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ORIGINAL RESEARCH

High D-dimer is a predictor for short-term mortality in patients with active cancer and acute pulmonary embolism

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Abstract

Objectives: Acute pulmonary embolism (PE) is the main cause of death in cancer patients, but there are limited prognostic tools for the patients with active cancer and acute PE. We aimed to identify prognostic factors of 30-day mortality in patients with active cancer and acute PE.

Methods: This retrospective observational study included all adult patients aged ≥18 years with active cancer and acute PE from February 2017 to February 2019 at the emergency department in tertiary care hospital, Seoul, Korea. The primary outcome is 30-day mortality.

Results: A total of 178 patients were included with a mean age of 63.9 years (SD 10.4) and males of 52.8%. The overall 30-day mortality rate was 30.9%. In a multivariable logistic analysis, high D-dimer, defined as ≥median value of 14.7 μg/mL, with odds ratio (OR) 2.47 (95% confidence interval [CI], 1.15–5.33), high Pulmonary Embolism Severity Index (PESI) scores with OR 2.95 (95% CI, 1.21–7.75) for class IV and OR 2.90 (95% CI, 1.06–7.90) for class V, and Eastern Cooperative Oncology Group (ECOG) performance status 3/4 with OR 3.22 (95% CI, 1.18–8.76) were independent predictors of 30-day mortality.

Conclusion: High D-dimer values, high PESI scores, and poor ECOG performance status may be reliable predictors of mortality in patients with active cancer and acute PE.

Keywords

Cancer; D-dimer; Mortality; Prognosis; Pulmonary embolism

1. Introduction

Acute pulmonary embolism (PE) is one of the life-threatening diseases. In a national cohort, the annual incidence of acute PE has been increased in recent years. Although the mortality rate has been decreasing, the 30-day mortality is reported to be still more than 10% [1]. Cancer is the most common comorbid condition among patients with acute PE. Especially, cancer is known to be associated with poor prognosis in patients with acute PE [2, 3].

Many prognostic tools have been introduced to risk-stratify patients with acute PE. Among those tools, the Pulmonary Embolism Severity Index (PESI) has been most extensively validated. The PESI prognostic tool categorizes patients with acute PE into five classes depending on the risk of short-term mortality [4]. In some validation studies, the PESI was shown to reliably identity PE patients according to the risk of death [5]. After that, a simplified version of PESI (sPESI) was derived to make the PESI simple. Similar to the PESI, the sPESI was also shown to be useful in identifying low-risk patients with PE [6]. However, the prognostic accuracy of the generic prognostic tools, including the PESI and sPESI was suboptimal in patients with active cancer and acute PE [7]. Several cancer-specific tools, such as POMPE-C and RIETE have been created [8]. POMPE-C consisted of eight variables and its good prognostic accuracy for 30-day mortality was shown in a previous study [8]. RIETE was suggested as a potential model to identify low risk groups suitable for home management among cancer patients with PE [9]. Still, the use of them is limited by obstacles such as the lack of practicability and low discrimination power.

In this study, we aimed to identify prognostic factors of 30-day mortality among the initial clinical items in patients with active cancer and acute PE.

2. Methods

2.1 Study subjects

We consecutively included all adult patients aged ≥18 years with active cancer and PE from 8th February, 2017 through 27 February, 2019, seen at the emergency department (ED) of a

tertiary care university-affiliated hospital in Seoul, Korea. The institutional review board of Asan Medical Center approved our study (Study number: 2017-1122), and informed consent was waived because of its retrospective design. The research is in accordance with the Helsinki Declaration of 1975, as revised in 2010.

The diagnosis of PE was confirmed using a computed tomography pulmonary angiography (CTPA) or a ventilation-perfusion scan. Active cancer was defined as (1) evidence of cancer burden on imaging examination; (2) newly diagnosed cancer; or (3) receiving chemotherapy, radiotherapy, or surgery within six months. Patients who had no active cancer or who were not diagnosed with PE were excluded. We also excluded patients who had become lost to follow up within 30 days after the time of ED admission.

