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ORIGINAL ARTICLE

External validation of three risk stratification rules in patients presenting with pulmonary embolism and cancer

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Abstract

Numerous risk stratification rules exist to predict post-pulmonary embolism (PE) mortality; however, few were designed for use in cancer patients. In the EPIPHANY registry, adapted versions of common rules (the Hestia criteria, Pulmonary Embolism Severity Index [PESI], and simplified PESI [sPESI]) displayed high sensitivity for prognosticating mortality in PE patients with cancer. These adapted rules have yet to be externally validated. Therefore, we sought to evaluate the performance of an adapted Hestia criteria, PESI, and sPESI for predicting 30-day post-PE mortality in patients with cancer. We identified consecutive, adults presenting with objectively confirmed PE and cancer to our institution (November 2010 to January 2014). The proportion of patients categorized as low or high risk by these three risk stratification rules was calculated, and each rule's accuracy for predicting 30-day all-cause mortality was determined. Of the 124 patients with PE and active cancer identified, 25 (20%) experienced mortality at 30 days. The adapted Hestia criteria categorized 23 (19%) patients as low risk, while exhibiting a sensitivity of 88% (95% confidence interval [CI] = 68–97%), a negative predictive value NPV of 87% (95% CI = 65–97%), and a specificity of 20% (95% CI = 13–30%). A total of 38 (31%) and 30 (24%) patients were low risk by the adapted PESI and sPESI, with both displaying sensitivities of 92% and NPVs > 93%. Specificities were 36% (95% CI = 27–47%) and 28% (95% CI = 20–38%) for PESI and sPESI. In our external validation, the adapted Hestia, PESI, and sPESI demonstrated high sensitivity but low specificity for 30-day PE mortality in patients with cancer. Larger, prospective trials are needed to optimize strategies for risk stratification in this population.

Keywords Mortality · Pulmonary embolism · Prognosis · Risk assessment · Severity of illness index

Introduction

In patients with solid tumors, thromboembolic events are a leading cause of death after disease progression [1]. Guidelines suggest that pulmonary embolism (PE) risk stratification rules can assist clinicians making challenging patient disposition decisions [2, 3]. While numerous PE risk stratification rules exist, few were specifically designed for patients with cancer [4–7]. Moreover, some rules automatically consider patients with cancer to be at high risk of early mortality [7], even though a portion of these patients may be low risk, as evidenced by the successful outpatient treatment of PE in those with cancer [8, 9]. Recognizing that existing risk stratification rules likely require modification in this population, Carmona-Bayonas et al. adapted three commonly used rules (Pulmonary Embolism Severity Index [PESI], simplified PESI [sPESI], and Hestia criteria) [10]. These modified rules have yet to be validated in an external dataset. Therefore, we sought to evaluate the performance of an adapted Hestia criteria, PESI, and sPESI for predicting 30-day post-PE mortality in patients with active cancer.

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Methods

In this retrospective analysis, consecutive adult patients with a diagnosis of acute PE (International Classification of Diseases, Ninth Revision, Clinical Modification code = 415.1x in the primary position with objective confirmation assessed via imaging) presenting to our institution (October 21, 2010, to January 31, 2014) were identified. We only included patients with active cancer (defined as cancer under the care of an oncologist or metastatic disease and determined by manual chart review [11]). All patients were treated according to standard practice at our institution.

Using a standardized data collection form, trained study personnel abstracted data necessary to categorize patients as low or high risk according to the adapted Hestia criteria, PESI, and sPESI (Table 1) [5–7]. Our primary objective was to calculate the prognostic accuracy of these rules for predicting all-cause 30-day mortality. Mortality status was determined through searches of the Social Security Death Index [12].

Baseline characteristics are described with means ± standard deviations (SDs) for continuous data and counts and proportions for categorical data. The sensitivity, specificity, negative and positive predictive value (NPV and PPV), and corresponding 95% confidence intervals (CIs) were calculated for each rule; the c-statistic was used to assess overall discriminative power. IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA) was used to perform all statistical analyses. This study was approved by the institutional review board at our institution.

Results

We identified 603 patients with objectively confirmed acute PE, of which 124 had active cancer and were included in our analysis (Table 2). Mean ± SD age was 66.2 ± 12.8 years, and 62 (50%) patients were male. Approximately half (57.3%) of patients had either lung, breast, or genitourinary cancer, with metastatic disease present in 49.2% ($n = 61$) of all patients. A total of 8 (6.5%) patients had confirmed PE discovered incidentally.

