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Derivation and validation of a multivariate model to predict mortality from pulmonary embolism with cancer: the POMPE-C tool

Jeffrey A. Kline¹, Pierre-Marie Roy², Martin P. Than³, Jackeline Hernandez¹, D. Mark Courtney⁴, Alan E. Jones⁵, Andrea Penazola⁶, and Charles V. Pollack Jr.⁷

¹Department of Emergency Medicine 1000 Blythe Boulevard MEB 3rd floor, Room 306 Charlotte, NC 28203 ²Emergency Department CHU Angers, Université d'Angers, France LUNAM Université, Angers, France PMRoy@chu-angers.fr ³Christchurch Hospital, Christchurch, New Zealand martin.than@cdhb.govt.nz ⁴Department of Emergency Medicine Feinberg School of Medicine, Northwestern University, Chicago, IL. mcourtney@nmff.org ⁵Department of Emergency Medicine University of Mississippi Medical Center Jackson, MS aejones@umc.edu ⁶Andrea Penaloza, MD Emergency Department Cliniques Universitaires St-Luc 10 Av. Hippocrate 1200 Brussels Belgium andrea.penaloza@uclouvain.be ⁷Department of Emergency Medicine Pennsylvania Hospital University of Pennsylvania Health System 800 Spruce St Philadelphia, PA 19107 cvpollack@gmail.com

Abstract

Background—Clinical guidelines recommend risk stratification of patients with acute pulmonary embolism (PE). Active cancer increases risk of PE and worsens prognosis, but also causes incidental PE that may be discovered during cancer staging. No quantitative decision instrument has been derived specifically for patients with active cancer and PE.

Methods—Classification and regression technique was used to reduce 25 variables prospectively collected from 408 patients with AC and PE. Selected variables were transformed into a logistic regression model, termed POMPE-C, and compared with the pulmonary embolism severity index (PESI) score to predict the outcome variable of death within 30 days. Validation was performed in an independent sample of 182 patients with active cancer and PE.

Results—POMPE-C included eight predictors: body mass, heart rate >100, respiratory rate, SaO₂%, respiratory distress, altered mental status, do not resuscitate status, and unilateral limb

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Correspondence to: Jeffrey A. Kline.

jkline@carolinas.org.

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swelling. In the derivation set, the area under the ROC curve for POMPE-C was 0.84 (95% CI: 0.82-0.87), significantly greater than PESI (0.68, 0.60-0.76). In the validation sample, POMPE-C had an AUC of 0.86 (0.78-0.93). No patient with POMPE-C estimate $\leq 5\%$ died within 30 days (0/50, 0-7%), whereas 10/13 (77%, 46-95%) with POMPE-C estimate $>50\%$ died within 30 days.

Conclusion—In patients with active cancer and PE, POMPE-C demonstrated good prognostic accuracy for 30 day mortality and better performance than PESI. If validated in a large sample, POMPE-C may provide a quantitative basis to decide treatment options for PE discovered during cancer staging and with advanced cancer.

Keywords

Pulmonary embolism; outpatient; risk-stratification; Risk stratification; malignancy; prognosis; decision rule; treatment

