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ORIGINAL ARTICLE

The prognostic value of respiratory symptoms and performance status in ambulatory cancer patients and unsuspected pulmonary embolism; analysis of an international, prospective, observational cohort study

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Abstract

Background: Optimal risk stratification of unsuspected pulmonary embolism (UPE) in ambulatory cancer patients (ACPs) remains unclear. Existing clinical predictive rules (CPRs) are derived from retrospective databases and have limitations. The UPE

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registry is a prospective international registry with pre-specified characteristics of ACPs with a recent UPE. The aim of this study was to assess the utility of risk factors captured in the UPE registry in predicting proximate (30-, 90- and 180-day) mortality and how they performed when applied to an existing CPR.

Objectives: To evaluate risk factors for proximate mortality, overall survival, recurrent venous thromboembolism and major bleeding, in the patients enrolled in the UPE registry cohort.

Methods: Data from the 695 ACPs in this registry were subjected to multivariate logistic regression analyses to identify predictors independently associated with proximate mortality and overall survival. The most consistent predictors were applied to the Hull CPR, an existing 5-point prediction rule.

Results: The most consistent predictors of mortality were patient-reported respiratory symptoms within 14 days before, and ECOG performance status at the time of UPE. These predictors applied to the Hull-CPR produced a consistent correlation with proximate mortality and overall survival (area under the curve [AUC] = 0.70 [95% CI 0.63, 077], AUC = 0.65 [95% CI 0.60, 070], AUC = 0.64 [95% CI 0.59, 068], and AUC = 0.61, 95% CI 0.57, 0.65, respectively).

Conclusion: In ACPs with UPE, ECOG performance status logged contemporaneously to the UPE diagnosis and respiratory symptoms prior to UPE diagnosis can stratify mortality risk. When applied to the HULL-CPR these risk predictors confirmed the risk stratification clusters of low-intermediate and high-risk for proximate mortality as seen in the original derivation cohort.

KEYWORDS
cancer associated thrombosis, clinical prediction rule, incidental pulmonary embolism, risk assessment model, unsuspected pulmonary embolism

1 | INTRODUCTION

The widespread use of multi-slice whole body computed tomography in diagnosis, staging, assessment of response to treatment, and cancer surveillance has resulted in an increase in the incidence of what has been termed incidental or unsuspected pulmonary embolism (UPE) in cancer patients.[1-3] Just over half of all pulmonary embolism (PE) diagnosed in oncology centers nowadays is unsuspected.[4,5] The prevalence of UPE in the cancer population is reported to be as high as 5%.[6]

Existing evidence suggests that there is no substantial difference in outcomes between clinically suspected PE and incidentally diagnosed PE cohorts[7,8] or between distal vs. more proximal UPE.[8,9] In general, international guidelines for UPE, mostly informed by evidence from retrospectively acquired cohort studies on clinically suspected PE or mixed clinically suspected PE and UPE in cancer patients, recommend the same management for cancer patients with UPE as for suspected PE.[10,11]

UPE patients are often seen as outpatients within limited time clinical encounters, when the clinician is called on to make a management decision guided only by basic laboratory information and clinical expertise. Among some patients that may have low level or no obvious extra clinical impairment there will be others with substantially worse clinical features occasionally in need of immediate inpatient care. Risk stratification for these ambulatory patients with a clinical prediction rule (CPR) is desirable for the standardized safe outpatient management, addressing the detrimental implications on quality of life and healthcare costs from unnecessary admissions to hospital.[12] It is also worth recognizing that the ambulatory setting is not the only one in which UPE is diagnosed. UPE and more generally

Essentials

- Performance of prognostic models in cancer outpatients with unsuspected PE is limited.
- This registry included the largest prospective cohort of ambulatory cancer patients with unsuspected PE.
- Respiratory symptoms before, and performance status at UPE diagnosis consistently correlated with risk of death.
- A clinical prediction rule combining these factors predicted early mortality with good accuracy.

venous thromboembolism (VTE) is occasionally found in the context of imaging of poor performance inpatients already very ill or dying from cancer progression or complications and for whom CPR stratification exercises are pointless.[13]

Finally other adverse outcomes associated with UPE treatment such as major or clinically relevant non-major bleeding or VTE recurrence, remain a challenge to predict. For example, a recent analysis of the data of this study using the Ottawa score failed to predict recurrent VTE.[14]