All-cause 30-day mortality occurred in 25 (20.2%) patients. The adapted Hestia criteria categorized 23 (18.5%) patients as low risk and exhibited a sensitivity of 88.0% (95%CI = 67.7–96.8%) and an NPV of 87% (95%CI = 65–97%) for 30-day all-cause mortality (Table 3). A total of 38 (30.6%) and 30 (24.2%) patients were categorized as low risk according to the adapted PESI and sPESI, with both rules displaying sensitivities of 92.0% and NPVs > 93.0%. Specificities were < 37% and PPVs were < 27% for all rules, while the c-statistic ranged from 0.54 (Hestia criteria) to 0.82 (PESI).

Table 1 Characteristics and scoring of included risk stratification rules

Adapted Hestia criteria[a]	
Low-risk: no criteria presents	
Systolic blood pressure < 100 mmHg	
Oxygen saturation < 90%	
Respiratory rate ≥ 30 breaths/min	
Pulse ≥ 110 beats/min	
Sudden or progressive dyspnea	
Clinically relevant hemorrhage	
High risk of bleeding	
Platelets < 50.000/mm	
Adapted Pulmonary Embolism Severity Index (PESI)[b]	
Low risk: score ≤ 85	
Age	Age in years
Male sex	+ 10
Metastatic cancer	+ 30
History of heart failure	+ 10
History of chronic lung disease	+ 10
Pulse ≥110 beats/min	+ 20
Systolic blood pressure < 100 mmHg	+ 30
Respiratory rate ≥ 30 breaths/min	+ 20
Temperature < 36 °C	+ 20
Altered mental status	+ 60
Oxygen saturation < 90%	+ 20
Adapted Simplified Pulmonary Embolism Severity Index (sPESI)[b]	
Low risk: score of 0	
Age > 80	1
Metastatic cancer	1
History of chronic cardiopulmonary disease	1
Pulse ≥ 110 beats/min	1
Systolic blood pressure < 100 mmHg	1
Oxygen saturation < 90%	1

[a] The six variables selected by Carmona-Bayonas et al. overlap significantly with the Hestia criteria (which consists of the following 11 variables: hemodynamically unstable, oxygen needed to maintain an oxygen saturation > 90% for > 24 h, need for intravenous pain medication for > 24 h, thrombolysis or embolectomy < 48 h, high risk of bleeding, PE on anticoagulation, pregnant, history of heparin-induced thrombocytopenia, medical or social reason for admission, creatinine clearance of less than 30 mL/min, and severe liver impairment

[b] The adapted version by Carmona-Bayonas et al. in the EPIPHANY registry replaced the typical "history of cancer" variable with metastatic cancer

Discussion

An adapted version of the Hestia criteria, PESI, and sPESI classified ≥ 19% of patients as low risk and exhibited high sensitivities (≥ 88%) and moderate specificities (≤ 37%) for predicting 30-day all-cause mortality in this real-world analysis of patients with PE and active cancer. In other words, the rules correctly classified nearly all patients that died within 30 days as high risk (as indicated by the high sensitivity);

Table 2 Characteristics of included pulmonary embolism patients with active cancer

Characteristic[a]	*N* (%) *N* = 124
Age (years, mean ± SD)	66.2 ± 12.8
Age > 80 years	15 (12.1)
Male sex	62 (50.0)
Cancer type	
Lung	36 (29.0)
Colorectal	9 (7.3)
Pancreas	4 (3.2)
Other gastrointestinal	4 (3.2)
Breast	16 (12.9)
Prostate	12 (9.7)
Brain	9 (7.3)
Hematologic	6 (4.8)
Genitourinary	19 (15.3)
Other	7 (5.6)
Unknown	2 (1.6)
Receiving chemotherapy or radiation	65 (52.4)
Metastatic disease	61 (49.2)
Current deep vein thrombosis	58 (46.8)
Chronic lung disease	36 (29.0)
Heart failure	6 (4.8)
Active bleeding	3 (2.4)
High risk for bleeding[b]	15 (12.1)
Platelet count ≤ 50,000/mm^3	1 (0.8)
Pulse (beats/min, mean ± SD)	96.3 ± 20.6
Pulse ≥ 110 beats/min	34 (27.4)
Systolic blood pressure (mmHg, mean ± SD)	127.6 ± 20.9
Systolic blood pressure < 100 mmHg	15 (12.1)
Respiratory rate (breaths/min, mean ± SD)	19.0 ± 2.8
Respiratory rate ≥ 30 breaths/min	1 (0.8)
O2 saturation (%, mean ± SD)	96.1 ± 3.7
O2 saturation < 90%	8 (6.5)
Temperature (degrees Celsius, mean ± SD)	36.5 ± 0.7
Temperature < 36 °C	25 (20.2)
Treatment in the intensive care unit	18 (14.5)
Early discharge (length-of-stay ≤3 days)	31 (25.0)