INTRODUCTION

Risk stratification of acute pulmonary embolism (PE) generally refers to the use of objective criteria to predict the probability of clinical deterioration or death during a short-term follow-up period after diagnosis. The majority of published literature focuses on categorizing PE patients as low, moderate, or high risk of death, respiratory failure, or circulatory failure during the inpatient period or up to 30 days.^{1,2} Methods of PE risk stratification include echocardiography, biomarkers, and scoring systems comprising clinical variables obtained from history and physical examination. In the emergency department setting, the category of risk can provide an objective basis to decide how and where to treat the patient.¹⁻⁴ Patients with active malignancy represent a subgroup at particularly high risk both of developing PE and of having an increased risk of death after diagnosis of PE, when compared with patients who have no history of cancer or a past medical history of cancer in remission at the time of PE diagnosis.⁵⁻¹² Patients with cancer and their oncologists also face the conundrum of how and where to treat unsuspected PE that is incidentally discovered on approximately 2% of computerized tomography pulmonary angiography scans ordered for the purpose of cancer staging or surveillance.^{13,14} It can be reasonably hypothesized that many cancer patients with these incidentally discovered PE desire to be treated at home, but current literature lacks a decision tool to quantify the short-term prognosis for patients with active cancer and PE.¹⁵ The most widely validated scoring system for PE is the PESI tool, and a recent randomized trial demonstrated equivalent outcomes for patients with a low-risk PESI score randomized to have treatment initiated in the outpatient setting compared with the inpatient setting.¹⁶ However, PESI has not been tested specifically in patients with active cancer or PE. The objective of this study was to derive a multivariate, quantitative decision tool to assess the probability of death within 30 days among patients with active cancer who present in the outpatient environment with PE, compare its performance to PESI, and to perform initial validation studies of its prognostic accuracy using four independent samples of patients with active cancer and PE and to create a web-based electronic userform of the model for future research use.

METHODS

The prediction instrument was derived as a preplanned secondary analysis of the multicenter EMPEROR (Emergency Medicine Pulmonary Embolism in the Real World) Registry dataset, which was collected in 22 community and academic emergency departments in the United States, from January 1, 2005 until December 29, 2008. The methods of data collection have been reported elsewhere.¹¹ Briefly, participating sites in EMPEROR prospectively collected 264 data elements on 1,880 patients diagnosed with PE in the

emergency department (ED), including 30 day outcomes. The data collection instrument was designed to collect detail about risk factors for PE as well as data known to predict adverse outcomes. The form included demographic data, vital signs, comorbidities, risk factors for thrombosis, values of biomarkers including troponins and natriuretic peptides, echocardiographic results, and radiographic results. For many of these elements, additional detail was collected. Importantly, the malignancy variable was further divided into active cancer (defined as metastatic disease or cancer under the care of an oncologist), metastatic malignancy, or inactive cancer (defined as in remission by the patient and no longer under the active care of an oncologist). That level of detail was collected in response to multiple studies that found that active cancer, but not cancer in remission, is a risk factor for death from PE.⁵⁻¹² We determined which patients with active cancer and PE discovered on imaging performed for other reasons such as staging or cancer surveillance using a retrospective chart review for the explicit definition of PE discovered on a CT scan done for initial staging of newly diagnosed cancer. In this subanalysis, we did not include patients who had a CT scan done to evaluate for possible worsening of known cancer, or abdominal CT scans with intravenous contrast that showed a pulmonary vascular filling defects in slices incidentally found in the lower lung zones. For a separate subanalysis, we also identified patients who had PE diagnosed in the ED and were discharged from the ED to home. Patients were followed prospectively for in-hospital adverse outcomes and for survival until 30 days after the ED visit.

Selection of predictor variables

The selection of variables, their analysis, model construction, goodness of fit, and validation were performed in accordance with published standards.¹⁷ We first conducted a comprehensive review of published studies that reported significant predictors of adverse outcome of PE.¹⁵ This review suggested 24 potential independent variables (appendix). The dependent variable was mortality at 30 days. The 24 potential predictor variables were screened for inclusion in the multivariate model using two methods: 1. Data were first analyzed with classification and regression technique (CART, Salford Systems Inc, San Diego, CA)¹⁸; 2. Bivariate analysis was then performed to screen for potentially important differences in means (using unpaired t-test) or frequency (using Chi square) for the 24 variables between survivors and decedents with variables. For a variables to move forward to the multivariate testing state, the variable had to have both a relative weight >0 from CART and $P < 0.1$ from bivariate analysis.. Retained continuous predictor variables (e.g., heart rate) underwent receiver operating characteristic (ROC) curve analysis to determine the cutoff corresponding to the lowest likelihood ratio negative for prediction of death at 30 days.