2.2 Data collection

We collected data by reviewing the electronic medical records in a retrospective manner. Data included age, gender, cancer type, cancer stage, Eastern Cooperative Oncology Group (ECOG) performance status, comorbid diseases, risk factors for PE, and laboratory variables. In our hospital, the D-dimer levels were measured for all the patients with suspected PE at ED admission. D-dimer was quantified up to 35 μg/mL and was reported as '$\geq$35 μg/mL' for values beyond. We classified patients as low and high, according to the D-dimer median value of 14.7 μg/mL. For cancer stage, localized cancer was defined as cancer is limited to the place where it started or has spread to nearby lymph nodes, tissues, or organs. Metastatic cancer was defined as cancer that has spread to distant parts of the body. For the repeated measurements, the initial values at the time of ED admission were used. PESI scores were also calculated with the initial values.

2.3 Statistics

Continuous variables were expressed as a mean $\pm$ standard deviation (SD) or median with interquartile range (IQR) if the data was skewed. Categorical variables were expressed as frequency and percentage. The continuous variables were compared between the two groups using the Student's *t*-test or Mann-Whitney U test if they were non-normally distributed. The categorical variables were compared using the chi-square test or Fisher exact test. A P-value < 0.05 was considered statistically significant. The primary outcome was 30-day mortality. A logistic regression model was used to examine the individual relationship between each variable. ECOG performance status and PESI classes were regrouped to get analyzable numbers for each group. Variables with the P-value < 0.1 in the univariate logistic regression and clinical significance were considered for inclusion in a multivariate logistic regression analysis [10]. The magnitude of association was determined by odds ratios (OR), and the corresponding 95% confidence intervals (CI) were calculated. All statistical analyses were performed using the SPSS software, version 21.0 (IBM Corp., Armonk, NY).

3. Results

Of the 1023 patients screened, we excluded 845 patients who had no evidence of PE on CT (n = 759), inactive cancer (n = 132), and follow-up loss within 30 days (n = 23). A total of 178 patients were included in this study, and 55 (30.9%) patients died within 30 days after admission.

Table 1 demonstrates the baseline characteristics of the total study subjects. The mean age was 63.9 years (SD 10.4), and the male was 52.8%. Non-survivors had worse ECOG performance scales than survivors, but the difference was not significant. Primary gastrointestinal cancers and lung cancers were dominant in 75.8%, and approximately 90% had advanced-stage cancer. The most frequent symptom was dyspnea in 78.1%. In comparison between survivors and non-survivors, there was no significant difference in age, gender, cancer types, cancer stage, and presenting symptoms. The chronic liver disease was shown more frequently in non-survivors than survivors (9.1% vs. 1.6%, P = 0.018), but there was no difference in chronic lung and renal diseases between the two groups. In the initial vital signs, non-survivors had higher pulse rates (PR) than survivors (102.2 $\pm$ 19.6 vs. 111.9 $\pm$ 18.9 beats per minute, P = 0.002). In contrast the mean values of systolic blood pressure (SBP), respiratory rate (RR), and SpO2 were similar. Two groups did not have any significant difference in history deep vein thrombosis, surgery in the previous four weeks, and the use of anticoagulants.

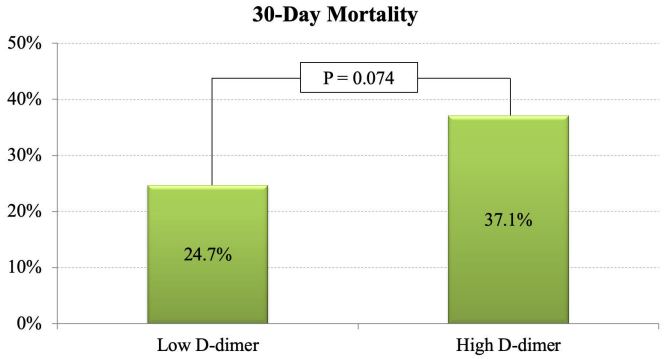

FIGURE 1. 30-day mortality according to D-dimer levels. Patients were categorized into two groups, low and high D-dimer lever, according to median value of 14.7 μg/mL.

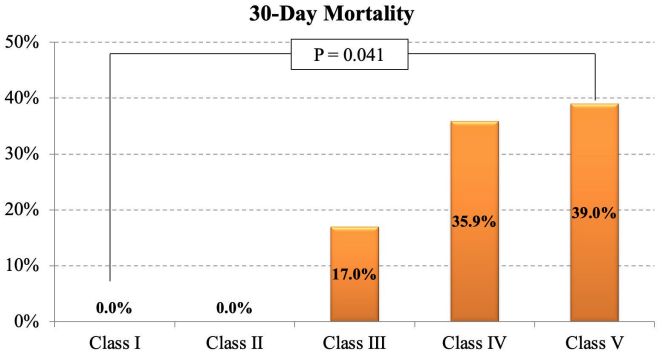

FIGURE 2. 30-day mortality according to PESI scores. PESI, Pulmonary Embolism Severity Index.

