ORIGINAL ARTICLE

Clinical prediction rules for mortality in patients with pulmonary embolism and cancer to guide outpatient management: a meta-analysis

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Essentials

- Clinical prediction rules (CPRs) can stratify patients with pulmonary embolism (PE) and cancer.
- A meta-analysis was done to assess prognostic accuracy in CPRs for mortality in these patients.
- Eight studies evaluating ten CPRs were included in this study.
- CPRs should continue to be used with other patient factors for mortality risk stratification.

Summary. *Background:* Cancer treatment is commonly complicated by pulmonary embolism (PE), which remains a leading cause of morbidity and mortality in these patients. Some guidelines recommend the use of clinical prediction rules (CPRs) to help clinicians identify patients at low risk of mortality and therefore guide care. *Objective:* To determine and compare the accuracy of available CPRs for identifying cancer patients with PE at low risk of mortality. *Methods:* A literature search of Medline and Scopus (January 2000 to August 2017) was performed. Studies deriving/validating ≥ 1 CPR for early post-PE all-cause mortality were included. A bivariate, random-effects model was used to pool sensitivity and specificity estimates for each CPR. Traditional random-effects meta-analysis was performed to estimate the weighted proportion of patients deemed at low risk of early mortality, mortality in low risk patients and odds ratios for death compared with higher-risk patients. *Results:* Eight studies evaluating 10 CPRs were included. The highest sensitivities were observed with Hestia (98.1%, 95% confidence interval [CI] = 75.6–99.9%) and the EPIPHANY index (97.4%, 95% CI = 93.2–99.0%); sensitivities of remaining rules ranged from 59.9 to 96.6%. Of the six CPRs with sensitivities ≥ 95%, none had specificities > 33%. Random-effects meta-analysis suggested that 6.6–51.6% of cancer patients with PE were at low risk of mortality, 0–14.3% of low-risk patients died and low-risk patients had a 43–94% lower odds of death compared with those at higher risk. *Conclusions:* Because of the limited total body of evidence regarding CPRs, their results, in conjunction with other pertinent patient-specific clinical factors, should continue to be used in identifying appropriate management for PE in patients with cancer.

Keywords: decision support techniques; mortality; neoplasms; pulmonary embolism; risk assessment.

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Introduction

Pulmonary embolism (PE) is a common occurrence, affecting 66 per 100 000 adults annually in the USA [1]. Patients with cancer, especially those on chemotherapy, are at a higher risk of an event than the general population as a result of patient-, cancer- and treatment-related factors [2,3]. Thrombotic events in cancer patients also confer a poor prognosis [4] and in ambulatory patients receiving cancer chemotherapy represent the second leading cause of death [5]. Given the hypercoagulable state of patients with cancer, applying venous thromboembolism (VTE)-related care recommendations for a general (i.e. non-cancer) population to those with malignancy may be inappropriate. Therefore, there is a need for cancer-specific VTE guidelines, resources and data [3,6]. This need has resulted in the creation of cancer-specific VTE-related tools such as the Khorana score, which predicts the risk of VTE in solid tumor and lymphoma patients initiating chemotherapy [7]. Although extensive work has been carried out in evaluating the VTE risk of patients with cancer [3,6,8], there is a paucity of data on the prognostication of adverse outcomes when these patients do experience an event.

Patients with cancer and PE are at an increased risk of early all-cause mortality and adverse outcomes [4,9–12]. Accurate identification of patients at low and higher risk of these outcomes, such as post-PE mortality, can assist in providing more appropriate levels of care tailored to the patient, particularly the safe administration of generally more affordable outpatient care. Some guidelines recommend the use of clinical prediction rules (CPRs) to help in this identification and recommend that patients with low risk of PE and adequate home circumstances be considered for home or early discharge treatment [3,13]. Less intensive care for low-risk patients can decrease the undue use of healthcare resources while still providing high-value care. Alternatively, patients at higher risk of adverse outcomes may receive more intensive care as appropriate. Many generic (i.e. non-cancer-specific) CPRs include cancer as a variable [14–17] and may inappropriately suggest the need for higher levels of treatment. Currently, no single CPR has been shown to be superior in stratifying patients with cancer who develop a PE. Thus, a systematic review and bivariate meta-analysis was performed to (i) identify CPRs for early post-PE all-cause mortality derived from and/or validated in patients with cancer, (ii) assess the prognostic accuracy of such CPRs and (iii) determine the proportion of low- and higher-risk patients as defined by the CPRs and the relative odds of early mortality for these patients.

Methods

Study identification and selection

A computerized search of Medline and Scopus bibliographic databases from January 2000 through August 2017 was conducted. Following the approach of previous reviews [14], our search dates were limited to favor the selection of studies using modern diagnostic and treatment practices for PE and cancer. The systematic search utilized previously validated search filters for prognostic studies [18] and incorporated Medical Subject Heading (MeSH) terms and key words relating to PE and cancer. The Medline search strategy is provided in Data S1. Additionally, reference lists from identified studies were reviewed to ensure that the search was inclusive of all relevant literature.

Titles and abstracts were independently screened by two investigators, with discrepancies resolved by discussion or a third investigator. Articles demonstrating possible relevance to this study were then reviewed by two independent investigators for inclusion, with disagreements resolved by discussion. In order to have been included in this analysis, studies must have (i) evaluated patients experiencing a PE with cancer, (ii) been a prognostic study deriving and/or validating at least one CPR consisting of a combination of multiple prognostic factors for early post-PE all-cause mortality, (iii) provided data on early all-cause mortality over at least the index PE hospital admission but not longer than 90 days and (iv) be a full-text article published in English.

Data extraction

Data were extracted by two independent investigators using a standardized tool. Results were compared and discrepancies were resolved by discussion. Data were collected on: author and year of publication; geographic location; patient population characteristics (i.e. age, treatment, metastasis status, concurrent deep vein thrombosis and incidental PE); sample size; study timing (retrospective, prospective or both); enrollment dates and inclusion/exclusion criteria; sampling technique (e.g. consecutive, convenience sample or random selection); PE diagnosis criteria (e.g. clinical signs and symptoms, diagnostic scans, medical records, billing codes, etc.); definition of cancer; hemodynamic status of patients at admission (stable or unstable, or both); method of mortality determination; CPR and methods of scoring; and patient 2×2 data needed to calculate sensitivity, specificity and other accuracy statistics relating to CPR prognostication. If all-cause mortality data were reported at various timepoints, 30-day mortality data were preferentially used in this analysis.