Derivation of the multivariate model

Retained predictors were then entered into a second logistic regression analysis, with the independent predictor being death at 30 days. Model fit was assessed by P values from the Pearson's goodness of fit Chi-Square, Hosmer Lemeshow test, the Pseudo (McFadden) R-square and area under the ROC curve in the derivation dataset (C statistic).^{19;20}

Preliminary validation of the model

We tested the prognostic accuracy of the derived instrument in six prospectively collected samples of patients diagnosed with PE in the ED. These studies included one multicenter sample from the US,²¹ three single-center samples from the US,^{22;23} one single center registry from New Zealand and one multicenter sample from Europe.²⁴ The clinical data for these samples were all collected prospectively by qualified research associates who had standardized training in data definitions. Data came from the most accurate source or combination of sources which included the patient in real time, the patient's primary

physician, the emergency care providers and the medical record. These databases were reduced to patients with active cancer and PE, and the percentage mortality estimate (i.e., the predicted probability of death within 30 days) was then determined by taking the antilog and solving the logistic regression equation for the P term. Using a criterion standard of 30 day all-cause mortality, prognostic accuracy was assessed from the area under the curve (AUC) for the ROC curve, with the assumption that lower limit 95% confidence interval for the AUC greater than 0.5 indicated potential validity. We also calculated the PESI score to all 1880 patients with PE in the derivation dataset and then for the 408 patients with PE and active cancer, and compared its prognostic accuracy to POMPE-C based upon AUC under the ROC and the percentage of the sample with a low risk PESI score (<66 points) and the 30 day rate of death in this low risk group.

Creation of web-based prototype

The validated model was then converted to an electronic form by creating an input form in Visual Basic designed to explain and capture each variable from the user and output the numeric probability of death using the derived and validated logit equation. The form was then uploaded to a server and a universal resource locator address assigned to allow public access.

RESULTS

Candidate variable selection

To assess the potential significance of all 25 predictor variables, the original EMPEROR database (N=1,880) was reduced to patients with active cancer and PE, excluding patients who had comfort care status only. This process excluded 1,346 patients with no history of cancer, 108 who had a history of cancer thought to be in remission, and 18 patients with active cancer and comfort care only status, leaving 408 patients with active cancer, of whom 51 (12.5%) died within 30 days of any cause. Table 1 lists the means and frequency data for the 25 predictor variables for survivors compared with patients who died for the 408 patients with active cancer and PE. Table 1 also shows the relative weights of each predictor determined from CART and the bivariate P values. Eight variables had a non-zero weight from CART and a P<0.1 from either the unpaired t-test or Chi-Square and were thus retained for the multivariate model.

Derivation of the multivariate model

The retained eight variables were: 1. Body weight, 2. Respiratory rate, 3. SaO₂%, 4. Heart rate over 99 beats/min, 5. Altered mental status, 6. Respiratory distress, 7. Do not resuscitate status, 8. Unilateral limb swelling. The first three variables are entered as continuous data and the last five variables are entered as dichotomous values. These variables and their definitions are presented in Table 2. In logistic regression analysis, all 8 variables were significant predictors of death, as demonstrated by the lower limit of the 95% confidence interval for the odds ratios associated with each variable (Table 2). The Pearson Chi-square goodness of fit P value was 0.94, the Hosmer Lemeshow P value was 0.48, the McFaddens' R² was 0.21. When the model was applied to the 408 patients with active cancer and PE in the derivation dataset, the AUC under the ROC was 0.84 (95% CI: 0.78 to 0.89). When applied to the entire dataset of 1880 patients with PE, the model had an AUC for the ROC of 0.80 (0.76 to 0.85). When applied to the 108 patients with a history of inactive cancer, the derived model had an AUC of 0.85 but because only seven of these 108 patients died within 30 days, the confidence intervals were wide (0.66 to 1.0). Taken together, these data indicate reasonable model fitness and predictive accuracy in the derivation set of patients with cancer and PE.^{19;20}

