Validation of the HULL Score clinical prediction rule for unsuspected pulmonary embolism in ambulatory cancer patients

Farzana Haque[1,2], Jessamine Ryde[1], Laura Broughton[2], Chao Huang[2], Sifut Sethi[1], Andrew Stephens[1], Annet Pillai[1], Shagufta Mirza[1], Victoria Brown[1], Ged Avery[1,2], Georgios Bozas[1] and Anthony Maraveyas[1,2]

[1]Hull University Teaching Hospital NHS Trust, Castle Hill Hospital, Hull, UK. [2]Hull York Medical School, Allam Medical Building, University of Hull, Hull, UK.

Corresponding author: Farzana Haque (farzana.haque4@nhs.net)

Shareable abstract (@ERSpublications)
Existing CPRs have a limited role in cancer outpatients with UPE. The HULL Score CPR uses ECOG-PS and self-reported symptoms at UPE diagnosis. Validation of the HULL Score CPR to predict early mortality facilitates outpatient management of UPE. https://bit.ly/3Resqpf

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Abstract

Background Clinical prediction rules (CPRs) developed to predict adverse outcomes of suspected pulmonary embolism (PE) and facilitate outpatient management have limitations in discriminating outcomes for ambulatory cancer patients with unsuspected PE (UPE). The HULL Score CPR uses a 5-point scoring system incorporating performance status and self-reported new or recently evolving symptoms at UPE diagnosis. It stratifies patients into low, intermediate and high risk for proximate mortality. This study aimed to validate the HULL Score CPR in ambulatory cancer patients with UPE.

Patients and methods 282 consecutive patients managed under the UPE-acute oncology service in Hull University Teaching Hospitals NHS Trust were included from January 2015 to March 2020. The primary end-point was all-cause mortality, and outcome measures were proximate mortality for the three risk categories of the HULL Score CPR.

Results 30-day, 90-day and 180-day mortality rates for the whole cohort were 3.4% (n=7), 21.1% (n=43) and 39.2% (n=80), respectively. The HULL Score CPR stratified patients into low-risk (n=100, 35.5%), intermediate-risk (n=95, 33.7%) and high-risk (n=81, 28.7%) categories. Correlation of the risk categories with 30-day mortality (area under the curve (AUC) 0.717, 95% CI 0.522–0.912), 90-day mortality (AUC 0.772, 95% CI 0.707–0.838), 180-day mortality (AUC 0.751, 95% CI 0.692–0.809) and overall survival (AUC 0.749, 95% CI 0.686–0.811) was consistent with the derivation cohort.

Conclusion This study validates the capacity of the HULL Score CPR to stratify proximate mortality risk in ambulatory cancer patients with UPE. The score uses immediately available clinical parameters and is easy to integrate into an acute outpatient oncology setting.

Introduction

Cancer patients are at a higher risk of being diagnosed with an unsuspected pulmonary embolism (UPE) than the general population. An UPE is a pulmonary embolism (PE) diagnosed by computed tomography (CT) performed for reasons other than a clinical suspicion of PE. The imaging, therefore, has been performed with a non-angiography protocol. The widespread use of whole-body multislice CT in cancer diagnosis, assessment of treatment response and surveillance has resulted in an apparent increase in the incidence of UPE [1–3]. A meta-analysis including over 10 000 patients reported a weighted mean prevalence of UPE in cancer patients of 3.1% compared to 2.5% in non-cancer patients [4]. In a recent review, the incidence varied from <1% to ⩾15% [5], representing half of the PE currently diagnosed in oncology [5, 6]. UPE is also increasingly described in cancer-associated thrombosis randomised controlled trials [7].

UPEs share similar risk factors and embolic burden with suspected PEs [8]. Likewise, consequences of UPE do not differ significantly from suspected PE, with a similar prognosis to symptomatic events and comparable 1-year recurrence risks, risks of major bleeding complications and overall survival (OS) and mortality rates [9–11]. Therefore, international clinical guidelines recommend treating all patients with UPE with the same long-term (at least 3–6 months) anticoagulation as for suspected PE [12].

There are several clinical prediction rules (CPRs) for risk stratification of PE diagnosed upon suspicion [13–16]. These are designed to facilitate outpatient management but have limitations in discriminating outcomes for ambulatory cancer patients with UPE [17]. There are also limitations with cancer-specific PE-CPRs when it comes to risk stratifying ambulatory cancer patients with UPE [18–20].

From the study of a cohort of 234 ambulatory cancer patients with UPE, we found that consistent predictors of proximate mortality were the patients' reports of new symptoms or worsening of pre-existing symptoms, along with Eastern Cooperative Oncology Group (ECOG) performance status (PS) impairment at the time of UPE diagnosis. Using these parameters, we derived a clinical prognostic score (the HULL Score CPR) predicting proximate mortality [17]. The validity of using symptoms and PS in this setting was recently reaffirmed in an external dataset, and the HULL Score CPR was validated [21].

This study aimed to provide a follow-on validation of the HULL Score CPR in ambulatory cancer patients with UPE managed at Hull University Teaching Hospitals (HUTH) NHS Trust.