Validity assessment

To assess validity, two independent investigators scored each study, with disagreements resolved by discussion. An adapted Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool, outlined by Whiting and colleagues [19], which assesses bias and applicability over multiple domains (patient selection, index test [clinical prediction rule], reference standard [mortality], and flow and timing), was used. Using this tool, a score of low, high or unclear risk of bias or concern regarding applicability was determined for each patient group/CPR analysis. McGinn and colleagues' Hierarchy of Evidence for Clinical Decision Rules was used to classify the overall body of evidence for each CPR in patients with PE and cancer. CPRs were assigned to one of four categories (level 1, at least one prospective validation in a different population and one impact analysis, demonstrating change in clinician behavior with beneficial consequences; level 2, demonstrated accuracy in either one large prospective study including a broad spectrum of patients and clinicians or validated in several smaller settings that differ from one another; level 3, validated in only one narrow prospective sample; level 4, derived but not validated or validated only in split samples, large retrospective databases, or by statistical techniques) [20].

Statistical analysis

The primary endpoint was sensitivity because it was assumed that clinicians would most prefer to minimize false negatives (i.e. minimize early all-cause mortality in patients with PE who may have been in need of more intensive care and thus possibly prevent death). A bivariate statistical model was used to retain the two-dimensional nature of study data [21–23]. Bivariate summary sensitivity, specificity and diagnostic odds ratios (DOR) are reported with accompanying 95% confidence intervals (CI) and area under-the-curve (AUC) estimates. The DOR (calculated as [true positive/false negative] divided by [false positive/true negative]) is a single measure of test performance, with higher values indicating greater accuracy [24].

A random-effects meta-analysis was also performed for each CPR. The percentage of patients deemed to be low risk from each CPR analysis, mortality in such low-risk patients and derived weighted summary proportions and 95% CIs were estimated. In addition, summary odds ratios (ORs) for death with accompanying 95% CIs were calculated by determining the proportion of patients with early mortality in low- and higher-risk groups; the higher-risk group was used as the referent group.

Statistical heterogeneity was assessed with the I^2 statistic, with values > 50% deemed as high. Publication bias was assessed through visual inspection of asymmetry of funnel plots, with standard error and log of the DOR plotted on the vertical and horizontal axes, respectively, and Egger's weighted regression statistic (a P-value < 0.05 was considered statistically significant) [25]; tests for publication bias were performed in all CPRs with > 3 evaluable patient groups.

Lastly, a sensitivity analysis was conducted, excluding studies with alternative (i.e., differing from investigator derived or commonly used) cut-off values for defining low- and higher-risk patients. Such alternative cut-off values can cause only very low-risk patients or, conversely, those with higher risks, to be classified as low-risk patients.

Bivariate meta-analysis was completed in R version 3.3.3 (The R Foundation for Statistical Computing) with the *mada* (Meta-Analysis of Diagnostic Accuracy) package [26]. Traditional meta-analysis and assessment of heterogeneity and bias were completed in StatsDirect version 2.8.0 (StatsDirect Ltd, Altrincham, UK). This manuscript was written in accordance with the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) statement [27]; no separate review protocol is available and complete methods are detailed in this manuscript.

Results

Study characteristics

Our literature search yielded 1104 non-duplicate citations, with 109 full-text articles assessed for eligibility (Fig. 1). Eight studies evaluating 10 CPRs in 3974 (range 124 to 1075) unique patients reported mortality data in low- and higher-risk PE patients with cancer and were included in our meta-analysis (Table 1) [28–34; E.R. Weeda, unpublished data]. Low-risk criteria for included CPRs can be found in Data S2. The Registro Informatizado de la Enfermedad TromboEmbólica (RIETE), Pulmonary Embolism Severity Index (PESI) and POMPE-C rules were evaluated most frequently, in six, four and four patient groups, respectively; evaluations of each of these CPRs included one study with an alternative cut-off value for distinguishing low- and higher-risk patients [32,33]. The Geneva Prognostic Score (GPS) was used in three patient groups; a clinical decision rule developed by Carmona-Bayonas *et al.*, criteria by Font and colleagues, and both modified PESI and simplified PESI (sPESI) rules were evaluated in two patient groups each; the Registro de Embolia Pulmonar en Pacientes con Neoplasias (EPIPHANY) index and Hestia score were used in one patient group each. In both the modified PESI and modified sPESI rules, investigators replaced the 'cancer' variable with a more specific requirement for 'metastatic' disease [29,31].

Included studies were published within the last 5 years (2012 to 2017) and enrolled patients from 2001 to 2015. Of the 10 patient group/CPR analyses, half were retrospective and half utilized both retrospective and prospective study designs; all used a consecutive sampling technique. Three patient group/CPR analyses contained international populations; the USA was included in a total of five analyses, France and Spain in three each and Korea and the Netherlands in one each. Mean/median patient age ranged from 59 to 71 years. All analyses required objective PE confirmation, whereas determination of cancer and mortality status varied. No studies specified inclusion/exclusion criteria related to hemodynamic stability and therefore enrolled both stable and unstable patients at admission. The majority of included patients were receiving chemotherapy and/or radiotherapy (50–75% of patients), and metastatic disease was observed in 49% to 74% of patients. Only three analyses reported data on concurrent deep vein thrombosis and