Prognostic accuracy of PESI

When applied to the entire 1880 patients in the derivation sample with PE, the PESI score demonstrated good overall diagnostic accuracy, with an AUC of 0.79 (0.75 to 0.83), and 610/1880 patients (34%) had PESI<66, and only 5/610 with PESI<66 died within 30 days, confirming the good overall performance of PESI as tool to identify low-risk patients with PE in the heterogenous derivation sample. However, when PESI was applied to the 408 patients with active cancer and PE, the AUC was significantly reduced to 0.68 (0.60 to 0.76) and only 3 patients (0.8%) had PESI<66. None of these three patients died within 30 days. Examination of higher cutoffs for PESI to allow a larger fraction of the population to be deemed low risk caused an unfavorable increase of inclusion of patients who died within 30 days. For example, 111/408 patients (27%) with active cancer and PE had a PESI score <100, and 8/111 (7%) died within 30 days.

Preliminary validation of the model

The six validation samples contained a total of 14,121 patients, of whom 202 had active cancer and PE+. The database from Europe also did not explicitly record the terms for altered mental status or do not resuscitate but in accordance with original inclusion and exclusion requirements for study enrollment, these were assumed to be absent for all patients. Data were missing [body mass (12), respiratory rate (5) and pulse oximetry (3)] in 20 patients, seven from the European sample and three from the New Zealand sample and these 20 patients were excluded. Thus, 182 patients had complete data, of whom, 27 died within 30 days (mortality 15%, 95% CI: 10 to 21%). Table 3 presents the mean percentage mortality estimate for patients from the individual studies comprising the total validation sample, stratified by survival status at 30 days. Figure 1 shows the ROC curve derived in the aggregated sample of all 182 validation patients. The area under the curve was 0.86 (95% CI: 0.78 to 0.93) indicating good overall discriminatory value in the validation sample. Figure 2 shows a frequency dot plot of each probability estimate, stratified by survival status at 30 days.

The percentage estimates of mortality from the logistic equation were examined for cutoffs that predicted a very low and very high probability of death within 30 days for each patient in the validation sample. The cutoff of 5% produced a very low probability of death. In the validation sample, 50 patients (27%) of patients in the validation set with a mortality estimate of 5% or less died within 30 days. Stated another way, all patients who died had a mortality estimate >5%, indicating a sensitivity of 27/27 (100%, 95% CI: 88 to 100%) and 106 patients who survived >30 days had a mortality estimate >5% (specificity 50/156 = 32%, 95% CI: 25 to 40%), producing a posterior probability of death equal to 0/50 (95% CI: 0 to 7%). The cutoff of 50% produced a very high probability of death; 13 patients had a mortality estimate >50%, and 10/13 died (posterior probability 73%, 95% CI: 46 to 95%).

From both the derivation set and the validation set, we identified 16 patients whom we confirmed to have PE discovered incidentally, of whom none (0%) were discharged from the emergency department and one died within 30 days, but after hospital discharge. The mean POMPE-C score for the 15 patients who survived was 5±5%, and 9 of 15 had a score <5%. The patient who died had a POMPE-C score of 46% and was the only patient with a do not resuscitate order. We also identified 19 other patients who were discharged from the ED, none of whom died within 30 days. The mean POMPE-C for these patients was 6±8% and 14 of 19 had a score ≤5%.

Web-based prototype

The electronic input form was programmed to collect and transform the five dichotomous and three continuous variables into a numeric probability (P) of death using the formula $P =$

$100 * (1 - 1 / (1 + \text{Exp}(3.718 + \text{DNR} * 1.551 + \text{RespDist} * 0.800 + \text{ULS} * 0.734 + \text{AMS} * 1.473 + \text{HR} + (\text{RR} * 0.044) + (\text{Sao2} * -0.063) + (\text{bodyweight} * -0.012))))$). The resultant prototype device can be tested at <http://www.studymaker.com/projects/pompe/index.php>