TABLE 1. Baseline characteristics.

Characteristics	Total	Survivors	Non-survivors	*P*-value
	(N = 178)	(N = 123)	(N = 55)	
Age (year), mean ± SD	63.9 ± 10.4	63.8 ± 10.5	64.3 ± 10.4	0.761
Male, n (%)	94 (52.8)	65 (52.8)	29 (52.7)	0.988
ECOG performance status, n (%)				0.123
0–1	65 (36.5)	50 (40.9)	15 (27.3)	
2	72 (40.5)	49 (39.1)	23 (41.8)	
3–4	41 (23.0)	24 (19.5)	17 (30.9)	
Cancer type, n (%)				0.743
Gastrointestinal	75 (42.1)	49 (39.8)	26 (47.3)	
Lung	60 (33.7)	43 (35.0)	17 (30.9)	
Gynecologic	12 (6.7)	8 (6.5)	4 (7.3)	
Breast	6 (3.4)	5 (4.1)	1 (1.8)	
Hematologic	6 (3.4)	6 (4.9)	0 (0.0)	
Others	19 (10.7)	12 (9.8)	7 (12.7)	
Cancer stage, n (%)				0.326
Localized	19 (10.7)	15 (12.2)	4 (7.3)	
Metastatic	159 (89.3)	108 (87.8)	51 (92.7)	
Comorbid diseases, n (%)				
Chronic liver disease	7 (3.9)	2 (1.6)	5 (9.1)	0.018
Chronic lung disease	7 (3.9)	4 (3.3)	3 (5.5)	0.485
Chronic renal failure	19 (10.7%)	14 (11.5%)	5 (9.1%)	0.795
Symptomology, n (%)				
Chest pain	22 (14.1)	17 (15.5)	5 (10.9)	0.453
Dyspnea	132 (78.1)	88 (75.9)	44 (83.0)	0.297
Hemoptysis	5 (3.9)	3 (3.1)	2 (6.1)	0.451
Unilateral leg swelling	40 (24.5)	30 (26.5)	10 (20.0)	0.370
Unilateral leg pain	19 (15.3)	14 (14.9)	5 (16.7)	0.814
Vital signs, mean ± SD				
Systolic BP (mmHg)	118.9 ± 24.7	119.6 ± 25.0	117.4 ± 24.2	0.575
Heart rate (beats/min)	105.2 ± 19.6	102.2 ± 19.2	111.9 ± 18.9	0.002
Respiratory rate (breaths/min)	22.5 ± 13.3	22.5 ± 15.6	22.3 ± 4.6	0.919
SpO2 (%)	94.8 ± 7.3	94.8 ± 7.9	94.8 ± 5.6	0.974
Past history of DVT or PTE, n (%)	25 (14.0)	17 (13.8)	8 (14.5)	0.898
Surgery in previous four weeks, n (%)	5 (2.8)	4 (3.3)	1 (1.8)	0.593
Use of anticoagulant, n (%)	19 (10.7)	10 (8.1)	9 (16.4)	0.100

BP, blood pressure; DVT, deep vein thrombosis; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation; PTE, pulmonary thromboembolism.

In a comparison of 30-day mortality, the patients with high D-dimer values had higher mortality than those with low D-dimer (37.1% vs. 24.7%, $P = 0.074$), although there was no significant difference (Fig. 1). When the total patients were categorized according to PESI scores, there were 0, 2, 53, 64, and 59 patients in PESI classes I, II, III, IV, and V, respectively. The 30-day mortality was 0/0 (0%) in class II, 9/53 (17.0%) in class III, 23/64 (35.9%) in class IV, and 23/59 (39.0%) in class V. There was a significant difference in mortality among PESI groups, as shown in Fig. 2 ($P = 0.041$).

Table 2 outlines the results of logistic regression for the 30-day mortality in the total patients. In the univariate analysis, the OR for high D-dimer values was 1.80 (95% CI 0.94–3.42, $P = 0.076$) compared to the low D-dimer. The ORs for ECOG 2 and ECOG 3/4 were 1.81 (95% CI 0.77–4.24, $P = 0.173$) and 2.60 (95% CI 1.02–6.66), respectively, compared to ECOG 0/1. For PESI scores, higher PESI classes were associated with higher mortality [OR 2.87 (95% CI: 1.19–6.90, $P = 0.019$) for

TABLE 2. Logistic regression for 30-day mortality.

