)	9/87 (1.3, 4.6-17.2)
50-59	5/68 (7.4, 1.5-13.2)	12/62 (19.4, 9.7-3.6)	11/49 (22.4, 1.2-34.6)
60-69	10/76 (13.2, 6.6-22.4)	7/65 (1.8, 3.1-18.5)	17/54 (31.5, 18.5-44.4)
≥70	14/108 (13.0, 6.5-19.4)	18/94 (19.1, 1.6-26.6)	34/76 (44.7, 32.9-56.5)
P	0.138	0.030	<0.001
Sex			
Female	24/194 (12.4, 7.7-17.0)	21/168 (12.5, 7.7-17.9)	40/144 (27.8, 2.1-35.4)
Male	10/160 (6.3, 2.5-1.6)	22/148 (14.9, 9.5-2.9)	31/122 (25.4, 18.0-32.8)
P	0.052	0.541	0.664
Pulse rate ≥110 bpm			
No	28/318 (8.8, 6.0-12.3)	40/286 (14.0, 1.1-18.5)	66/239 (27.6, 22.2-33.5)
Yes	6/36 (16.7, 5.6-3.6)	3/30 (1.0, 0-2.0)	5/27 (18.5, 3.7-33.3)
P	0.137	0.780	0.311
Systolic BP <100 mm Hg			
No	31/327 (9.5, 6.4-12.8)	42/292 (14.4, 1.6-18.5)	64/244 (26.2, 2.5-32.0)
Yes	3/27 (11.1, 0-25.9)	1/24 (4.2, 0-12.5)	7/22 (31.8, 13.6-54.5)
P	0.734	0.222	0.570
Respiratory rate ≥30/min			
No	31/340 (9.1, 6.2-12.4)	40/305 (13.1, 9.8-17.4)	68/258 (26.4, 2.9-32.2)
Yes	3/14 (21.4, 0-42.9)	3/11 (27.3, 0-54.5)	3/8 (37.5, 12.5-75.0)
P	0.141	0.177	0.444
Body temperature <36°C			
No	34/352 (9.7, 6.8-12.8)	43/314 (13.7, 9.9-17.5)	71/264 (26.9, 21.6-33.0)
Yes	0/2 (0, -)	0/2 (0, -)	0/2 (0, -)
P	1.000	1.000	1.000
Altered mental status			
No	30/325 (9.2, 6.2-12.6)	39/291 (13.4, 9.3-16.8)	64/246 (26.0, 2.7-31.3)
Yes	4/29 (13.8, 3.4-27.6)	4/25 (16.0, 4.0-32.0)	7/20 (35.0, 15.0-55.0)
P	0.505	0.760	0.382
Arterial oxygen saturation <90%			
No	21/267 (7.9, 4.9-11.2)	36/243 (14.8, 1.3-19.3)	57/201 (23.4, 17.4-29.8)
Yes	13/87 (14.9, 8.0-21.8)	7/73 (9.6, 2.8-16.4)	24/65 (36.9, 26.2-47.7)
P	0.052	0.253	0.032
History of cancer			
No	16/245 (6.5, 3.7-9.8)	15/227 (6.6, 3.5-1.1)	34/207 (16.4, 11.6-21.3)
Yes	18/109 (16.5, 1.1-23.9)	28/89 (31.5, 22.5-41.6)	37/59 (62.7, 5.8-74.6)
P	0.003	< 0.001	< 0.001
History of heart failure			
No	25/304 (8.2, 5.3-11.5)	36/276 (13.0, 9.4-17.4)	61/235 (26.0, 2.9-32.3)
Yes	9/50 (18.0, 8.0-3.0)	7/40 (17.5, 7.5-3.0)	10/31 (32.3, 16.1-48.4)
P	0.039	0.442	0.456
History of chronic lung disease			
No	21/280 (7.5, 4.6-1.7)	31/255 (12.2, 8.2-16.5)	53/218 (24.3, 18.8-3.3)
Yes	13/74 (17.6, 9.5-27.0)	12/61 (19.7, 9.8-31.1)	18/48 (37.5, 25.0-5.0)
P	0.009	0.124	0.061