DISCUSSION

We derived POMPE-C to address an unmet need for an accurate prognostic tool in patients with acute PE and active cancer. The POMPE-C tool demonstrated good overall diagnostic accuracy in both the derivation dataset (area under the receiver operating characteristic curve = 0.84, 95% CI: 0.78 to 0.89) and the validation sample (area = 0.86, 0.78 to 0.93) of patients with PE and active cancer.²⁵ Moreover, in the validation sample, 27% (n=50) of patients had a POMPE-C estimate $\leq 5\%$, and none of these 50 died within 30 days (0/50, 95% CI: 0 to 7%), suggesting clinical utility to the 5% threshold to define low risk in a future clinical trial designed to increase home treatment of PE for cancer patients. We chose the 30 day mortality endpoint because this is the primary endpoint for the PESI score, and Aujesky et al has demonstrated that patients with PESI <66 generally have good outcomes when treated as outpatients. In patients with active cancer, the prognostic accuracy of the PESI was significantly degraded when compared with its accuracy in the whole derivation population, and PESI demonstrated a significantly lower area under the receiver operating characteristic curve than POMPE-C in the active cancer subgroup. Only 3/408 (0.8%) of patients with active cancer and PE had a low risk PESI score (<66 points), and raising the low-risk PESI threshold to 100, such that 27% of the derivation group was considered low risk, led to an unacceptable 7% death rate at 30 days. Taken together these data indicate that POMPE-C can accurately prognose PE in patients with active cancer, and indicate that POMPE-C may be more accurate than PESI for this goal.

A primary motivation of this study stems from the need for a validated clinical pathway in the management of cancer patients who, in undergoing staging imaging that includes contrast-enhanced pulmonary vasculature imaging, are incidentally discovered to have PE. Prior work has suggested that this occurs in approximately 1.5-2.5% of such scans.^{13;14} Published evidence suggests that not all incidental clots are benign, especially in the case of larger clots.^{26;27} Following the work of Aujesky et al, the goal of this effort is to use POMPE-C in a clinical trial of outpatient management for low risk patients with active cancer and PE, including those with incidentally discovered PE, and with a POMPE-C mortality estimate of 5% or less.¹⁶ Additionally, for selected patients with advanced cancer and PE, an accurate quantitative prediction instrument may better align the care patients want with the care they receive near the end of life.

The scope and selection of prediction variables warrants specific consideration. First, the data the EMPEROR registry was designed to include including specific variables relevant to prognosis of cancer patients with PE. We used a rigorous data mining process, including the combined use of stochastic methods and classification and regression to enhance the sensitivity and specificity of the final model.²⁸ This process resulted in the selection of eight predictor variables, five of which we submit are fairly well recognized general predictors of outcome from PE (heart rate, respiratory rate, SaO2%, respiratory distress, and altered mental status), as well as three predictors that appear to be more specific to patients with cancer and PE (body weight, do not resuscitate status, and unilateral limb swelling). Body mass probably serves as a very crude but reliable surrogate to the stage of cancer, and body mass was chosen over body mass index (BMI), because it is simpler and BMI did not improve the model fitness. The “do not resuscitate” (DNR) status can be viewed as both a predictive and deterministic variable. However, from a probabilistic standpoint, two facts remain true: 1. When a patient with cancer is diagnosed with PE, the patient's DNR status can be determined as either positive or negative, and 2. The DNR status strongly influences

outcome. Thus, we argue that a decision rule that fails to advantage itself of the predictive power of DNR status will also fail to be as accurate as is reasonably possible. Unilateral limb swelling probably reflects the worsened prognosis of concomitant DVT either in the leg or arm, the latter of which is often associated with an indwelling catheter, which may imply additional vulnerability such as ongoing chemotherapy. Several registries have demonstrated increased risk of death from PE with concomitant DVT and this factor is present in the Geneva risk score.²⁹

The selected eight variables were entered into a logistic regression instead of a classification tree as the final model as the goal was to produce a numeric percentage probability estimate of death, and because logistic regression often produces better results in validation in studies of short term prognosis of acute cardiovascular disorders.^{30;31} The resulting equation found all variables significant, and the final model demonstrated good fit in the derivation set, but most importantly had good accuracy in independent samples that included patients from multiple countries. Taken together, these methods should confer durable external validity to the model.