In the present analysis, we assessed the association between several patient-, tumor-, and UPE-related characteristics and clinical outcomes, including recurrent VTE, major bleeding, and death. In addition, we evaluated the performance of the predictors that were found to consistently predict proximate (up to 6 months) and overall mortality when applied to an existing CPR for UPE, the Hull CPR.[9]

2 | PATIENTS AND METHODS

2.1 | Design and patients

Detailed study protocol of the study (ClinicalTrials.gov; NCT01727427) can be found in the primary manuscript.[8]

2.2 | Patients

Unselected adults with active solid or hematological cancer and a first diagnosis of unsuspected PE were included. Unsuspected PE had to be diagnosed in the 2 months prior to inclusion and was defined as an intraluminal filling defect in one or more pulmonary arteries on CT in the absence of a clinical suspicion of PE. Patients were excluded if they already received anticoagulant therapy at unsuspected PE diagnosis, or if they had a life expectancy of less than 3 months.

2.3 | Predefined outcomes and analyses

The main study outcomes of recurrent VTE, major bleeding, and all-cause mortality have already been reported.[8] In this study the primary analysis aimed to investigate the impact of baseline clinical characteristics on the incidence of recurrent VTE, major bleeding, mortality at the 30-, 90- and 180-day time points, and overall survival. A composite endpoint of bleeding and recurrent VTE was also considered, as a gross representation of anticoagulant treatment failure.

2.4 | Definitions

Active cancer was defined as objectively confirmed recurrent, regionally advanced, or metastatic cancer, or cancer that was diagnosed or treated within the 12 months prior to enrolment.

The ISTH definition for major bleeding was adopted. Major bleeding is defined as clinically overt bleeding associated with a decrease in hemoglobin of 2 g/dl or more, requiring transfusion of two or more units of red blood cells, occurring in a critical site, or as fatal bleeding.

Recurrent VTE was defined as 'objectively confirmed symptomatic or incidental DVT of the lower extremity or PE, or PE-related death'.

2.5 | Data collection

The baseline variables of the main study used for this analysis were collected in a standardized electronic case report form (Oracle Clinical Remote Data Capture 4.6.6, Oracle USA, Inc.) and included demographic characteristics, medical history, medication use including cancer therapy, laboratory test results, UPE characteristics and treatment, and signs and symptoms prior to UPE diagnosis. The study collected data on PS using the Karnofsky score. To assess a comparator to existing CPR in the literature,[9] a conversion of Karnofsky to ECOG performance status (PS) was undertaken.

2.6 | Analysis - statistical considerations

Baseline characteristics and clinical measures were summarized with descriptive statistics. Survival and incidences of mortality, VTE recurrence, and major bleeding were reported for the overall study period as well as at 30-, 90- and 180-day follow-up.

Variables explored as predictors included age (with a cut-off of 70 years), gender, ECOG PS, cancer type, presence of metastatic disease, presence of respiratory symptoms within the previous 14 days from UPE diagnosis (Table 1), presence of abnormal vital signs (tachycardia, hypotension, atrial fibrillation) and finally the location and extent of imaged UPE. Cancer types were grouped as in the Khorana predictive score for VTE in cancer to explore the potential prognostic merit of VTE-prone cancer histology. Exploratory analyses regarding potential correlations of baseline symptomatology with the type of cancer, metastatic disease, and the extent of the imaged UPE were also performed.

Correlation analyses between baseline symptomatology (yes/no), ECOG PS, and incidence of proximate mortality were performed (see Supplementary Material).

Multivariate logistic regression analysis was used to assess the association between baseline ECOG PS categories, UPE anatomical location and extent, presence of metastatic disease, symptoms/clinical signs and incidence risks of mortality, VTE recurrence and major bleeding at 30-, 90- 180-day and overall study period, adjusting for age (>70 years) and gender. Survival analyses were then undertaken to evaluate the association between these factors and long-term incidence risks of recurrent VTE and major bleeding using Fine and Gary competing risk model, in which death not related to UPE or bleeding was treated as a competing event. Hazard ratios and relative 95% confidence intervals (95% CI) on overall survival were calculated by Cox regression.