	Univariate			Multivariate		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age	1.01	0.97–1.04	0.759			
Male	1.00	0.53–1.88	0.988			
Metastasis	1.77	0.56–5.60	0.331			
ECOG status						
0–1	1.00	Ref.		1.00	Ref.	
2	1.81	0.77–4.24	0.173	1.79	0.73–4.36	0.201
3–4	2.60	1.02–6.66	0.046	3.22	1.18–8.76	0.022*
High $PAaO_2$	1.74	0.83–3.65	0.142			
P/F ratio < 250	1.85	0.83–4.15	0.134			
PESI score						
Class ≤ 3	1.00	Ref.		1.00	Ref.	
Class 4	2.87	1.19–6.90	0.019	2.95	1.12–7.75	0.028*
Class 5	3.27	1.35–7.92	0.009	2.90	1.06–7.90	0.037*
High D-dimer	1.80	0.94–3.42	0.076	2.47	1.15–5.33	0.021*

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; OR, odds ratio; $PAaO_2$, Alveolar-arterial gradient; PESI, pulmonary embolism severity index; P/F ratio, arterial PO_2 divided by the FiO_2.

class IV and OR 3.27 (95% CI 1.35–7.92, $P = 0.009$) for class V]. Other parameters, including age, gender, metastatic stage, high $PAaO_2$, and P/F ratio < 250, were not associated with mortality. In the multivariate analysis, high D-dimer was an independent poor prognostic factor [OR 2.47 (95% CI 1.15–5.33), $P = 0.021$]. High PESI scores were also associated with poor prognosis [OR 2.95 (95% CI 1.21–7.75) for class IV and OR 2.90 (95% CI 1.06–7.90) for class V, $P < 0.05$ for two]. ECOG performance status 3/4 [OR 3.22 (95% CI 1.18–8.76), $P = 0.022$] was associated with higher mortality compared to ECOG 0/1, but ECOG 2 was not associated.

4. Discussion

In this study, we found that high D-dimer values, high-risk PESI scores, and poor ECOG PS are independent predictors of the short-term mortality in patients with active cancer and acute PE. The 30-day mortality was 24.7% vs. 37.1% in patients with low D-dimer and high D-dimer values. High D-dimer was associated with 2.5 times higher mortality than low D-dimer.

D-dimer is known to be one of the diagnostic parameters for PE [11, 12]. Negative D-dimer is highly specific to rule out PE [13, 14]. In addition to the diagnostic value, many studies showed that D-dimer is associated with PE outcomes [15–17]. Several studies demonstrated that D-dimer is related to thrombus burden and disease severity [18, 19]. In those studies, patients with high D-dimer were more severe and more often treated with thrombolysis. Another study showed that elevated D-dimer values are associated with high mortality in patients with PE [15, 16, 20]. In the RIETE registry, D-dimer ≥ 5 μg/mL was associated with a 2.9-fold increased risk of 3-month overall mortality with a dose-related effect [16]. Similarly, patients with D-dimer levels in the fourth quartile had an increased risk for even greater short-term death within 15 days (OR 1.8) [17]. However, most of those studies focused on the association of D-dimer values with mortality in non-cancer patients with PE. There is a lack of studies on the prognostic accuracy of D-dimer in cancer patients with PE. In the current study, we found that elevated D-dimer was an independent predictor of short-term mortality in patients with active cancer and acute PE.

In addition to D-dimer, PESI was also an independent predictor of 30-day mortality in cancer patients with PE. In the current study, approximately 70% of the patients had high-risk PESI scores, while no one had very low-risk PESI scores and only two low-risk scores. The two patients in class II were alive at 30 days after admission. Among patients with PESI class III or higher, the mortality rates were escalated as the PESI scores increased. Classes IV and V were associated with approximately three times higher mortality for each compared to class III or lower. According to PESI scores, the patients' severity in this study deviated toward the high risk rather than evenly distributed. Nevertheless, high-risk PESI scores were significantly associated with three times higher mortality than in intermediate-risk PESI scores. In the previous studies, PESI tended to have a discriminatory power in cancer patients with PE [21]. However, the prognostic accuracy of PESI in patients with cancer diminished compared with its accuracy in the whole population [8]. Similarly, it was demonstrated that PESI showed high sensitivity but low specificity for 30-day mortality in cancer patients with PE [7, 22]. Weeda *et al.* [23] reported that cancer-specific prognostic models, including POMPE-C, RIETE, and Font criteria, show better prognostic accuracy than generic tools, including PESI. Therefore, further studies are necessary to validate the accuracy of PESI in patients with cancer and acute PE. Furthermore, more efforts

should be made to look for reliable predicting factors for cancer patients.