Limitations to this study include the lack of a large prospective validation sample, which will be the next research step.³² Neither EMPEROR nor any of the validation studies were designed to capture patients with incidentally discovered PE on staging CT scans. Nonetheless, we identified 16 patients with PE discovered in this situation, as well as 19 other patients who were discharged from the ED, and POMPE-C estimated a low risk of death (i.e., $\leq 5\%$) in two-thirds of these patients. The POMPE-C model lacks information about malignancy type and staging because they were not collected in the derivation sample. We believe these variables should be collected in a larger validation study and then tested in simulation analyses to determine if they can improve the already good diagnostic accuracy of POMPE-C. We defined active cancer using similar language employed by the Well's score for pretest probability assessment for PE, although we acknowledge that distinguishing active versus inactive cancer will inherently have some ambiguity especially in the ED setting. This concern is mitigated somewhat because the area under the ROC for POMPE-C was 0.85 for patients with inactive cancer, although the confidence intervals were very wide (0.66 to 1.0). Some users may prefer to use an integer-based scoring system, derived from the coefficients taken from a logit equation that uses only dichotomized variables. However, in trial derivation, the process of dichotomizing respiratory rate, pulse oximetry, and body weight caused a loss of both precision and accuracy. The creation of a web-based userform fits into the larger initiative of many health care systems to convert medical records into an electronic format. Moreover, our prior published experience has suggested that emergency medicine clinicians frequently commit errors in their recall and use of decision rules for pulmonary embolism.^{33;34}

Conclusion

This study reports the derivation and initial validation of an eight variable quantitative decision rule that demonstrated good overall accuracy in predicting all-cause, near-term mortality for patients with active cancer and acute pulmonary embolism. Further validation in a larger sample of patients with active cancer and PE will be necessary.

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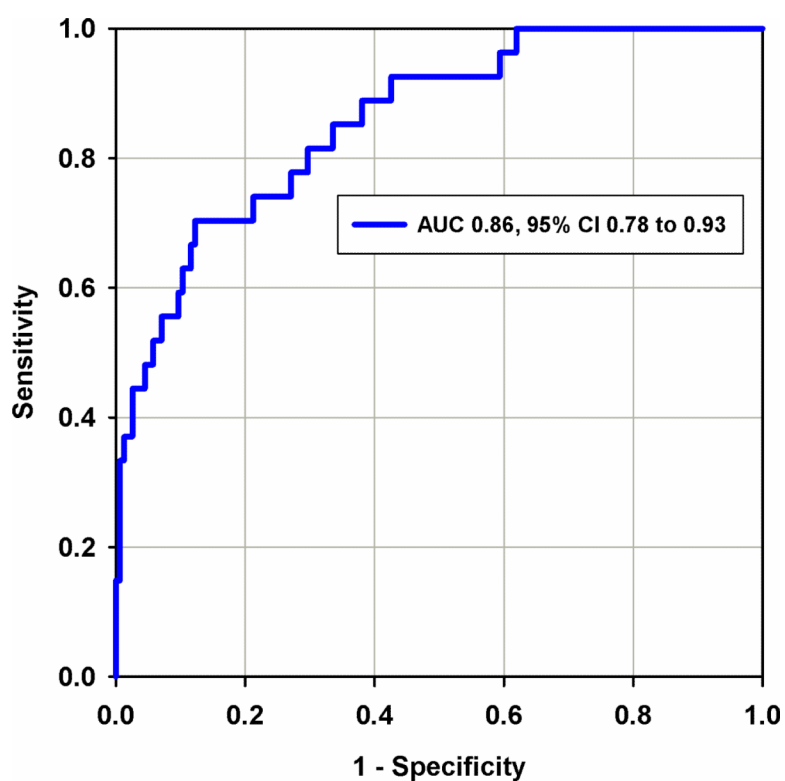


Figure 1. Receiver operating characteristic curve using the percentage probability estimate of mortality from the logistic regression equation as the diagnostic test, and the outcome was 30 day mortality in the validation sample.