TABLE 1 Characteristics of the 695 patients with unsuspected pulmonary embolis

Variable	
Age in years mean (SD)	(12)
>70 years, *n* (%)	256 (37.8%)
Male sex, n (%)	404 (58.1%)
Cancer type	
High risk (pancreas, esophagus, gastric)	98 (14.1%)
Non-high risk (all others)	597 (85.9%)
Distant metastases, n (%)	448 (64.5%)
Karnofsky performance status, median (IQR)	80 (70–90)
**ECOG Performance Status*	
0	125 (18.6%)
½	379 (54.5%)
¾	124 (17.8%)
Missing	67 (9.6%)
Risk factors for venous thromboembolism, n (%)	
Previous venous thromboembolism	69 (9.9%)
Recent surgery*	52 (7.5%)
Recent immobilization of at least 3 days*	91 (13.1%)
Central venous catheter	181 (26.0%)
Ongoing chemotherapy*	374 (53.8%)
Ongoing hormonal therapy*	37 (5.3%)
Symptoms (within 14 days of unsuspected PE diagnosis), n (%)	
Fatigue	194 (27.9%)
Dyspnea on exertion	120 (17.3%)
Chronic dyspnea	74 (10.7%)
Signs, n (%)	
Tachycardia	50 (7.2%)
Hypotension	35 (5%)
Atrial Fibrillation	3 (0.4%)
Platelet count, n × 100 000/ml, median (IQR)	229 (167–295)
<150 000/ml, *n* (%)	125 (18%)
Creatinine clearance, ml/min, median (IQR)	79 (63–93)
<50 ml/min, *n* (%)	51 (7.3%)
Most proximal extent incidental PE, n (%)	
Central	100 (15%)
Lobar	285 (41%)
Segmental	238 (34%)
Subsegmental	63 (9.1%)
Unknown	9 (1.3%)
Number of branches involved by thrombus	
'Multiple' >6	72 (10.4%)
'Multiple' 2–5	375 (54.0%)
Single	172 (24.8%)

A previously described analysis of a single center prospectively assembled cohort of ambulant UPE patients (9) had resulted in the derivation of a CPR, the Hull-CPR, based on symptoms and PS. This CPR is a five-point prediction score combining ECOG PS category and patient symptoms and producing three risk clusters [low (0), intermediate (1–2), high risk (3–4)] (Table S1) which showed significant predictive ability for 30-, 90- and 180-Day mortality. We proceeded to an exploratory evaluation of this CPR in the current cohort, utilizing the "respiratory symptoms within 14 days" variable as a surrogate to the "any new or worsening symptoms variable" utilized in the Hull CPR.[9] Six hundred and twenty-five patients (90%) were included in this analysis. There were 70 patients without calculable Hull CPR scores: 67 patients with missing ECOG data and five patients with missing symptoms. Two patients were missing both.

Receiver operator characteristic analysis was used to assess the discriminatory performance of the Hull CPR on 30-90-180-day mortality as well as overall survival.

All analyses were performed in Stata v16.0.

3 | RESULTS

A total of 695 patients were included. Mean age was 66 years, 58% were male, and the median Karnofsky PS was 80% (interquartile range [IQR] 70, 90). Median follow-up duration was 305 days (IQR 170, 377). Anticoagulant treatment was initiated in 675 patients (97%) The most frequently reported reasons for withholding anticoagulant therapy were bleeding risk ($n = 7$) and thrombocytopenia.

The majority of patients were treated with low-molecular-weight heparins ($n = 600$, 89%). Anticoagulant treatment was permanently discontinued in 189 patients (28%) during follow-up, mainly due to end of the intended treatment period ($n = 69$; 37%), resolution of the index incidental PE on imaging ($n = 40$; 21%), or bleeding ($n = 26$; 14%). Median overall treatment duration was 216 days (IQR, 136 to 360). It was 214 days (IQR, 138 to 360) for low-molecular-weight heparins, 227 days (IQR, 110 to 331), for direct oral anticoagulants, and 269 days (IQR, 200 to 367) for vitamin K antagonists.

Symptoms possibly related to PE in the 14 days prior to UPE diagnosis were reported by 44% of patients. UPE was confined to the subsegmental arteries in 63 patients (9.1%). A comprehensive description of all characteristics and demographics can be found in the parent publication.[8] Table 1 includes the main characteristics and demographics.