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Table 4. (cont.) Distribution of long-term mortality after acute PE according to PESI predictors and comorbidities

	31-90-day mortality* *n/N* (%, 95% CI)	91-day-1-year mortality* *n/N* (%, 95% CI)	1-5-year mortality* *n/N* (%, 95% CI)
History of previous DVT			
No	32/324 (9.9, 6.8-13.0)	38/288 (13.2, 9.0-17.7)	64/243 (26.3, 21.0-31.7)
Yes	2/30 (6.7, 0-16.7)	5/28 (17.9, 7.1-32.1)	7/23 (30.4, 13.0-47.8)
P	0.754	0.561	0.630
History of previous PE			
No	31/340 (9.1, 5.9-12.4)	41/305 (13.4, 9.5-17.4)	68/257 (26.5, 21.4-32.3)
Yes	3/14 (21.4, 0-42.9)	2/11 (18.2, 0-45.5)	3/9 (33.3, 0-66.7)
P	0.141	0.650	0.704
History of diabetes mellitus			
No	25/299 (8.4, 5.4-11.4)	33/270 (12.2, 8.5-15.9)	55/231 (23.8, 18.6-29.9)
Yes	9/55 (16.4, 7.3-25.5)	10/46 (21.7, 10.9-34.8)	16/35 (45.7, 28.6-62.9)
P	0.064	0.082	0.006
History of hypertension			
No	21/219 (9.6, 5.9-13.7)	28/194 (14.4, 9.3-19.6)	38/161 (23.6, 17.4-29.8)
Yes	13/135 (9.6, 5.2-14.8)	15/122 (12.3, 6.6-18.0)	33/105 (31.4, 22.9-41.0)
P	0.990	0.589	0.158
History of coronary artery disease			
No	29/305 (9.5, 6.6-12.8)	36/272 (13.2, 9.6-17.3)	58/232 (25.0, 19.8-30.6)
Yes	5/49 (10.2, 2.0-20.4)	7/44 (15.9, 4.6-27.3)	13/34 (38.2, 20.7-52.9)
P	0.798	0.637	0.103
History of atrial fibrillation			
No	30/336 (8.9, 6.0-11.9)	41/302 (13.6, 9.9-17.9)	66/254 (26.0, 20.9-31.5)
Yes	4/18 (22.2, 5.6-38.9)	2/14 (14.3, 0-35.7)	5/12 (41.7, 16.7-66.7)
P	0.082	1.000	0.313
Acute phase anticoagulant			
Low-molecular-weight heparin	27/223 (12.1, 7.6-16.1)	31/193 (16.1, 10.9-21.8)	49/159 (30.8, 23.9-37.7)
Unfractionated heparin	6/127 (4.7, 1.6-8.7)	12/120 (10, 5.0-15.0)	21/104 (20.2, 12.5-27.9)
Untreated	1/4 (25.0, 0-75.0)	0/3 (0, -)	1/3 (33.3, 0-100.0)
P	0.026	0.284	0.102

*Five patients without follow-up data after 30 days, four patients without follow-up data after 90 days, and seven patients without follow-up data after one year were only included in mortality analysis of the periods with available follow-up data
n - number of deaths; *N* - number of patients with available follow-up information; CI - confidence interval; DVT - deep venous thrombosis; PE - pulmonary embolism; PESI - pulmonary embolism severity index

Cox regression analysis of PESI predictors together with other clinical parameters, including concomitant deep venous thrombosis, the anticoagulant used in the acute phase treatment, a history of previous DVT, previous PE, DM, HT, CAD, and AF showed that a history of cancer was significantly related to long-term mortality in all sub-periods. The 31-90-day mortality was related to a history of chronic lung disease and a history of heart failure. In contrast, the male sex was found to be protective for mortality in 31-90-day sub-period. Advancing age was found to be significantly related to mortality in both the 91-day-one-year and one-five-year sub-periods, and a statistical significance was also observed between a history of DM and one-five-year mortality.