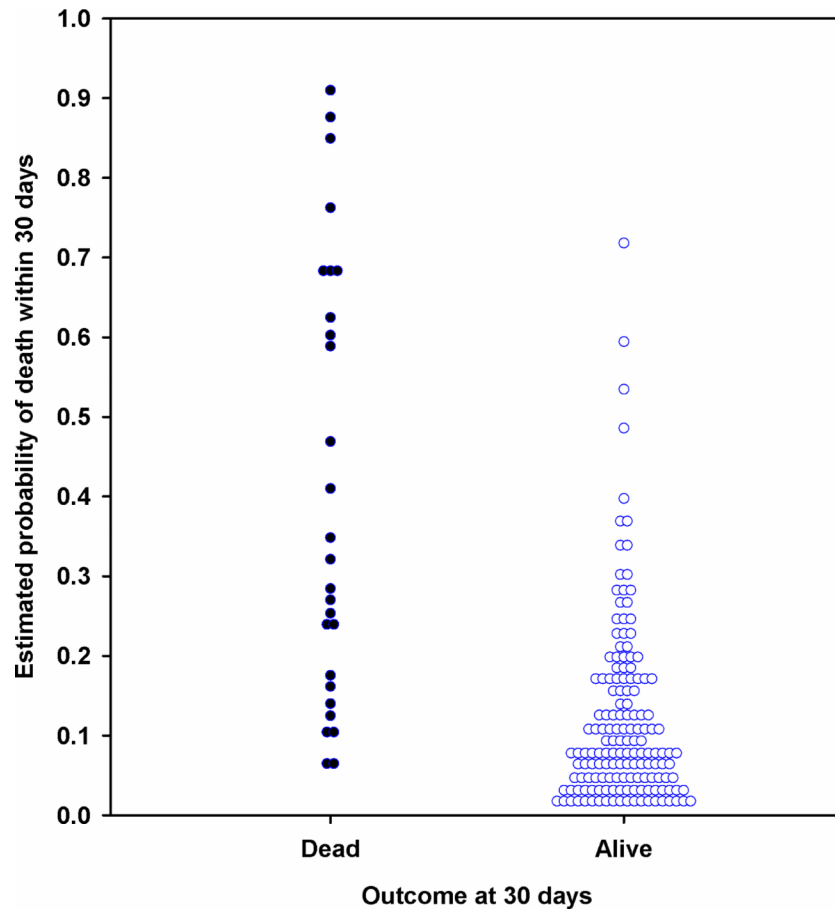


Figure 2.

Dot plot of the estimated probability of death from the logistic regression equation (Y axis), stratified according to survival status at 30 days (X axis).

Table 1

Results of bivariate and CART analysis on 25 candidate predictor variables in the derivation population (N=408 with active cancer and PE)