Exploratory univariate correlation analyses are presented in the supplementary material (Tables SB1-7). Reported symptomatology demonstrated a correlation with the number of imaged thrombi ($p = .03$) but not with their central proximity ($p = .64$). Symptoms were also associated with high-risk cancer type ($p < .01$), but not with the presence of metastatic disease ($p = .92$). Also baseline ECOG PS did correlate with the presence of metastatic disease ($p < .001$; see Supplementary Material Section C).

3.1 | Recurrent venous thromboembolism

The cumulative incidence of on-treatment recurrent VTE during 12-month follow-up was 4.9% (95% CI 3.4 to 6.8). Overall recurrent VTE was diagnosed in 41 patients (5.9%), corresponding to a 12-month

cumulative incidence of 6.0% (95% CI 4.4 to 8.1). Recurrent VTE was symptomatic in 53% of patients and incidentally detected in 47%.

Multivariate logistic regression and survival analysis performed with clinical and laboratory factors for recurrent VTE found no factors associated with this outcome at any time point (Table SD1 & 2).

3.2 | Major bleeding

Major bleeding occurred in 39 patients (12-month cumulative incidence, 5.7%, 95% CI 4.1 to 7.7).

Multivariate logistic regression and survival analysis performed with clinical factors for major bleeding found no factor to be associated with this outcome at any time point (Table SD1 & 2).

Similarly, no clinical factors were associated with the composite of major bleeding and recurrent VTE (Tables 2 and 3).

3.3 | Mortality

Overall, 283 patients died corresponding to a cumulative incidence at 12 months of 41% (95% CI 39 to 46). Cancer was the most frequent cause of death (41%). Bleeding and PE accounted for 3.8% of deaths. Detailed data have been previously published.[8]

3.4 | Prognostic factors for mortality

The most consistent predictors of mortality were the patient-reported symptoms in the 14 days prior to UPE diagnosis, and the ECOG PS score at the time of UPE diagnosis. The presence of metastatic-incurable cancer had strong association with overall survival, 90- and 180-day mortality but not with 30-day mortality, whilst cancer type was associated with 30-day mortality and OS but not with 90- and 180-day mortality (Table 4).

3.5 | Exploratory application of the Hull Clinical Prediction Rule

As was seen for the original derivation study of the Hull CPR, the current analysis also identified three risk clusters (Figure 1).

Consistent correlation was found with 30-, 90-, 180-day mortality and overall survival (AUC = 0.70, 95% CI 0.63, 077, AUC = 0.65, 95% CI 0.60, 070, AUC = 0.64, 95% CI 0.59, 068 and AUC = 0.61, 95% CI 0.57, 0.65, respectively; Table S2 and Figure S1).

4 | DISCUSSION

In this study we found that the most consistent predictors of mortality were the patient-reported respiratory symptoms 14 days before, and ECOG PS score at the time of UPE diagnosis. A modified CPR

TABLE 2 Multivariate logistic regression analyses for 30- 90- &180- day (proximate) mortality, and composite recurrent VTE /major bleeding

	Risk of 30 days rVTE/MB		Risk of 30 days mortality		Risk of 90 days rVTE/MB		Risk of 90 days mortality		Risk of 180 days rVTE /MB		Risk of 180 days mortality	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age (>70)	1.39 (0.52, 3.76)	.51	1.34 (0.66, 2.73)	.42	1.61 (0.76, 3.43)	.22	1.33 (0.83,2.13)	.24	1.06 (0.57, 1.98)	.85	1.21 (0.82, 1.80)	.34
Gender (male)	0.48 (0.18, 0.30)	.15	1.11 (0.55, 2.26)	.77	0.95 (0.45, 2.03)	.90	1.19 (0.74, 1.91)	.47	0.89 (0.49, 1.64)	.72	1.24 (0.84, 1.84)	.28
ECOG PS 0 (REF.GR)												
ECOG PS 1-2	0.54 (0.17, 1.72)	.29	2.44 (0.55, 10.86)	.24	0.44 (0.19, 1.04)	.06	3.64 (1.41, 9.42)	<.01**	0.48 (0.24, 0.98)	.04*	2.82 (1.47, 5.43)	<.01**
ECOG PS 3-4	0.47 (0.10, 2.11)	.32	5.40 (1.13, 25.90)	.04*	0.30 (0.09,1.02)	.05	5.09 (1.83, 14.11)	<.01**	0.40 (0.15, 1.04)	.06	3.57 (1.72, 7.42)	<.01**
Cancer Dx (high risk)	2.13 (0.66, 6.86)	.21	2.46 (1.12, 5.39)	.03*	1.34 (0.49, 3.67)	.57	1.38 (0.76, 2.52)	.29	1.08 (0.46, 2.54)	.86	1.53 (0.92, 2.55)	.10
Metastasis (yes)	1.38 (0.47, 4.11)	.56	1.67 (0.74, 3.78)	.22	1.49 (0.65, 3.42)	.34	1.71 (1.00, 2.92)	.05	1.20 (0.63, 2.30)	.58	2.01 (1.30, 3.13)	<.01**
Symptoms – 14D	0.84 (0.30, 2.36)	.74	4.19 (1.86, 9.43)	<.01**	1.10 (0.51, 2.39)	.81	2.18 (1.35, 3.53)	<.01**	1.21 (0.65, 2.25)	.54	1.88 (1.27, 2.79)	<.01**
Signs – Any	1.03 (0.22, 4.79)	.97	1.45 (0.59, 3.59)	.42	1.28 (0.42, 3.93)	.66	1.31 (0.69, 2.51)	.41	1.66 (0.72, 3.82)	.24	1.32 (0.75, 2.30)	.33