The prognosis of acute PE in the long term has been a research interest. However, the studies on late mortality in patients with acute PE are heterogeneous in patient groups (e.g., patients with PE only vs. DVT or PE + DVT), study design, sample size, and methodology (4). In a study by Heit et al. (8) in 1999, they have divided mortality as early and late mortality, but the cut-off for late mortality was just seven days. Prolongation of the defined early phase in more recent studies might result from the development of prognostic indices for predicting the risk of 30-day mortality. The approach for late mortality is more diverse than early mortality. In 2006, Schulman et al. (9) have investigated long-term mortality in patients with PE by prolonging their cohort from two to 10 years and reported the mortality within the entire follow-up period. Similarly, in 2018, Kheirkham-Sabetghadam et al. (10) evaluated long-term mortality and its predictors in 378 patients with acute PE and analyzed parameters for mortality during the entire follow-up. Reitter et al. (11)

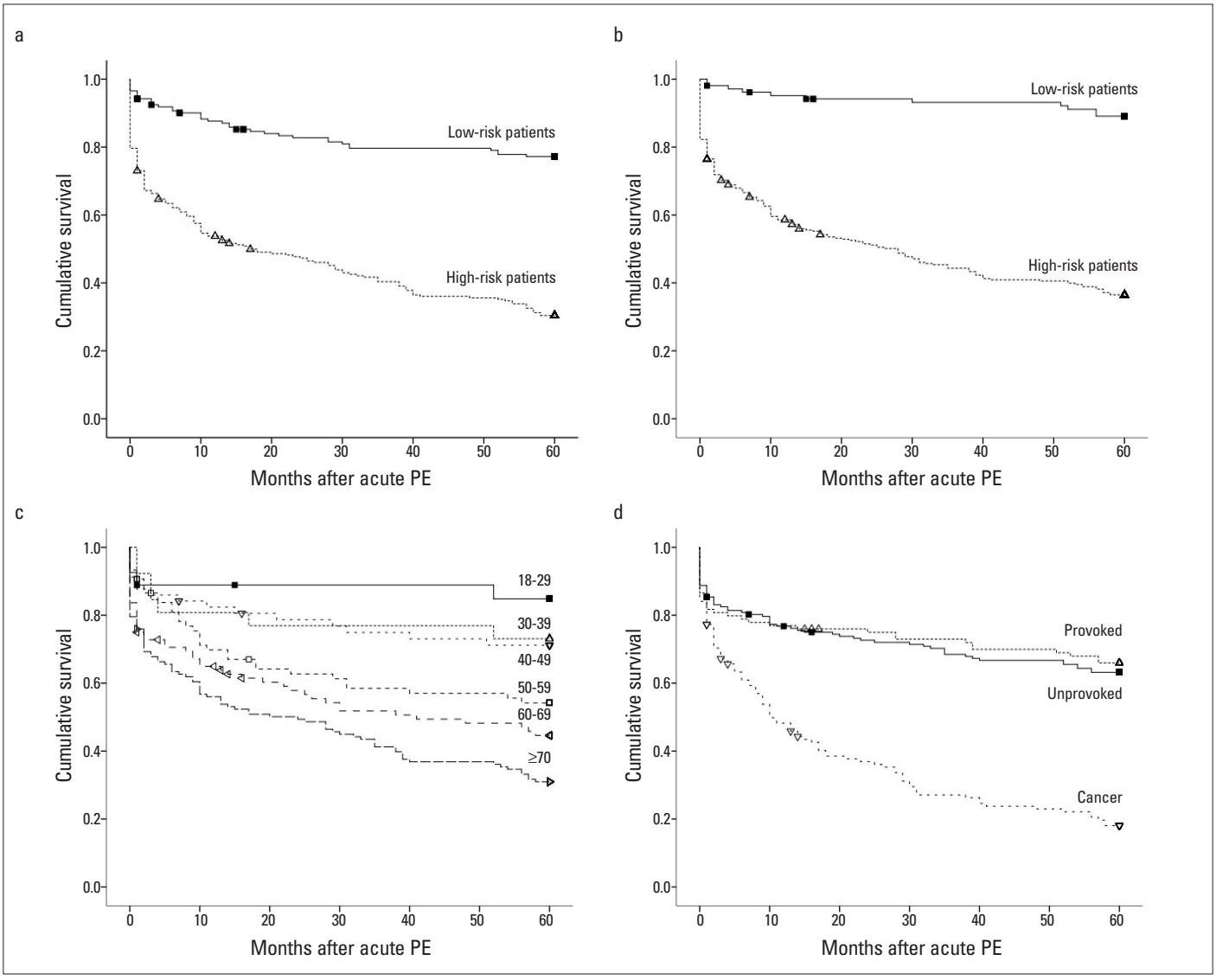

Figure 2. Kaplan–Meier curves for overall survival according to low- vs. high-risk classification for the original (a) and simplified pulmonary embolism severity index (b) scores, according to the increasing age gradient (c), and etiological classification into provoked, unprovoked, and cancer groups (d) The log-rank test *P*<0.001 for all analyses. The triangles and squares in all the panels indicate censored data

have also evaluated 3,209 patients who were cancer-free with a history of a non-fatal first event of venous thromboembolism (VTE). Their study focused primarily on long-term mortality within a median of 6.6 years of follow-up.