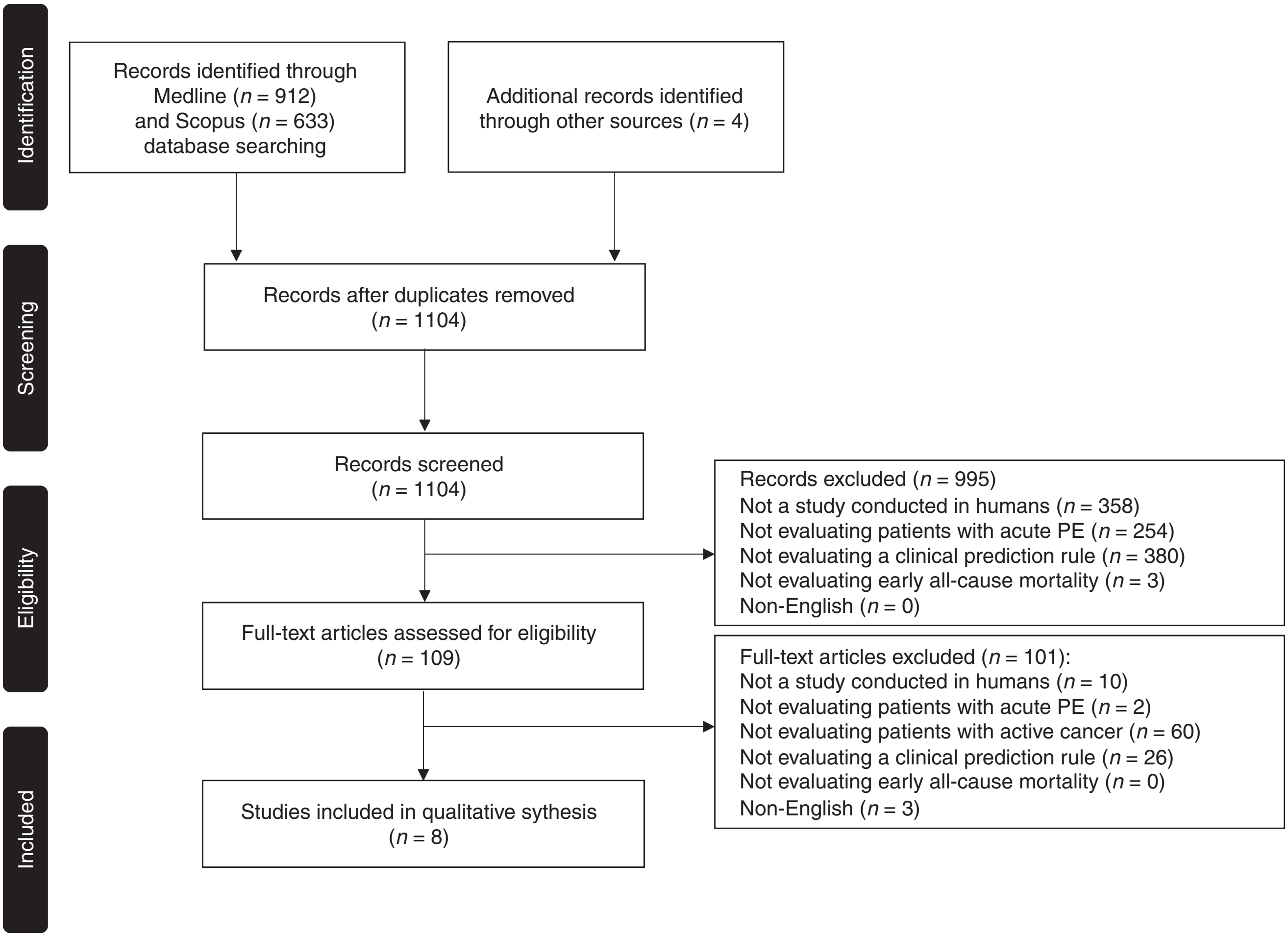

Fig. 1. PRISMA flow diagram.

incidental PE rates, which occurred in 28% to 50% and 7% to 54% of patients, respectively; however, five analyses included only symptomatic patients.

Using the QUADAS-2 tool, all studies were deemed to have a low risk of bias for patient selection and flow and timing (Fig. 2). Only the analyses carried out by Weeda *et al*. had a low risk of bias across all four domains; all other studies had either unclear or high bias for the index test and reference standard domains (Table S1). Applicability concerns were low across all studies and domains. Of the 10 unique CPRs, only POMPE-C and RIETE were categorized as McGinn level 3, whereas all other rules were categorized as McGinn level 4.

Data synthesis

All studies reported 30-day mortality data and the reported measures of prognostic test accuracy for all 27 patient group/CPR analyses are available in Table 2. The results of our bivariate and traditional meta-analysis are summarized in Table 3. Hestia and the EPIPHANY index displayed the highest sensitivities (98.1%, 95% CI = 75.6% to 99.9%; and 97.4%, 95% CI = 93.2% to 99.0%, respectively); however, only one study was included in both of these analyses. Summary sensitivity values ≥ 95% were seen with the clinical decision rule by Carmona-Bayonas *et al.* (96.6%, 95% CI = 62.2% to 99.8%), POMPE-C (95.6%, 95% CI = 89.3% to 98.2%), PESI (95.4%, 95% CI = 87.0% to 98.5%) and the modified sPESI (95.0%, 95% CI = 84.8% to 98.5%); the other tools (Font, RIETE and modified PESI) displayed sensitivities between 87.8% and 93.8%, except for the GPS, which had the lowest sensitivity of 59.9% (95% CI = 49.2% to 69.7%). Statistical heterogeneity as measured by the I^2 statistic was <50% for all CPRs with the exception of RIETE (I^2 = 82.1%). Of the six CPRs with sensitivities ≥ 95%, all had specificities ≤ 32.6%. Although the GPS and criteria by Font and colleagues displayed the lowest sensitivities, they had the highest specificities (53.6%, 95% CI = 43.4% to 63.4%; and 48.9%, 95% CI = 42.3% to 55.4%, respectively). Statistical heterogeneity in specificity was low (< 50%) for most CPRs, except for the GPS (I^2 = 78.3%) and PESI, POMPE-C and RIETE (I^2 ≥ 93.8% for all). Publication bias was deemed to be low for the PESI, POMPE-C and RIETE rules, as assessed through visual inspection of

Table 1 Characteristics of included studies

Study ID (*N* = patients)	Clinical prediction rule	Study design	Country	Age, years, mean ± SD	Enrollment dates/key inclusion criteria	PE diagnosis criteria	Cancer definition	Mortality determination	Treatment/ metastasis/concurrent DVT/incidental PE
Carmona-Bayonas 2017 (*N* = 1075)	EPIPHANY index	P/R	Spain	64 ± 12	2004–2015 ≥ 18 years old, active cancer or receiving adjuvant chemotherapy, objectively confirmed PE, and receiving anticoagulant therapy Excluded if PE had occurred > 1 month prior to diagnosis of cancer or > 1 month after completion of adjuvant chemotherapy, and if received anticoagulant therapy without justification according to international clinical practice guidelines	Presence of at least one filling defect inside the lumen of the pulmonary artery; diagnosis confirmed by objective imaging (CT angiography scans, high probability scintigraphy, or CT scheduled to assess tumor response or for other reasons)	Active cancer or receiving adjuvant chemotherapy	Medical records, patients, clinicians*	Major surgery: 7% Chemotherapy: 54% Targeted therapy: 13% Hormone therapy: 8% ESA: 5% Metastasis: 74% Concurrent DVT: NR Incidental PE: 54%
Weeda 2017 (*N* = 124)†	Carmona-Bayonas CDR, modified PESI, modified sPESI, Font criteria, GPS, Hestia, PESI, POMPE-C, RIETE	R	USA	66 ± 13	October 2010 to January 2014 Adults, active cancer, objectively confirmed acute PE with PE diagnosis code in primary position	Objective confirmation by imaging	Under the care of an oncologist or metastatic disease	Social Security Death Index	Chemotherapy: 47% Radiation: 17% Chemotherapy and radiation: 11% Metastasis: 49% Concurrent DVT: 46% Incidental PE: 7%
Ahn 2016 (*N* = 230)	PESI	R	Korea	59 ± 11	January 2007 to June 2014 ≥ 18 years old, active cancer, objectively diagnosed symptomatic PE Excluded transfers after PE diagnosis, lost to follow-up, on anticoagulants at presentation, or those that did not receive anticoagulation because of a contraindication	Positive spiral computer tomography scan with intraluminal filling defect or a high probability ventilation/perfusion scan	Diagnosis before PE, on or planning treatment for cancer, had received treatment within previous 6 months, or on supportive care for progressive malignancy	Discharge summaries, death certificate or other hospital records	Chemotherapy or radiotherapy: 65% Palliative including metastasis: 76% Metastasis: NR Concurrent DVT: 50% Incidental PE: all patients symptomatic