Abbreviation: OR, Odds Ratio.

*Indicates the *p* value is significant at .05 level.

**Indicates it is significant at .01 level.

TABLE 3 Competing risk model for recurrent VTE/major bleeding as composite outcome[a]

	VTE recurrence/major bleeding		Overall survival	
	HR[b] (95% CI)	*p* value	HR (95% CI)	*p* value
Age (>70)	0.72 (0.42, 1.25)	.25	1.20 (0.93, 1.55)	.17
Gender (male)	0.87 (0.53, 1.44)	.60	1.09 (0.85, 1.41)	.50
ECOG PS 0 (REF. GR)				
ECOG PS 1-2	0.65 (0.35, 1.23)	.19	1.57 (1.05, 2.36)	.03*
ECOG PS 3-4	0.51 (0.21, 1.20)	.12	2.08 (1.32, 3.28)	<.01**
Cancer diagnosis (high risk)	1.28 (0.66, 2.49)	.47	1.66 (1.21, 2.29)	<.01**
Metastasis (yes)	0.99 (0.58, 1.71)	.98	2.01 (1.49, 2.70)	<.01**
Symptoms-14D	0.93 (0.55, 1.58)	.80	1.46 (1.13, 1.90)	<.01**
Any signs	1.19 (0.55, 2.59)	.65	1.35 (0.94, 1.93)	.10

[a]We observed 64 composite events and 283 deaths in the overall survival analyses.

[b]Hazard Ratio (95% Confidence Interval).

*Indicates the *p* value is significant at .05 level.

**Indicates it is significant at .01 level.

TABLE 4 Summarized significant prognostic risk factors for mortality

	Proximate mortality risk, odds ratios (95% CI) and *p* values		Long term mortality risk hazard ratios (95% CI) and *p* values	
Significant risk factors	**30 days**	**90 days**	**180 days**	**Overall survival**
ECOG PS categories (ECOG PS 0 as Reference group)	Overall $p = .05$*	Overall $p < .01$**	Overall $p < .01$**	Overall $p < .01$**
ECOG PS 1-2	2.44 (0.55, 10.86)	3.64 (1.41, 9.42)	2.82 (1.47, 5.43)	1.57 (1.05, 2.36)
ECOG PS 3-4	5.40 (1.13, 25.90)	5.09 (1.83, 14.11)	3.57 (1.72, 7.42)	2.08 (1.32, 3.28)
Symptoms-14D	$p < .01$**	$p < .01$**	$p < .01$**	$p < .01$**
	4.19 (1.86, 9.43)	2.18 (1.35, 3.53)	1.88 (1.27, 2.79)	1.46 (1.13, 1.90)
Metastases present	$p = .22$	$p = .05$*	$p < .01$**	$p < .01$**
	1.67 (0.74, 3.78)	1.71 (1.00, 2.92)	2.01 (1.30, 3.13)	2.01 (1.49, 2.70)
Cancer RS diagnosis	$p = .03$*	$p = .29$	$p = .10$	$p < .01$**
	2.46 (1.12, 5.39)	1.38 (0.76, 2.52)	1.53 (0.92, 2.55)	1.66 (1.21, 2.29)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status; RS, risk stratified.