Thus far, several studies presented prognostic models for mortality in cancer patients with acute PE [8, 24, 25]. Among them, the POMPE-C tool included eight predictors [8]. Among 50/182 patients with POMPE-C <5% in the validation cohort, no patient died within 30 days. The c-statistics of POMPE-C was significantly higher than that of PESI (0.84 vs. 0.68) for 30-day mortality. In the RIETE registry, a prediction model was developed with six clinical variables reflecting underlying cancer conditions for cancer patients with acute PE [26]. The 30-day mortality was 4.4% and 0%, respectively, in the internal and external validation cohorts of RIETE among patients classified as low risk. However, the c-statistics of RIETE was 0.76, which was not strong enough. In a comparison study with four prognostic scales (PESI, Geneva Prognostic Score, POMPE-C, and RIETE registry), POMPE-C showed the best results in identifying a low-risk group [26]. However, because the POMPE-C tool contains a complex equation, it is not easy to measure it without a calculator. The multicenter EPIPHANY study showed that VTE history, upper gastrointestinal cancers, metastatic disease, cancer progression, performance status, arterial hypotension <100 mmHg, heart rate >110/min, SpO2 <90%, and suspicious PE were associated with the 30-day mortality [27]. However, to the best of our knowledge, there was no cancer-specific prognostic model that contained D-dimer. D-dimer was shown to be associated with long-term prognosis in cancer patients regardless of PE presence in many studies [28, 29]. As indicated in this study, it was suggested that D-dimer is one of the reliable prognostic factors in cancer patients with PE in addition to performance status and vital signs in PESI.

In the current study, the 30-day mortality was 30.9%. Cancer is known to increase the mortality of acute PE [18]. Similarly, cancer patients with venous thromboembolism (VTE) have been shown to have a poorer prognosis compared to those without VTE [19]. Cancer patients with acute PE had higher mortality compared to non-cancer patients in recent studies [20, 21]. In a meta-analysis, the overall 30-day mortality rate was 2.3% in the low-risk group and 11.4% in the high-risk group among cancer patients with incidental PE [17]. In the RIETE database, those with cancer-associated PE showed 12.5% of 30-day mortality [20]. In the EPIPHANY study, the mortality rate was 14% in 30 days. However, the mortality risk increased in inpatient settings, symptomatic or suspicious PE, and abnormal vital signs [21, 22]. In the current study, the enrolled patients had inpatient settings and suspicious PE. Therefore, it may explain that the patients fall into a group at higher risk than those with asymptomatic PE or incidental PE.

This study has several limitations. First, as described above, this study was conducted at a single tertiary university hospital. Therefore, the enrolled patients tended to be more severe based on PESI scores compared to the previous studies. This phenomenon was also seen in other studies that risk-stratified cancer patients with PE using generic tools [26]. Considering that cancer patients are at high risk, cancer-specific tools may categorize the patients' severity more appropriately rather than generic tools. Second, we had the measurement limitations for D-dimer values, as illustrated previously. The reference values may vary depending on the target population. It may be more helpful to determine the cut-off value of D-dimer for poor outcomes in cancer patients with PE. Lastly, this was a retrospective study. Data collection might be limited. However, there were few missing data because we used our standardized protocol for cancer patients with acute PE.

5. Conclusions

Our study suggested that D-dimer may be a reliable predictor of mortality in patients with active cancer and acute PE, as well as ECOG PS and PESI. Besides performance status and variables in PESI, D-dimer may improve the prognostic accuracy of the existing cancer-specific prognostic tools.

AUTHOR CONTRIBUTIONS

EJH: analysis and interpretation of data, and critical writing. HK, BC, and YJK: analysis and interpretation of data. YSL: conception and design, analysis and interpretation of data, critical writing and final approval.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The institutional review board of Asan Medical Center approved our study (Study number: 2017-1122), and informed consent was waived because of its retrospective design. The research is in accordance with the Helsinki Declaration of 1975, as revised in 2010.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY

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

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