Table 1 (Continued)

Study ID (*N* = patients)	Clinical prediction rule	Study design	Country	Age, years, mean ± SD	Enrollment dates/key inclusion criteria	PE diagnosis criteria	Cancer definition	Mortality determination	Treatment/ metastasis/concurrent DVT/incidental PE
Carmona-Bayonas 2016 (*N* = 585‡)	Carmona-Bayonas CDR, GPS, modified PESI, POMPE-C, RIETE, modified sPESI,	P/R	Spain	65 ± 12	January 2004 to March 2015 ≥ 18 years old, cancer, and confirmed acute symptomatic PE Excluded if PE had occurred > 1 month prior to diagnosis of cancer or > 4 weeks after completion of adjuvant chemotherapy, and if received anticoagulant therapy that was not considered in international guidelines	Intraluminal contrast-filling defect of at least 2 mm (visualized on at least two consecutive CT slices) as well as PE symptoms or signs; PE confirmation with CT-angiography of the pulmonary arteries or high-probability ventilation/perfusion scintigraphy	NR	Review of clinical history and death certificate	Major surgery: 9% Chemotherapy: 50% Targeted therapy: 9% Hormone therapy: 10% ESA: 5% Metastasis: 72% Concurrent DVT: 28% Incidental PE: 0%, all patients symptomatic and incidental PE excluded
Font 2014 (*N* = 138)	Font criteria, GPS, PESI, POMPE-C§, RIETE¶	P/R	Spain	63 ± 11	May 2006 to December 2009 ≥ 18 years old, active cancer or receiving adjuvant chemotherapy, and symptomatic or incidental PE Excluded pregnant women and those with PE detected during previous hospitalization	Intraluminal filling defect in lung arteries on at least 2 consecutive transverse images; PE confirmation with radiologic methods: CT with pulmonary angiography, ventilation/perfusion pulmonary scintigraphy in those with renal failure or hypersensitivity to contrast medium	Active cancer or receiving adjuvant chemotherapy	Scheduled medical visits, hospital admissions, EHR input, and/or telephone calls*	Major surgery: 12% Chemotherapy: 64% Radiotherapy: 9% Hormonal therapy: 14% ESA: 24% G-CSF: 3% Metastasis: 80% Concurrent DVT: NR Incidental PE: 48%
den Exter 2013 – derivation (*N* = 1048)	RIETE	R	International¶	71 (61–78) (median, IQR)	NR Active cancer and objectively confirmed acute symptomatic PE	Objective testing: high-probability ventilation-perfusion scan result, lower-limb venous compression US positive for a proximal DVT in patients with inconclusive or non-diagnostic ventilation-perfusion scans, or acute PE diagnosed on contrast enhanced PE-protocol helical chest CT	Diagnosed within 6 months before index PE, metastatic cancer or any malignancy that required curative or palliative treatment within the previous 6 months	Patient/proxy interviews and/or hospital chart review	Chemotherapy: 56% Radiotherapy: 11% Chemotherapy or radiotherapy: 60% Metastasis: 67% Concurrent DVT: NR Incidental PE: All patients symptomatic

Table 1 (Continued)

Study ID (N = patients)	Clinical prediction rule	Study design	Country	Age, years, mean ± SD	Enrollment dates/key inclusion criteria	PE diagnosis criteria	Cancer definition	Mortality determination	Treatment/ metastasis/concurrent DVT/incidental PE
den Exter 2013 – internal validation (N = 508)	RIETE	R	International**	70 (60–78) (median, IQR)	NR Active cancer and objectively confirmed acute symptomatic PE	Objective testing: high-probability ventilation-perfusion scan result, lower-limb venous compression US positive for a proximal DVT in patients with inconclusive or non-diagnostic ventilation-perfusion scans, or acute PE diagnosed on contrast enhanced PE-protocol helical chest CT	Diagnosed within 6 months before index PE, metastatic cancer or any malignancy that required curative or palliative treatment within the previous 6 months	Patient/proxy interviews and/or hospital chart review	Chemotherapy: 54% Radiotherapy: 11% Chemotherapy or radiotherapy: 58% Metastasis: 67% Concurrent DVT: NR Incidental PE: all patients symptomatic
den Exter 2013 – external validation (N = 261)	RIETE	R	Netherlands	63 (53–72) (median, IQR)	2001–2010 ≥ 18 years old, active cancer, objectively confirmed acute symptomatic PE, and complete variables and follow-up data	Intraluminal filling defect on PE-protocol contrast-enhanced helical chest CT scan or a high-probability ventilation-perfusion scan according to criteria of the Prospective Investigation of Pulmonary Embolism Diagnosis	Solid or hematologic malignancies diagnosed within 6 months before the diagnosis of PE or diagnosed during the initial 4 weeks of follow-up, recently recurrent or progressive cancer, or any malignancy that required curative or palliative treatment within the previous 6 months	Pathology report, medical records and death certificates	Chemotherapy: 39% Radiotherapy: 14% Chemotherapy or radiotherapy: 45% Metastasis: 63% Concurrent DVT: NR Incidental PE: all patients symptomatic
Kline 2012 –derivation (n = 408)	PESI††	P/ R	USA	62–63	January 2005 to December 2008 ≥ 18 years old, active cancer, and PE diagnosed in the emergency department Excluded patients with comfort care status only	Image proven PE diagnosed at index visit; imaging included positive CPTA, high-probability nuclear ventilation-perfusion lung scan, pulmonary angiogram or pulmonary vascular magnetic resonance angiography interpreted as positive for PE, DVT on a duplex ultrasound of the lower or upper extremities performed within 30 days before enrollment and in association with chest pain or shortness of breath	Metastatic disease or cancer under the care of an oncologist	Patient, telephone interviews, medical record*	NR