*Indicates the *p* value is significant at .05 level.

**Indicates it is significant at .01 level.

that incorporated these determinants showed consistent correlation with 30-, 90- and 180-day mortality and overall survival.

Clinical prediction rules for PE in the general population have slowly but certainly shifted the management of many patients to the outpatient setting.[15] Their utility has been recently comprehensively reviewed.[16] However, the generic CPRs in the risk stratification of cancer related PE have substantial limitations. For example the Pulmonary Embolism Severity Index (PESI)[17-19] or the simplified PESI,[20,21] two of the more often used scores developed from generic suspected PE cohorts, give parameters such as age and the existence of cancer substantial weighting. In the Hull CPR cohort, only 28 of 234 patients fell into the PESI I-II categories with the majority of patients (185 of 234) being PESI III-IV, despite 87% of these patients being managed as outpatients.[9] It is not surprising therefore that these CPRs perform poorly in the prediction of 30-, 90- and 180-day mortality in ambulatory cancer patients with UPE.[9,22]

Prognostic scores have been suggested specifically for patients with cancer and PE although these tools relate predominantly to the suspected PE setting.[22,23] The RIETE score[22] when tested in an ambulatory cohort of cancer patients with UPE proved limited in separating high and low risk groups for proximate mortality.[9,22] The POMPE-C appeared even more limited for the ambulatory cancer patient with UPE, as discriminating factors for mortality were linked to terminal cancer status and hospitalization.[23]

The prognostic relevance of symptoms in UPE has gained substantial attention in the literature with evidence that the symptoms may convey a poor prognosis.[6,24] The EPIPHANY index which was developed from a mixed cohort of cancer patients with suspected PE (47%) and UPE (53%) did take symptomatology into account.[25]

However, these patients had high 30- and 90-day mortality (11% and 27% respectively), notably the 90-day mortality for the symptomatic UPE patients (47%) was double that of the highest risk group

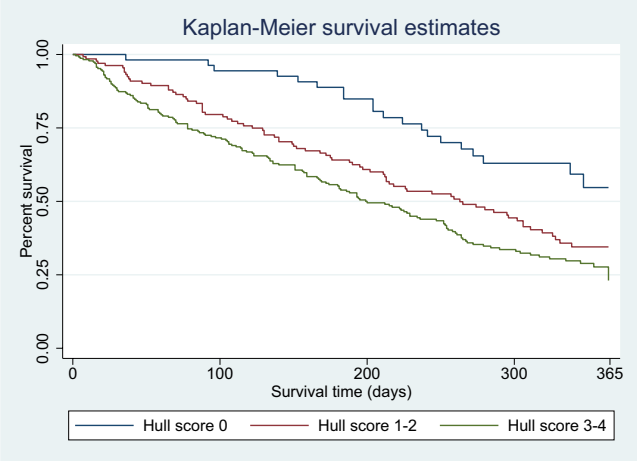

FIGURE 1 Kaplan-Meier survival curves for the 625 patients included in the present analysis by Hull CPR groups based on ECOG PS and the presence of symptoms.[9] (Low Risk: 0 - blue -, Intermediate Risk: 1-2 - red -, High Risk: 3-4 - green-)

seen in this study (Table 5). This suggests that purely radiological inclusion criteria have enrolled an unselected cohort that includes very ill non-ambulatory patients. Even the 4S derivative rule from the EPIPHANY dataset does little more than categorize the truly asymptomatic UPE (TAUPE)- only subgroup of the ambulatory population[26,27] leaving the rest of the cohort un-stratified.

In contrast, the population included in this study, where the selection criteria required an estimation of an at least 3-month survivorship by the investigator, had a low 30-day mortality (5.6%) and 80% of patients had an ECOG PS 0-2 reflective of a truly ambulatory cohort. Similar low 30-day mortality and proportion of patients with ECOG 0-2 were seen in the few other prospective cohorts of selected UPE ambulatory patients (Table 5).

To our knowledge, the only available prospectively collected UPE cohorts of ambulatory cancer patients, one single center and this registry, with similarities in patient characteristics seem to reach the same conclusion: a simple assessment based on easily derived clinical parameters can be used to risk stratify ambulatory cancer patients with UPE(Figures 1 and S1).