Predictor variable	Survive d > 30 days	SD or %	Death within 30 days	SD or %	P value (t-test or Chi-Square)	CART relative weight
Survival status	357	88%	51	13%	NA	NA
Age (years)	62	15	63	13	0.716	8.6
Systolic blood pressure (mm Hg)	128	25	124	26	0.342	7.2
Body weight (pounds)	180	49	158	40	0.004	97.8
Heart rate (beats/min)	97	21	105	22	0.009	23.9
Respiratory rate (breaths/min)	21	6	24	8	0.004	34.1
SaO ₂ (%)	95	5	92	7	0.000	100
Hemoglobin	12.0	2.4	11.4	2.4	0.119	0
Creatinine	1.1	0.7	1.0	0.8	0.937	0
White blood count	11.8	34.6	11.7	6.5	0.985	0
Male gender	181	51%	30	59%	0.270	0
Respiratory distress	68	19%	21	41%	0.003	64.8
Syncope	18	5%	2	4%	0.739	0
PE most likely diagnosis	70	20%	6	12%	0.178	0
Altered mental status	14	4%	8	16%	<0.001	30.3
Do not resuscitate status	13	4%	10	20%	<0.001	45.2
Immobilized >72 h	20	6%	5	10%	0.242	0
Hospitalization within previous week	104	29%	13	25%	0.591	0
Prior history of lung disease*	40	11%	7	14%	0.598	0
Prior history of heart failure	16	4%	3	6%	0.657	0
Other comorbidity	95	27%	11	22%	0.442	0
Indwelling venous catheter	45	13%	8	16%	0.540	0
Surgery within previous month	47	13%	3	6%	0.138	0
Prior History of pulmonary embolism	8	2%	3	6%	0.133	0
Unilateral limb swelling	69	19%	16	31%	0.048	7.2
Biomarker or echocardiography abnormal+	79	34%	16	46%	0.198	0

Abbreviations: CART-classification and regression tree analysis

Table 2

Odds ratios for the eight predictor variables from logistic regression

Variable	Coefficient	Odds Ratio	Bias corrected 95% CI
Intercept	3.718		
Patient weight (lb) ¹	1.551	0.99	0.98 to 1
Highest respiratory rate (breaths/min) ²	0.7996	1.05	1.01 to 1.09
SaO2 (%) ³	0.734	0.94	0.89 to 0.99
Heart rate >99 beats/min ⁴	1.473	2.8	1.38 to 5.64
Altered mental status ⁵	1.027	4.36	1.47 to 13
Respiratory distress ⁶	0.044	2.22	1.12 to 4.43
Do not resuscitate status ⁷	-0.063	4.72	1.75 to 12.76
Unilateral limb swelling ⁸	-0.0116	2.08	1 to 4.36

Variable definitions:

¹Body weight measured or by patient's estimate²Highest documented respiratory rate within previous six hours³Most recent pulse oximetry measured with patient breathing room air.⁴Positive if heart rate documented over 99 beats/min in previous six hours.⁵Positive if patient has acute impairment in consciousness, new disorientation, delirium, or confusion⁶Positive if the patient shows obvious anxiety from dyspnea or evidence of increased work of breathing⁷Positive for new or existing verbal or written desire of patient to not be resuscitated from death⁸Positive for either a leg or arm has new, presently noticeable swelling causing it to be asymmetrical compared with the contralateral limb.

Table 3

Description of validation samples

Source	Description *	N **	Outcome, active cancer, PE+	Mean estimate of mortality probability
Kline et al 2006, USA	Single center, prospective study of PE prognosis (N=200, all PE+)	19	Survived > 30 days Died within 30 days	18 1
Kline et al 2007, USA	Single center, prospective study of PE diagnosis (N=178, 24 PE+)	9	Survived > 30 days Died within 30 days	6 3
Courtney et al 2009, USA	Multicenter prospective study of PE diagnosis (N=7,940, 481 PE+)	70	Survived > 30 days Died within 30 days	62 8
Kline et al 2010, USA	Multicenter prospective study of PE diagnosis (N=702, 114 PE+)	12	Survived > 30 days Died within 30 days	10 2
Than 2011, New Zealand	Single center, prospective study of PE diagnosis (N=2,134, 103 PE+)	22	Survived > 30 days Died within 30 days	14 8
Roy et al 2009, Europe	Multicenter prospective study of PE diagnosis (N=3,174, 661 PE+)	50	Survived > 30 days Died within 30 days	45 5
Total		182	Survived > 30 days Died within 30 days	156 27
				12% 44%

* PE+ refers to image-proven PE diagnosed at index visit; excludes patients with isolated DVT or PE diagnosed on follow-up

** number with active cancer and PE