[a] A total of 1 (0.8%) patient had unknown values for temperature, respiratory rate, and platelets. No patients had missing values other than the included prognostic factors

[b] Gastrointestinal bleeding in the preceding 14 days, stroke in the preceding 4 weeks, procedure in the preceding 2 weeks, or uncontrolled hypertension (systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg)

however, a substantial proportion of the high-risk group was alive at 30 days (as shown by low-to-moderate specificities). Although a perfect risk stratification rule would display both high sensitivity and specificity, there is an inherent trade-off between the two measures. As one measure increases, the other generally decreases. In the case of PE risk stratification, high sensitivity is preferred, as misclassifying a low-risk patient may result in an unnecessary extension in hospital stay but incorrectly classifying a high-risk patient may lead to inappropriate reductions in needed care.

While PESI and sPESI have displayed high sensitivity for prognosticating mortality in patients with cancer, these rules (including versions adapted for cancer populations) have failed to identify a substantial proportion of low-risk patients in previous studies [8, 10, 13]. The original PESI (i.e., with the typical history of cancer rather than metastatic cancer as a covariate) was validated in 230 PE patients with active cancer treated at a single center in Korea, displaying high sensitivity (96.0% [95% CI = 77.7–99.8]) for prognosticating 30-day all-cause mortality but only classifying 15.7% of patients as low risk [13]. Similar results were observed in single-center study of 138 Spanish patients with PE and active cancer, where the sensitivity of the original PESI score for 30-day mortality was 93.3% (95% CI = 71.7–98.9%) but only 8.6% of patients were classified as low risk [8]. Even when Carmona-Bayonas et al. replaced the "history of cancer" covariate with "metastatic cancer" in the multicenter EPIPHANY registry, PESI only identified 10.1% (59/585) of symptomatic PE patients with cancer as low risk, albeit with a high sensitivity (95.2% [95% CI = 89.8 to 98.2%]) [10]. In this same analysis, sPESI was scored with the "history of cancer" covariate replaced by "metastatic cancer" and it identified only 12% (72/585) as low risk, demonstrating a sensitivity of 96.8% (95%CI = 92.0–99.1%). Although metastasis has prognostic implications in patients with PE [14] and the adapted PESI and sPESI demonstrated acceptable predictive accuracy in our own analysis, the weight of the evidence suggests that these rules only categorize a small portion of patients as low risk [10].

While there is a growing body of evidence for the use of Hestia-like PE risk stratification rules, larger prospective studies are needed to confirm the utility of this rule in patients with cancer [8–10, 15, 16]. In a small, retrospective analysis at a US hospital, 19/113 (16.8%) patients with PE and cancer were deemed low risk and sensitivity for 30-day mortality was 100% (95% CI = 82.8–100%) [15]. In ambispective and retrospective (our current analysis) settings, adapted versions of this criteria classified 10 to 28% of patients as low risk and displayed sensitivities ranging from 88.0 to 99.2% [10, 16]. Adapted versions of the Hestia criteria have also been used to prospectively identify patients presenting with PE and active cancer that may qualify for outpatient treatment [8, 9]. Font et al. identified 62/138 (44.9%) low-risk patients with cancer for outpatient PE treatment with an adapted version of the Hestia criteria, which displayed a sensitivity of 87.5% (95% CI = 64.0–96.5) for mortality at 30 days [8]. Siragusa et al. used similar criteria to select 36/68 (52.9%) low-risk PE patients

Table 3 Prognostic test characteristics for 30-day mortality

	Adapted Hestia criteria[a]	Adapted PESI[b]	Adapted sPESI[b]
Low risk *n* (%)	23 (18.5)	38 (30.6%)	30 (24.2%)
Low-risk mortality *n*/*N* (%)	3/23 (13.0)	2/38 (5.3%)	2/30 (6.6%)
High-risk mortality *n*/*N* (%)	22/101 (20.8%)	23/86 (26.7%)	23/94 (24.5%)
Sensitivity (95% CI)	88.0% (67.7–96.8%)	92.0% (72.5–98.6%)	92.0% (72.5–98.6%)
Specificity (95% CI)	20.2% (13.1–29.7%)	36.4% (27.1–46.7%)	28.3% (19.9–38.4%)
NPV (95% CI)	87.0% (65.3–96.6%)	94.7% (80.9–99.1%)	93.3% (76.5–98.8%)
PPV (95% CI)	21.8% (14.4–31.3%)	26.7% (18.0–37.6%)	24.4% (16.4–34.6%)
C-statistic (95% CI)	0.54 (0.42–0.66)	0.82 (0.72–0.91)	0.64 (0.52–0.75)

CI confidence interval, *PESI* pulmonary embolism severity index, *sPESI* simplified pulmonary embolism severity index