Our study investigated long-term mortality within five years after acute PE rather than examining overall mortality for the entire follow-up period. In 2011, Ng et al. (12) retrospectively evaluated 1,023 patients with acute PE and reported cumulative mortality rates as 8.3% at three months, 11.1% at six months, 16.3% at one year, 26.7% at three years, and 31.6% at five years of follow-up, respectively. The higher mortality in our study (e.g., 21.8% at 90 days, 32.6% at one year, and 51.0% at five years) could be related to our study's higher prevalence of malignancy (31.9% vs. 22.4%). In 2012, Duru et al. (13) have similarly accepted the mortality after 30 days of acute PE diagnosis as late mortality in 205 Turkish patients with acute PE and found late mortality during their follow-up as 11.2%, but the duration of follow-up was not mentioned.

Several studies investigated the accuracy of prognostic scoring systems, including indices developed to predict short-term mortality or original scoring models, to predict long-term mortality in patients with acute PE (5, 14, 15). Of those, Subramaniam et al. (15) have examined the Geneva prognostic score and found a significant difference between patients with a score of ≤2 vs. ≥3 at the 12-month follow-up (p<0.0001). In 2013, Dentali et al. (5) have evaluated the performance of the original and simplified PESI to predict the three-month, six-month, and one-year mortality rate in patients with PE. According to PESI, the long-term mortality was significantly related to risk classes (p<0.001) for mortality at three months, six months, and 12 months). According to the original and simplified PESI scores, the low vs. high-risk classification showed high sensitivity

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Table 5. Analysis of long-term mortality after acute PE according to the cancer type