Whether the use of more granular validated tools that assess and score symptoms would improve on these findings is not known but an interesting issue for future research.

Lastly, this study was not able to generate any risk factors for major bleeding, recurrent VTE or composite endpoint (Table 2). This is likely to be because of the low incidence of both these events.

Although the application of the predictors of this study to the existing CPR (the Hull CPR) produced consistent results with those of the Hull CPR derivation cohort,[9] the current analysis falls somewhat short of a full external validation of this CPR. The 'symptoms' data collection scope was subtly different. In this study qualifying symptoms were existence of respiratory related symptoms (chronic dyspnea, dyspnea on exertion, cough) and fatigue 14 days before diagnosis, while in the Hull CPR derivation cohort any new or worsening existing symptoms before the UPE diagnosis were considered. It is conceivable that this wider definition could have included symptoms such as swollen legs, abdominal or lower back pain not captured by the stricter definition used in the UPE registry. The differences in proportion of patients with symptoms, 52% in the Hull cohort compared to 44% in this study, may point to this. Patients were included in this study up to 2 months after UPE diagnosis, so recall bias may have occurred with regard to preceding signs and symptoms. In addition, the PS recording was not contemporaneous to UPE diagnosis for all patients and it is possible that for some patients status had worsened or improved at the time of evaluation.

Several other limitations also deserve acknowledgment. This one-off assessment at baseline of symptoms or PS score is not discriminatory of causality and there is also an argument that symptoms are qualitative and not quantifiable. However, the findings from this study and Hull CPR derivation cohort suggest that patients can accurately recognize symptom appearance, evolution, or timing. There are multiple questionnaire-based tools that inform the

TABLE 5 Mortality characteristics of prospectively collected patient cohorts of UPE

Study/Cohort	Patient number	30 Day (%)	90 Day (%)	180 day (%)
UPE-REGISTRY ***(All)***	695	5.6	15	25.2
HULL score 3–4 (HIGH RISK)	324	9.6	20.4	32.4
HULL CPR derivation cohort	234	3.4	15	31
SELECT-D-UPE Enrolled[a]	211	5	15	29
EPIPHANY: All UPE	283	11	27	NR
S-UPE[b]	129	20	43	NR
TA-UPE[c]	154	3	12	NR

[a]Personal communication professor Annie Young 211 patients enrolled in the SELECT-D study had UPE.[30] Patients were followed up for a maximum of 24 months; the median survival for the patients with an UPE was 14.1 months (95% CI 9.8–18.6 months). The survival rate was: 95% (95% CI 91–97%) at 1 month, 89% (95% CI 84–93%) at 2 months, 85% (95% CI 79–89%) at 3 months and 71% (95% CI 64–77%) at 6 months.

[b]S-UPE 'Symptomatic unexpected pulmonary embolism'.

[c]TA-UPE 'Truly asymptomatic unexpected pulmonary embolism'.

management and prognosis of cancer patients based on their symptoms.[28] Also, the contemporaneous status of the tumor response was not recorded; yet, establishing response status with formal response evaluation criteria in solid tumors may not be a deliverable output in the acute outpatient setting of assessing an UPE. The lack of additional discriminatory power of metastatic disease, also seen in the Hull dataset, suggests that the patients recorded as symptomatic and with impaired PS may already encompass the poor prognosis of a progressing cancer, whether or not extra symptoms or additional PS impairment is contributed by the UPE. The lag time to treatment from diagnosis of UPE was not recorded, with the possibility of a bias on the mortality data, however it has been shown previously that whether a patient is referred from radiology in a 'first pass' setting, i.e. while still in the department, or at a belated 'second pass' subsequent to routine radiology review, does not substantially impact on proximate mortality.[29]

Strengths of this study include the prospective design, large study group, the clinically orientated inclusion criteria and the low rate of loss to follow-up. Information entered in the electronic case report form and adjudication forms were regularly assessed for inconsistencies, ensuring high-quality data. The risk of outcome bias was low as all clinical outcomes were centrally adjudicated by a committee whose members were blinded to treatment.