[a] The six variables selected by Carmona-Bayonas et al. represent an adapted version of the Hestia criteria (see Table 1)

[b] The adapted version by Carmona-Bayonas et al. in the EPIPHANY registry replaced the typical "history of cancer" variable with metastatic cancer

with cancer for outpatient management [9]. Compared to patients treated in the hospital, outpatients had similar rates of death (37.0% vs 30.5%) and morbidity (i.e., venous thromboembolism [VTE] 9.3% vs. 5.5% and major bleeding 0% vs. 2.7%) at 6 months ($p > 0.05$ for all endpoints). Interestingly, more patients were classified as low risk in these prospective clinical studies compared to the aforementioned analyses containing retrospective data. Unfortunately, both prospective studies were small (< 200 patients in total).

There are two risk stratification rules that were derived in patients with cancer (Registro Informatizado de la Enfermedad TromboEmbólica [RIETE] and POMPE-C) and serve as an alternative to adapted versions of generic rules such as Hestia, PESI, and sPESI [11, 14]. RIETE assigns points to six variables (age > 80 years [1 point], pulse ≥ 110/min [1 point], systolic BP < 100 mmHg [1 point], weight < 60 kg [1 point], immobilization [2 points], and presence of metastases [4 points]) and defines low risk as < 1 point, whereas POMPEC calculates a probability of death (based on weight, respiratory rate, O2 saturation, pulse, altered mental status, respiratory distress, do not resuscitate status, and unilateral limb swelling) and a probability ≤ 5% is low risk [11, 14]. In their original studies, both rules classified 22–38% of patients as low risk and exhibited sensitivities > 95%. When RIETE and POMPE-C were compared to the cancer-adapted PESI and sPESI by Carmona-Bayonas et al. in their multicenter registry of 585 patients with PE and active cancer, both had better discriminatory ability (i.e., exhibited c-indices > 0.05 higher than the adapted PESI and sPESI) [10]. Whether these cancer-specific rules consistently outperform adapted versions of generic PE prognostic rules in cancer patients has yet to be determined.

It is important to note that only 6.5% of patients in our study had a PE that was discovered incidentally (i.e., found on imaging ordered for surveillance of cancer). In contrast, ~ 50% of patients had incidental PE in the EPIPHANY registry [17, 18]. In this registry, there was a significantly lower occurrence of 30-day mortality among patients with asymptomatic or symptomatic incidental PE when compared to those with PE that was not discovered incidentally (3% or 20%, vs. 21%, $p < 0.001$); however, no difference in recurrent VTE was observed between these cohorts. Unfortunately, we could not evaluate the prognostic ability of risk stratification rules in patients with incidental PE in this study due to a limited sample size.

This study has other limitations that deserve consideration; mainly, data are from a single center, which limits generalizability. Further, we only had access to data during the patient's index PE and could not evaluate other measures of PE morbidity (i.e., re-hospitalization for venous thromboembolism or major bleeding). Lastly, our analysis was retrospective and subject to biases. For example, misclassification bias is possible due to missing data. However, the rate of missing data for covariates in our analysis was < 1%.

Conclusion

In this external validation of patients with active cancer, the adapted Hestia, PESI, and sPESI displayed high sensitivity for 30-day post-PE mortality, while classifying 19–31% of patients as low risk. While there is a growing body of evidence for PE risk stratification rules in patients with active cancer, larger, prospective studies are needed before rules can be confidently applied in clinical practice.

Authors' contributions Study concept and design: ERW, CGK, CIC, and EN. Acquisition of data: ERW, CGK, JTC, CIC, and EN. Analysis and interpretation of data: ERW, CGK, JTC, CIC, and EN. Drafting the manuscript: ERW, CGK, JTC, GHL, NMK, CIC, and EN. Critical revision of the manuscript for important intellectual content: ERW, CGK, JTC, GHL, NMK, CIC, and EN. Administrative, technical, or material support: ERW, CGK, and CIC. Study supervision: CGK. CGK had full access to all the

study data and take full responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICJME) and were fully responsible for all content and editorial decisions and were involved in all stages of the manuscript development.

Compliance with ethical standards

Conflicts of interest CIC has received grant funding and consultancy fees from Janssen Scientific Affairs, LLC; Bayer Pharma AG; and Boehringer-Ingelheim Pharmaceuticals, Inc. ERW has received support for research from Pfizer Inc. NMK reports personal fees from Janssen, Myriad, Daiichi, Coherus, and Halozyme. No other authors have conflicts of interest germane to this manuscript.

Research involving human participants and/or animals/informed consent This study was approved by the Institutional Review Board at our Institution. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent was not required.

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