	31-90-day mortality*		91-day-1-year mortality*		1-5-year mortality*	
	n/N (%, 95% CI)	*P***	*n/N* (%, 95% CI)	*P***	*n/N* (%, 95% CI)	*P***
Overall	34/354 (9.6, 6.8-12.7)		43/316 (13.6, 10.1-17.4)		71/266 (26.7, 21.4-32.0)	
No cancer	16/245 (6.5, 3.7-9.8)		15/227 (6.6, 3.5-10.1)		34/207 (16.4, 11.1-21.7)	
Cancer						
Lung	4/20 (20.0, 5.0-35.0)	0.052	8/16 (50.0, 25.0-75.0)	<0.001	6/7 (85.7, 57.1-100.0)	< 0.001
CNS	0/11 (0, -)	1.000	3/10 (30.0, 0-60.0)	0.032	4/7 (57.1, 28.6-85.7)	0.020
Gynecological	5/17 (29.4, 11.8-52.9)	0.007	3/11 (27.3, 0-54.5)	0.041	5/8 (62.5, 25.0-87.5)	0.006
Hematological	2/13 (15.4, 0-38.5)	0.227	1/11 (9.1, 0-27.3)	0.543	4/10 (40.0, 10.0-70.0)	0.076
Stomach	4/10 (40.0, 10.0-70.0)	0.004	4/6 (66.7, 33.3-100.0)	<0.001	2/2 (100.0, -)	0.029
Colorectal	1/10 (10.0, 0-30.0)	0.505	2/9 (22.2, 0-55.6)	0.130	6/7 (85.7, 57.1-100.0)	< 0.001
Breast	0/9 (0, -)	1.000	3/9 (33.3, 11.1-66.7)	0.024	4/6 (66.7, 33.3-100.0)	0.010
Pancreas	0/4 (0, -)	1.000	0/4 (0, -)	1.000	3/4 (75.0, 25.0-100.0)	0.018
Prostate	0/4 (0, -)	1.000	0/4 (0, -)	1.000	1/4 (25.0, 0-75.0)	0.519
Kidney	1/3 (33.3, 0-100)	0.193	1/2 (50.0, 0-100.0)	0.135	1/1 (100.0, -)	1.000
Other	1/8 (12.5, 0-37.5)	0.431	3/7 (42.9, 0-85.7)	0.011	2/3 (66.7, 0-100.0)	0.077

*Five patients without follow-up data after 30 days, four patients without follow-up data after 90 days, and seven patients without follow-up data after one year were only included in mortality analysis of the periods with available follow-up data
**Compared to patients without any type of cancer
n - number of deaths; *N* - number of patients with available follow-up information; CI - confidence interval; CNS - central nervous system; PE - pulmonary embolism

(92.7% and 95.8%, respectively) and high negative predictive values (91.5% and 93.9%, respectively). Our study analyzed the accuracy of the original and simplified PESI for long-term mortality within sub-periods (i.e., 31-90-day, 91-day-one-year, and one-five-year) to avoid the effects of the mortality in preceding periods. Both stratification into risk classes according to the PESI score and low- vs. high-risk classification of the original and simplified PESI significantly correlated with 30-day, 31-90-day, 91-day-one-year, and one-five-year mortality ($p<0.01$ for all of these). However, lower sensitivity and negative predictive values were observed. That could result from excluding the mortality in preceding periods as both indices were developed to predict 30-day mortality.

Recent guidelines for the management of acute PE suggest the management according to the risk of early mortality, which is determined according to basal patient status, including comorbidities and vital signs and some laboratory and imaging findings, which indicate the cardiopulmonary status during the acute phase of the disease (1). In terms of long-term mortality after acute PE, our results indicated that significant PESI predictors were advancing age, a history of cancer, and a history of heart failure depending on the sub-period. The multiple regression analysis of PESI predictors together with other parameters detected significant parameters as male sex (found protective), history of cancer, chronic lung disease, and heart failure at 31-90-day, advancing age and history of cancer at 91-day-one-year, and advancing age, history of cancer, and DM at one-five-year. These findings point to the fact that PESI predictors on acute manifestations, such as hypotension, tachycardia, and oxygen desaturation, have little or no clinical value in predicting long-term mortality in acute phase survivors who have been diagnosed and treated timely. In those patients, significant predictors for long-term all-cause mortality include comorbidities, such as cancer and heart failure, besides advancing age. Carson et al. (16) have similarly demonstrated that cancer, left-sided congestive heart failure, and chronic lung disease were significantly related comorbidities to one-year mortality in patients with acute PE. In a study by Gupta et al. (17) in 2020, all-cause mortality over a median follow-up of 4.1 years was evaluated in 183 patients with acute PE. Independent predictors for mortality after 30 days of acute PE diagnosis included cancer, DM, and liver disease. The female sex, age, baseline leukocyte count, and a massive PE were also significantly related, although only three of seven patients with massive PE survived after the first 30 days. Combining these results, we consider that morbidities significantly related to long-term mortality could vary according to the study population's features. Future prospective studies may elucidate the effect of various comorbidities on long-term mortality in patients with acute PE.