Table 1 (Continued)

Study ID (*N* = patients)	Clinical prediction rule	Study design	Country	Age, years, mean ± SD	Enrollment dates/key inclusion criteria	PE diagnosis criteria	Cancer definition	Mortality determination	Treatment/ metastasis/concurrent DVT/incidental PE
Kline 2012 –validation (*N* = 182)	POMPE-C	P/R	France, New Zealand, USA	NR	2002–2006 PE and active cancer	Objective confirmation by imaging, varied by sample/sites	NR	Patient, primary physician, emergency care providers, medical record*	NR

CDR, clinical decision rule; CT, computed tomography; CTPA, computerized tomographic pulmonary angiogram; DVT, deep vein thrombosis; EHR, electronic health record; EPIPHANY, Registro de Embolia Pulmonar en Pacientes con Neoplasias; ESA, erythropoiesis-stimulating agent; G-CSF, granulocyte colony-stimulating factor; GPS, Geneva Prognostic Score; IQR, interquartile range; N, sample size; NA, not applicable; NR, not reported; P, prospective; PE, pulmonary embolism; PESI, Pulmonary Embolism Severity Index; sPESI, simplified Pulmonary Embolism Severity Index; R, retrospective; RIETE, Registro Informatizado de la Enfermedad TromboEmbólica; SD, standard deviation; US, ultrasound. *Represents source of overall study data. †Data reported in two separate manuscripts that include the same patient population; second manuscript submitted for publication, data obtained from investigators. ‡Population overlaps with that included in Carmona-Bayonas 2017. §Investigators used a cut-off of < 10% to categorize patients as low risk, compared with ≤ 5% in other studies assessing POMPE-C. ¶Investigators used a cut-off of < 5 points to categorize patients as low or intermediate risk, compared with < 2 points (for low risk only) in other studies assessing RIETE. **International including: Andorra, Argentina, Belgium, Bolivia, Brazil, Canada, Columbia, Czech Republic, Ecuador, France, Greece, Honduras, Iran, Ireland, Israel, Italy, Latvia, Republic of Macedonia, Mexico, Portugal, Spain, Sweden, Switzerland, USA. ††Investigators used a cut-off of class < 2 to categorize patients as low risk, compared with class ≤ 2 in other studies assessing PESI.

funnel plots and Egger's weighted regression statistic *P*-values ($P \geq 0.37$ for all); we were unable to assess publication bias with the other CPRs due to the small number of studies.

The sensitivity analysis excluding studies that contained alternative cut-offs was conducted in the PESI, POMPE-C and RIETE tools (Table 4). The study excluded in the PESI analysis used a more restrictive cut-off for low-risk patients [34], whereas the study excluded in the POMPE-C and RIETE analyses allowed for more patients to be included in the lower-risk groups [32]. These exclusions resulted in sensitivity remaining the same, decreasing and increasing in PESI, POMPE-C and RIETE, respectively; specificity increased in PESI and POMPE-C and decreased in RIETE.

Summary values from the traditional random-effects meta-analysis of the proportion of low-risk patients for early mortality ranged from 6.6% with PESI to 51.6% with the GPS; excluding the CPRs with sensitivities < 90% (i.e. GPS and the criteria by Font and colleagues), the upper end of this range decreased to 29.3% (Table 3). I^2 values were >50% in the GPS, PESI, POMPE-C and RIETE analyses (I^2 = 59.8%, 95.2%, 94.3% and 95.1%, respectively). Odds of death in patients deemed at low risk ranged from 6% with the EPIPHANY index and Hestia to 57% with the GPS. Statistical heterogeneity for the OR for death was low (< 50%) in all CPRs except the GPS and RIETE (I^2 = 64.3% and 68.3%, respectively).

Discussion

The systematic review and meta-analysis reported here identified eight studies including a total of 10 CPRs evaluating early post-PE all-cause mortality in patients with cancer; 27 individual patient group/CPR analyses are reported. Upon bivariate meta-analysis, six CPRs had sensitivities ≥ 95% (Hestia, EPIPHANY index, Carmona-Bayonas clinical decision rule, POMPE-C, PESI and modified sPESI) and eight had sensitivities ≥ 93% (with addition of RIETE and modified PESI to the previous list). High sensitivity indicates that most of the included CPRs were able to stratify correctly patients who experienced early death. However, the CPRs displayed specificity ranging from 6.0% to 53.6%, indicating a relatively lower ability to stratify correctly those who lived. Although a perfect clinical prediction rule would be both 100% sensitive and specific, there is an inherent trade-off between the two measures. As evident in the decision to select sensitivity as the primary endpoint, high sensitivity may be preferable to high specificity because it may be more harmful to undertreat (i.e. recommend outpatient or early discharge care) patients who are in need of more intensive care. With that said, specificity is still an important measure, as providing patients with undue exposure to the healthcare system has its own ramifications. In

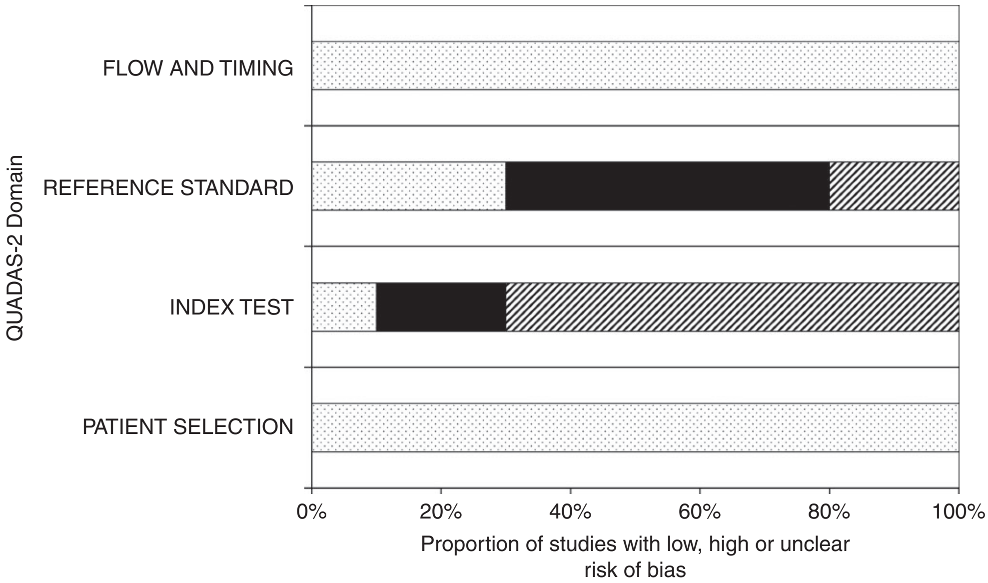

Fig. 2. QUADAS-2 risk of bias results. Low, dots; high, black; unclear, diagonal lines.

some scenarios, a higher specificity should be given more importance even at the expense of sensitivity. Lastly, the random-effects meta-analysis showed that CPRs classified 6.6% to 51.6% of patients as low risk and 0% to 14.3% of these patients experienced mortality; patients categorized as low risk had between 43% and 94% lower odds of death versus their higher-risk counterparts, depending on the CPR used.