Confirmation of this type of easy to use prediction rule could allow many patients to benefit from a same day discharge outpatient management of ambulatory patients with UPE.[9] Indeed the experience in Hull where a nurse led service manages these patients based on the Hull CPR, is that less than 15% of patients require admission.[12]

In conclusion, this study identified that important risk factors for death for ambulatory patients with a UPE diagnosis were the type of malignancy, the existence of metastases, the ECOG PS logged at the time of the UPE diagnosis and the patient experiencing respiratory symptoms within the 14 days prior to UPE diagnosis. However, only ECOG PS and self-reported recent respiratory symptoms consistently stratified risk of death and when applied to the Hull CPR produced comparable results to the Hull CPR derivation cohort.

CONFLICT OF INTEREST

Anthony Maraveyas Honoraria: Bristol-Myers Squibb, Bayer, Pfizer, Boehringer Ingelheim, Rovi; Consulting or Advisory Role: Bristol-Myers Squibb, Bayer, Pfizer, Halozyme Speakers' Bureau: Bristol-Myers Squibb, Bayer Research Funding: Bristol-Myers Squibb (Inst), Bayer; Isabelle Mahé Consulting or Advisory Role: Bristol-Myers Squibb Speakers' Bureau: LEO Pharma, Sanofi, Bayer Research Funding: Bristol-Myers Squibb (Inst), Pfizer (Inst), LEO Pharma (Inst); Travel, Accommodations, Expenses: LEO Pharma, Bristol-Myers Squibb; Laurent Bertoletti Consulting or Advisory Role: Bayer, Bristol-Myers Squibb, LEO Pharma, Aspen Pharma, Sanofi Travel, Accommodations, Expenses: Aspen Pharma, Bristol-Myers Squibb, Bayer; Jan Beyer-Westendorf Honoraria: Bayer, Boehringer Ingelheim, Daiichi Sankyo, Pfizer; Consulting or Advisory Role: Bayer, Boehringer Ingelheim, Daiichi Sankyo, Pfizer; Research Funding: Bayer, Boehringer Ingelheim, Daiichi Sankyo, Pfizer; Travel, Accommodations, Expenses: Bayer, Boehringer Ingelheim, Daiichi Sankyo, Pfizer; Francis Couturaud Consulting or Advisory Role: Bristol-Myers Squibb, Bayer, AstraZeneca; Travel, Accommodations, Expenses: AstraZeneca, GlaxoSmithKline, Bayer, Bristol-Myers Squibb; Andrés Muñoz Consulting or Advisory Role: Celgene, Sanofi, Pfizer, Bristol-Myers Squibb, LEO Pharma, Daiichi Sankyo, Bayer, Halozyme, Speakers' Bureau: Rovi, Research Funding: Sanofi, LEO Pharma, Patents, Royalties, Other Intellectual Property: Risk assessment model in venous thromboembolism in patients with cancer. Travel, Accommodations, Expenses: Celgene, Roche, Merck Serono; Mercedes Biosca Honoraria: LEO Pharma, Sanofi, Rovi. Consulting or Advisory Role: LEO Pharma, Sanofi Speakers' Bureau: LEO Pharma, Sanofi, Rovi Travel, Accommodations, Expenses: LEO Pharma, Sanofi, Rovi; Nick van Es Consulting or Advisory Role: LEO Pharma (Inst); Marcello Di Nisio Consulting or Advisory Role: Daiichi Sankyo, Bayer, Pfizer, LEO Pharma, Aspen Pharma; No other potential conflicts of interest are reported.

AUTHOR CONTRIBUTIONS

Conception and design: Anthony Maraveyas, Georgios Bozas, Chao Huang, Noémie Kraaijpoel, Marcello Di Nisio; Provision of study materials or patients: Laurent Bertoletti Annemarieke Bartels-Rutten, Isabelle Mahe, Francis Couturaud, Mercedes Biosca, Anthony Maraveyas; Collection and assembly of data: Noémie Kraaijpoel, Isabelle Mahe, Andres Muñoz, Laurent Bertoletti, Annemarieke Bartels-Rutten, Nick van Es, Diana I. Iosub, Francis Couturaud, Mercedes Biosca, Teresa Lerede, Marcello Di Nisio; Data analysis and interpretation: Anthony Maraveyas Georgios Bozas, Chao Huang, Noémie Kraaijpoel, Marcello DiNisio, Nick van Es; Manuscript writing: All authors; Final approval of manuscript: All authors; Accountable for all aspects of the work: All authors.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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APPENDIX 1

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