In this study, the only parameter significantly related to mortality within all sub-periods of long-term follow-up was found to be a history of cancer. Other researchers similarly observed the relationship between cancer and long-term mortality in patients with acute PE. Flinterman et al. (18) have included 4,947 patients with a first non-fatal VTE from the Multiple Environmental and Genetic Assessment study on risk factors for venous thrombosis (MEGA study) and 6,154 controls without venous thrombosis, including DVT, who were followed up for eight years. Their study evaluated risk factors and comorbidities and analyzed mortality according to risk factors, using categories similar to those in this

Table 6. Univariate and multiple Cox regression analyses of PESI predictors for long-term mortality after acute PE*

	31-90-day mortality** (*N*=354)		91-day-1-year mortality** (*N*=316)		1-5-year mortality** (*N*=266)	
	HR (95% CI)	*P****	HR (95% CI)	*P****	HR (95% CI)	*P****
Univariate regression analysis						
Age (1-year increase)	1.03 (1.00-1.05)	**0.033**	1.02 (1.00-1.04)	**0.026**	1.04 (1.03-1.06)	**<0.001**
Male sex	0.49 (0.24-1.03)	0.060	1.22 (0.67-2.22)	0.513	0.90 (0.56-1.44)	0.651
History of cancer	2.57 (1.31-5.04)	**0.006**	5.54 (2.96-10.37)	**<0.001**	5.58 (3.49-8.91)	**<0.001**
History of heart failure	2.29 (1.07-4.90)	**0.033**	1.40 (0.63-3.16)	0.411	1.25 (0.64-2.44)	0.511
History of chronic lung disease	2.43 (1.22-4.85)	**0.012**	1.66 (0.85-3.23)	0.137	1.63 (0.96-2.79)	0.073
Pulse rate ≥110 beats per minute	2.00 (0.83-4.83)	0.123	0.70 (0.22-2.26)	0.552	0.66 (0.27-1.65)	0.376
Systolic blood pressure <100 mm Hg	1.20 (0.37-3.94)	0.760	0.28 (0.04-2.00)	0.202	1.30 (0.59-2.83)	0.514
Respiratory rate ≥30 per minute	2.53 (0.77-8.29)	0.125	2.26 (0.70-7.31)	0.173	1.60 (0.50-5.08)	0.427
Altered mental status	1.53 (0.54-4.34)	0.426	1.19 (0.43-3.34)	0.737	1.51 (0.69-3.30)	0.300
Arterial oxygen saturation <90%	1.94 (0.97-3.87)	0.061	0.63 (0.28-1.41)	0.260	1.61 (0.99-2.64)	0.057
Multiple regression analysis						
Age (1-year increase)	1.01 (0.99-1.04)	0.336	1.02 (1.00-1.05)	0.071	1.04 (1.02-1.06)	**<0.001**
Male sex	0.47 (0.22-1.03)	0.059	0.93 (0.50-1.75)	0.821	0.94 (0.57-1.55)	0.806
History of cancer	3.31 (1.64-6.68)	**0.001**	5.45 (2.86-10.40)	**<0.001**	5.53 (3.41-8.98)	**<0.001**
History of heart failure	2.35 (1.04-5.32)	**0.041**	1.51 (0.63-3.65)	0.355	0.83 (0.40-1.72)	0.621
History of chronic lung disease	2.02 (0.93-4.35)	0.074	1.49 (0.73-3.04)	0.275	1.57 (0.87-2.81)	0.133
Pulse rate ≥110 beats per minute	1.74 (0.57-5.38)	0.334	0.66 (0.15-2.80)	0.571	0.67 (0.21-1.53)	0.262
Systolic blood pressure <100 mm Hg	0.88 (0.21-3.83)	0.873	0.37 (0.04-3.19)	0.367	2.01 (0.82-4.95)	0.128
Respiratory rate ≥30 per minute	1.26 (0.31-5.18)	0.752	1.66 (0.40-6.81)	0.484	1.09 (0.33-3.57)	0.887
Altered mental status	1.84 (0.55-6.11)	0.319	2.17 (0.72-6.51)	0.167	1.76 (0.78-4.02)	0.176
Arterial oxygen saturation <90%	1.33 (0.63-2.81)	0.463	0.53 (0.23-1.27)	0.156	1.05 (0.60-1.84)	0.874