Of the 10 CPRs included in the meta-analysis, Hestia and the EPIPHANY index displayed the highest sensitivities; although this is worth acknowledging, it must also be considered in combination with other factors in the usability of the CPRs. Both tools were deemed to be of McGinn level 4 (i.e. rules that need further evaluation before they can be applied clinically) given that they were only evaluated in one analysis each. It is of importance that all of the included CPRs, with the exception of POMPE-C and RIETE, were given the McGinn level 4 designation. Along with evidence supporting CPRs, practicality of implementation in clinical practice is another important consideration. Extensive rules may not be easily applicable in a general busy practice. The EPIPHANY index is a multi-step decision tree [28], which may make it more difficult to use, as clinicians have displayed low recall for specific elements of CPRs [35]. Nonetheless, its creators note that five of its six variables (Eastern Cooperative Oncology Group-Performance Status [ECOG-PS], tumor response assessment, previous tumor resection, oxygen saturation and the presence of PE-specific symptoms) can be assessed at the patient's bedside. The authors chose to pursue a decision tree model to imitate real-world decision-making [28]. CPR pragmatism must also be balanced with validity. For example, POMPE-C consists of an equation with five dichotomous and three continuous variable inputs [34]. When investigators trialed dichotomizing all variables, precision and accuracy decreased. POMPE-C is available as a web-based platform, which may negate potential difficulties in its formulaic nature given the availability of electronic medical applications [36].

In the study reported here, the performance of tools prognosticating early all-cause mortality in patients experiencing a PE with cancer was evaluated. Of the CPRs included in the analysis, only the POMPE-C and RIETE tools were created for this specific endpoint in a cancer population, whereas the other CPRs were not [15,17,28,31–34,37]. For example, the EPIPHANY index was derived to classify 15-day risk of serious complications (i.e. events that lead to serious clinical deterioration or death), although its use was intended for patients with cancer [28]. Likewise, the criteria established by Carmona-Bayonas *et al.* and Font *et al.* represent exclusion criteria for home treatment [31,32]. The GPS, Hestia and PESI CPRs represent non-cancer-specific (i.e. generic) tools that have been applied to populations with malignancy in the studies included in our analysis.

Differences in the performance of generic CPRs when applied to a general population versus those with cancer accentuate the need for cancer-specific data. This can be seen through comparison of our results with a similar meta-analysis conducted by Kohn and colleagues, which also evaluated the performance of CPRs for early post-PE all-cause mortality in a non-cancer-specific population; malignancy was observed in 5% to 42% of their included patients [14]. Their analysis of GPS, Hestia and PESI included six (n = 1863 patients), one (n = 496) and 16 (n = 20 600) studies, respectively. These tools all displayed lower sensitivities of 41%, 82% and 89%, respectively, and higher specificities of 85%, 56% and 48%, respectively, compared with our results. Both the GPS

Table 2 Risk of all-cause 30-day mortality and clinical prediction rule sensitivity and specificity

Study ID (*N* = patients)	Clinical prediction rule	Mortality in low-risk patients, *n*/*N* (%)	Mortality in higher-risk patients, *n*/*N* (%)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	DOR (95% CI)
Weeda 2017 (*N* = 124)*	Carmona-Bayonas CDR	3/23 (13.0)	22/101 (21.8)	88.0 (67.7–96.8)	20.2 (13.1–29.7)	1.86 (0.51–6.83)
Carmona-Bayonas 2016 (*N* = 585)	Carmona-Bayonas CDR	1/59 (1.7)	124/526 (23.6)	99.2 (95.6–99.9)	12.6 (9.7–15.9)	17.89 (2.45–130.49)
Carmona-Bayonas 2017 (*N* = 1075)	EPIPHANY index	4/305 (1.3)	149/770 (19.4)	97.4 (93.5–99.0)	32.6 (29.7–35.7)	18.06 (6.63–49.20)
Weeda 2017 (*N* = 124)	Font criteria	3/51 (5.9)	22/73 (30.1)	88.0 (67.7–96.8)	48.5 (38.4–58.7)	6.90 (1.94–24.55)
Font 2014 (*N* = 138)	Font criteria	2/62 (3.2)	14/76 (18.4)	87.5 (64.0–96.5)	49.2 (40.5–57.9)	6.77 (1.48–31.08)
Weeda 2017 (*N* = 124)	GPS	12/54 (22.2)	13/70 (18.6)	52.0 (31.8–71.7)	42.4 (32.7–52.8)	0.80 (0.33–1.93)
Carmona-Bayonas 2016 (*N* = 585)	GPS	45/317 (14.2)	80/268 (29.9)	64.0 (54.9–72.3)	59.1 (54.4–63.6)	2.57 (1.71–3.88)
Font 2014 (*N* = 138)	GPS	6/76 (7.9)	10/62 (16.1)	60.0 (33.2–76.9)	56.9 (47.7–65.0)	2.24 (0.77–6.57)
Weeda 2017 (*N* = 124)	Hestia	0/23 (0)	25/101 (24.8)	100 (83.4–100)	23.2 (15.6–33.0)	15.67 (0.92–267.28)
Weeda 2017 (*N* = 124)	PESI	1/7 (14.3)	24/117 (20.5)	96.0 (77.7–99.8)	6.1 (2.5–13.2)	1.14 (0.18–7.08)
Ahn 2016 (*N* = 230)	PESI	1/36 (2.8)	24/194 (12.4)	96.0 (77.7–99.8)	17.1 (12.3–23.1)	3.40 (0.63–18.39)
Font 2014 (*N* = 138)	PESI	1/11 (9.1)	15/127 (11.8)	93.3 (71.7–98.9)	8.1 (3.9–13.4)	0.96 (0.16–5.78)
Kline 2012 – derivation (*N* = 408)	PESI†	0/3 (0)	51/405 (12.6)	100 (91.4–100)	1.0 (0.4–2.6)	1.02 (0.05–19.97)
Weeda 2017 (*N* = 124)*	Modified PESI	2/38 (5.3)	23/86 (26.7)	92.0 (72.5–98.6)	36.4 (27.1–46.7)	6.57 (1.46–29.50)
Carmona-Bayonas 2016 (*N* = 585)	Modified PESI	6/59 (10.2)	119/526 (22.6)	95.2 (89.8–98.2)	11.5 (8.7–14.8)	2.58 (1.08–6.16)
Weeda 2017 (*N* = 124)	POMPE-C	2/40 (5.0)	23/84 (27.4)	92.0 (72.5–98.6)	38.4 (28.9–48.7)	5.89 (1.50–23.03)
Carmona-Bayonas 2016 (*N* = 585)	POMPE-C	3/60 (5.0)	122/525 (23.2)	97.6 (93.1–99.5)	12.3 (9.5–15.7)	4.99 (1.66–14.95)
Font 2014 (*N* = 138)	POMPE-C‡	0/15 (0)	16/123 (13.0)	100 (80.6–100)	12.2 (7.5–19.1)	4.76 (0.27–83.37)
Kline 2012 – validation (*N* = 182)	POMPE-C	0/50 (0)	27/132 (20.5)	100 (84.5–100)	32.3 (25.1–40.3)	26.33 (1.57–440.33)
Weeda 2017 (*N* = 124)	RIETE	1/53 (1.9)	24/71 (33.8)	96.0 (77.7–99.8)	52.5 (42.3–62.6)	18.05 (3.32–98.29)
Carmona-Bayonas 2016 (*N* = 585)	RIETE	5/121 (4.1)	120/464 (25.9)	96.0 (90.9–98.6)	25.2 (21.3–29.4)	7.41 (3.07–17.86)
Font 2014 (*N* = 138)	RIETE§	8/80 (10.0)	8/58 (13.8)	50.0 (24.6–75.3)	59.0 (49.7–67.8)	1.44 (0.52–3.97)
den Exter 2013 –derivation (*N* = 1048)	RIETE	5/232 (2.2)	220/816 (27.0)	97.6 (94.6–98.9)	27.6 (24.7–30.8)	15.29 (6.47–36.13)
den Exter 2013 – internal validation (*N* = 508)	RIETE	5/113 (4.4)	118/395 (29.9)	95.9 (92.4–99.4)	28.1 (23.6–32.5)	8.42 (3.48–20.38)
den Exter 2013 – external validation (*N* = 261)	RIETE	0/47 (0)	42/214 (19.6)	100 (89.8–100)	21.5 (16.0–26.9	23.41 (1.41–387.41)
Weeda 2017 (*N* = 124)*	Modified sPESI	2/30 (6.7)	23/94 (24.5)	92.0 (72.5–98.6%)	28.3 (19.9–38.4)	4.54 (1.00–20.52)
Carmona-Bayonas 2016 (*N* = 585)	Modified sPESI	4/72 (5.6)	121/513 (23.6)	96.8 (92.0–99.1)	14.9 (11.8–18.5)	5.25 (1.88–14.68)

CDR, clinical decision rule; CI, confidence interval; DOR, diagnostic odds ratio; EPIPHANY, Registro de Embolia Pulmonar en Pacientes con Neoplasias; GPS, Geneva Prognostic Score; N, sample size; PESI, Pulmonary Embolism Severity Index; RIETE, Registro Informatizado de la Enfermedad TromboEmbólica; sPESI, simplified Pulmonary Embolism Severity Index. *Manuscript submitted for publication, data obtained from investigators. †Investigators used a cut-off of class < 2 to categorize patients as low risk, compared with class ≤ 2 in other studies assessing PESI. ‡Investigators used a cut-off of <10% to categorize patients as low risk, compared with ≤ 5% in other studies assessing POMPE-C. §Investigators used a cut-off of < 5 points to categorize patients as low or intermediate risk, compared with < 2 points (for low risk only) in other studies assessing RIETE.

Table 3 Results of bivariate and traditional meta-analysis for 30-day mortality

Clinical prediction rule (*N* = patient groups; patients)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	DOR (95% CI)	AUC	Low risk, %* (95% CI)	Mortality in low-risk patients, %* (95% CI)	OR death*† (95% CI)
Hestia (*N* = 1; 124)	98.1 (75.6–99.9)	23.5 (16.2–32.8)	15.67 (0.92–267.28)	0.87	18.5 (12.1–26.5)	0 (0–14.8)	0.06 (0–0.58)
EPIPHANY index (*N* = 1; 1075)	97.4 (93.2–99.0)	32.6 (29.7–35.7)	18.06 (6.63–49.20)	0.88	28.4 (25.7–31.2)	1.3 (0.4–3.3)	0.06 (0.01–0.15)
Carmona-Bayonas CDR (*N* = 2; 709)	96.6‡ (62.2–99.8)	15.8‡ (9.5–25.2)	5.06‡ (0.56–45.96)	0.27	13.8‡ (6.6–23.1)	6.6‡ (0.1–22.0)	0.19 (0.02–2.26)
POMPE-C (*N* = 4; 1029)	95.6 (89.3–98.2)	22.0‡ (11.6–37.8)	5.98 (2.72–13.13)	0.83	19.3‡ (9.5–31.5)	3.2 (0.7–7.2)	0.14 (0.06–0.33)
PESI (*N* = 4; 900)	95.4 (87.0–98.5)	6.0‡ (1.8–18.3)	1.53 (0.58–4.02)	0.78	6.6‡ (1.1–16.3)	6.9 (1.9–14.6)	0.50 (0.16–1.54)
Modified sPESI (*N* = 2; 709)	95.0 (84.8–98.5)	20.4‡ (10.3–36.5)	5.01 (2.14–11.72)	0.69	17.6‡ (7.6–30.7)	6.7 (2.7–12.3)	0.20 (0.09–0.47)
Modified PESI (*N* = 2; 709)	93.8 (86.2–97.4)	21.3‡ (6.0–53.6)	3.34 (1.48–7.58)	0.88	19.2‡ (3.7–42.7)	8.9 (4.1–15.3)	0.30 (0.13–0.68)
RIETE (*N* = 6; 2664)	93.2‡ (80.2–97.9)	34.2‡ (23.3–47.1)	7.76‡ (3.51–17.15)	0.62	29.3‡ (21.4–37.9)	3.8‡ (1.9–6.4)	0.12‡ (0.05–0.28)
Font criteria (*N* = 2; 262)	87.8 (73.9–94.8)	48.9 (42.3–55.4)	6.85 (2.58–18.16)	0.51	43.2 (37.3–49.2)	5.1 (1.8–9.9)	0.15 (0.06–0.39)
GPS (*N* = 3; 847)	59.9 (49.2–69.7)	53.6‡ (43.4–63.4)	1.75‡ (0.84–3.66)	0.59	51.6‡ (45.3–57.8)	14.3‡ (8.5–21.2)	0.57‡ (0.27–1.20)