*The body temperature criterion could not be evaluated for long-term mortality because any mortality was not observed in patients meeting that parameter and surviving after 30 days
**Five patients without follow-up data after 30 days, four patients without follow-up data after 90 days, and seven patients without follow-up data after one year were only included in mortality analysis of the periods with available follow-up data
***Bold values indicate statistical significance
N - number of patients with available follow-up information; HR - hazard ratio; CI - confidence interval; PESI - pulmonary embolism severity index

study (e.g., malignancy+ for cancer patients and malignancy– for non-cancer patients, also subdivided into provoked and idiopathic groups). There was a four-fold and > five-fold increase in mortality risk in all the patients and malignancy+ patients, respectively, compared with matched controls. More recently, Alotaibi et al. (19) have investigated short- and long-term mortality in 8,641 patients with acute PE and divided the patients into cancer-associated, provoked, and unprovoked PE. Similar to our study, the largest group was unprovoked PE (42.2%). The results indicated significantly higher short- and long-term all-cause mortality after cancer-associated PE, although the cancer-associated PE group was 19.9%, which is lower than our study. We also analyzed the long-term mortality according to the cancer type. Chew et al. (20) have evaluated the effect of VTE on survival within the first year of cancer diagnosis and have found a significant relationship with local, regional, and remote stages of prostate, breast, lung, colorectal, uterus, bladder, pancreas, stomach, and ovarian cancers. As our results include a five-year duration of follow-up, the cancer diagnosis may be the primary reason for decreased survival. Moreover, our results should be interpreted with caution owing to the relatively small patient numbers for various cancer types.

Study limitations

The primary limitation of our study was its retrospective single-center design. The retrospective design could increase the margin of error as many parameters were taken into account in calculating PESI scores. Moreover, despite obtaining complete follow-up data for 96.1% of the patients, other data including radiological and laboratory findings, characteristics (e.g., stage, class, severity, treatment, or control status) of cancer, heart failure, and other comorbidities, use of long-term anticoagulant drugs (e.g., duration of treatment, treatment compliance, and treatment-related complications), recurrence of PE or DVT, CTEPH development, and cause of death were not evaluated. Such factors might be predictive for late mortality; and therefore, our findings should be considered according to this limitation. We do believe that additional prospective studies that employ pre-

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defined protocols, including evaluating a more comprehensive range of parameters, might yield higher quality data.

Conclusion

Evaluating the risk of late mortality in patients with acute PE and developing similar prognostic evaluation algorithms for early mortality might help clinicians provide optimal long-term management. The results of this study indicate a significantly high long-term mortality in patients with high-risk acute PE according to both original and simplified PESI scores. Advancing age, history of cancer, and other comorbidities, including heart failure and chronic lung disease, might be important factors associated with an increased risk of late mortality. Long-term mortality in patients with acute PE requires additional research, and findings from this study and earlier studies might be used as a basis for future prospective cohort studies.

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