AUC, area under the curve; CDR, clinical decision rule; CI, confidence interval; DOR, diagnostic odds ratio; EPIPHANY, Registro de Embolia Pulmonar en Pacientes con Neoplasias; GPS, Geneva Prognostic Score; N, sample size; OR, odds ratio; PESI, Pulmonary Embolism Severity Index; RIETE, Registro Informatizado de la Enfermedad TromboEmbólica; sPESI, simplified Pulmonary Embolism Severity Index. *Pooled using a random-effects approach. †Higher risk used as referent group. ‡$I2 > 50\%$.

Table 4 Results of sensitivity analysis excluding studies with alternative cut-offs for 30-day mortality

Clinical prediction rule (*N* = patient groups; patients)	Sensitivity, % (95% CI)	Specificity, % (95% CI)
PESI* (*N* = 3; 492)	95.4 (86.5–98.5)	10.2 (5.3–18.8)
POMPE-C† (*N* = 3; 891)	94.9 (86.8–98.1)	25.8 (12.4–46.1)
RIETE‡ (*N* = 5; 2526)	96.2 (93.9–97.7)	30.0 (21.5–40.1)

CI, confidence interval; N, sample size; PESI, Pulmonary Embolism Severity Index; RIETE, Registro Informatizado de la Enfermedad TromboEmbólica; sPESI, simplified Pulmonary Embolism Severity Index. *Excluded analysis by Kline *et al.* (derivation), which used a cut-off of class < 2 to categorize patients as low risk, compared with class ≤ 2 in other studies assessing PESI. †Excluded analysis by Font *et al.*, which used a cut-off of < 10% to categorize patients as low risk, compared with ≤ 5% in other studies assessing POMPE-C. ‡Excluded analysis by Font *et al.*, which used a cut-off of < 5 points to categorize patients as low or intermediate risk, compared with < 2 points (for low risk only) in other studies assessing RIETE.

and PESI include cancer as a variable, so in patient groups composed entirely of those with malignancy, as seen in our included studies, one would expect more patients to be stratified as higher risk and therefore a higher sensitivity. However, this comes to the decrement of specificity, where our values were 31%, 33% and 42% lower than those seen in an all-comer PE population for GPS, Hestia and PESI, respectively [14]. Although we have already stressed the importance of high sensitivity, the impact of lower specificity needs to be given adequate consideration, especially as such results may prompt unnecessary hospitalization for these patients with cancer who are already facing high economic and quality-of-life burdens [38,39].

Accurate prognostic stratification of PE patients with cancer can assist in determining appropriate sites of care (i.e. inpatient versus outpatient treatment), especially as previous studies have shown that these patients can be effectively treated without a hospital admission [32,40]. Font and colleagues prospectively applied their exclusion criteria (included in this present study) to 138 patients (45% treated at home and 55% admitted to the hospital); there were no readmissions for PE complications in all patients selected for home treatment [32]. Similarly, Siragusa *et al.* prospectively evaluated 68 patients with PE and cancer for home or in-hospital care; those with poor clinical conditions related to concomitant medical disorders, illness that independently required hospitalization, poor compliance, high risk of bleeding or active bleeding, renal insufficiency, acute anemia or pain requiring parenteral narcotics were selected for hospital admission [40]. Between the 53% and 47% of home- and hospital-treated patients, respectively, there were no significant differences ($P \geq 0.05$) in recurrent VTE, bleeding or death at 6 months of follow-up.

The meta-analysis presented here has several limitations worth noting. Firstly, we only included CPRs evaluating early post-PE all-cause mortality. Although mortality is an important outcome of interest, other investigators have argued that serious complications within 15 days deserve attention given that such complications can cause patients to be reclassified as higher risk [28]. Although we agree with this consideration, we chose to focus on all-cause mortality given its importance and the relatively increased amount of available data for this outcome. Secondly, only limited sensitivity analyses could be performed given the number of identified patient/CPR groups. As a result, the performance of CPRs by population characteristics such as PE presentation (i.e. symptomatic vs. incidental) could not be evaluated, which may possibly have important ramifications for early mortality. Likewise, studies with varying inclusion criteria were pooled. However, the analyses suggest low heterogeneity in most patient groups/CPR analyses. Next, all of our included studies were retrospective or had retrospective components, which can introduce bias as a result of study design. Such biases may include selection bias, lack of available/recorded data and loss to follow-up. This was given appropriate consideration through our risk of bias assessment as well as our classification of the overall body of evidence using the hierarchy established by McGinn and colleagues [19,20]. Therefore, we did not rank any CPR higher than a McGinn level 3. Lastly, the systematic review was limited to English-language articles. Analyses have suggested that 'language bias' resulting from the exclusion of non-English-language studies has been shown to have a minimal effect on summary treatment estimates in meta-analyses [41,42]. In addition, the probability of publication bias was deemed to be low for all analyses in our meta-analysis, as suggested by Eggers weighted regression statistics.

In treating patients with cancer experiencing a PE, researchers and clinicians must derive and seek out cancer-specific data given the unique circumstances of this population. Several CPRs for prognosticating early post-PE all-cause mortality in these patients have been evaluated, but their pooled performance and the totality of evidence suggest that further research is needed. Therefore, the results of CPRs as well as other patient-specific clinical factors should continue to be used in identifying patients suitable for outpatient care until such data are available.

Addendum

E. Nguyen, C. I. Coleman, E. R. Weeda, and C. G. Kohn contributed to the concept and design, analysis and interpretation of data, critical writing, and final approval of the version to be published. J. T. Caranfa, C. Stribis, and M. Wysocki contributed to the analysis and interpretation of data, critical writing, and final approval of the version to be published. G. H. Lyman and N. M. Kuderer contributed to revising the intellectual content and final approval of the version to be published.

Disclosure of Conflict of Interests

N. M. Kuderer reports personal fees from Janssen, Myriad, Daiichi, Coherus, and Halozyme, outside the submitted work. The other authors state that they have no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Medline search strategy
Data S2. Low-risk criteria for included CPRs
Table S1. QUADAS-2 risk of bias results by study

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