Patients and methods

In the Queen's Centre for Oncology and Haematology, HUTH NHS Trust, all patients with UPE are managed uniformly under a nurse-led "Unsuspected PE Pathway". This is a dedicated referral and treatment pathway for oncology patients with UPE found on routine CT scans [22]. These patients are risk-stratified by the HULL Score CPR [17], which stratifies patients into risk categories for proximate mortality (30, 90 and 180 days). It uses a 5-point scoring system (HULL Score (HS)) incorporating ECOG-PS and self-reported new or recently evolving symptoms at UPE diagnosis. The presence of new or worsening symptoms is weighted 1 point, ECOG 1 or 2 is weighted 2 points, and ECOG 3 or 4 is weighted 3 points. Cancer patients with UPE are categorised into the low-risk group if they score 0, intermediate-risk group if the score is 1 or 2 and high-risk group if the score is 3 or 4 (supplementary table S1).

Patients

A prospective cohort of ambulatory cancer patients with UPE was managed between January 2015 and March 2020. Active cancer was defined as cancer present or receiving treatment (*i.e.* adjuvant treatment) or having received treatment for cancer within the past 6 months.

Outcome measures

The objective of this study was to validate the potential of the HULL Score CPR to risk stratify the patient groups for proximate mortality in a follow-on cohort of patients from the same centre. Patients were followed until death or the end of follow-up, whichever occurred first. The primary end-point was all-cause mortality by HULL Score CPR risk categories. Outcome measures were death within 30 days, 90 days and 180 days of presentation with UPE and in the overall study period. The HULL Score CPR was evaluated by individual category level for 30-day, 90-day and 180-day mortality and OS, and the number of outcome events was reported by HULL Score CPR categories.

Data collection

Extensive demographic, clinical, laboratory and patient-reported outcome tools were collected at baseline presentation to the department as previously described [17]. These data was stored in the Hull "UPE database" in the oncology information system (OIS-ARIA). Outcome data for this study were collected from the electronic medical record system Lorenzo and IMPAX. The database was closed on 30 September 2020 (audit number 2013.287). All information entered in the electronic database and clinical outcome was adjudicated by cancer and venous thromboembolism (VTE) multidisciplinary team members in the HUTH NHS Trust. The UPE events were not independently blindly adjudicated.

Analysis and statistical consideration

Descriptive statistics were used to analyse patient characteristics. Survival was calculated from the date of PE diagnosis.

Survival analyses were performed using Kaplan–Meier with the log-rank test to assess the predictive ability of the HULL Score CPR for proximate (30-day, 90-day and 180-day) mortality. Hazard ratios were

calculated by a Cox proportional hazards model to evaluate the association of proximate mortality with the prognostic risk group. Receiver operator characteristics analysis was used to determine the discriminatory performance of the HULL Score CPR. A probability level of 5% was used as the cut-off for statistical significance in all analyses. All analyses were performed with SPSS v25 (IBM Corp.) and Stata v17.0.

Results and discussion

The HULL Score CPR was developed from a prospectively collected UPE cohort (derivation cohort) of 234 consecutive cancer patients from a single centre referred to a standardised diagnostic and management outpatient pathway from 2010 to 2014 [17, 22].

The present study analysed a prospective cohort of 282 patients in a single centre database (registry) from the same clinical setting as the derivation cohort. This cohort included consecutive ambulatory cancer patients with UPE from 2015 to 2020. As a validation study for the HULL Score CPR, our target was to have a sample size similar to the original one. We successfully recruited 282 patients for this validation cohort and this sample size provided sufficient data for the proposed analyses. There was no overlap of patients between the validation cohort and the derivation cohort or the international UPE registry.

The median age was 69 years (range 36–91 years) and 57.8% were male. The median follow-up duration was 11.6 months (IQR 4.9–21.4 months). At the time of database closure, 78 patients were alive.

Table 1 lists the baseline characteristics of the validation cohorts. The most common cancer types were colorectal (17.7%), lung (10.3%) and breast cancer (9.2%). 72% of patients had metastatic cancer. UPE was confined to the sub-segmental arteries for 14.9% of patients. New symptoms or worsening symptoms were reported by 41.5% of patients.

The PS of patients in the derivation and validation cohorts was comparable. In the validation cohort, 47.2% had an ECOG-PS of 0 and 44.7% had an ECOG-PS of 1–2 (45% and 43% in the derivation cohort, respectively). Only 6% had ECOG-PS of 3–4 (10% in the derivation cohort). These were consistent with an ambulatory outpatient cohort (91.9% with an ECOG-PS of 0–2), and indeed 96.1% of patients were managed as outpatients for UPE in the validation cohort.

The HULL Score CPR stratified the validation cohort into low-risk (n=100, 35.5%), intermediate-risk (n=95, 33.7%) and high-risk (n=81, 28.7%) categories for proximate mortality. 30-, 90- and 180-day mortality rates for the whole cohort were 2.5% (n=7), 15.2% (n=43) and 28.4% (n=80), respectively.

Figure 1a compares the 30-, 90- and 180-day mortality by HULL Score CPR in the derivation and validation cohorts. 30-day mortality was 0% and 1% in the low-risk group, 0.9% and 1.1% in the intermediate-risk group and 9% and 6.2% in the high-risk group for the derivation and validation cohorts, respectively. Likewise, 90-day and 180-day mortality in the validation cohort demonstrated similar frequencies as reported in the derivation cohort. Higher mortality was observed in the intermediate- and high-risk groups compared to the low-risk group, which is consistent with the derivation cohort. For example, 180-day mortality in the validation cohort was 49.4% in the high-risk group (55.2% in the derivation cohort) and 4% in the low-risk group (4.4% in the derivation cohort).

Similarly, the Kaplan–Meier survival curves (figure 1b, c) illustrate the statistically significant differences in survival in the first 12 months of follow-up for each category of HULL Score CPR in the derivation (figure 1b) and validation (figure 1c) cohorts. The median OS was 13 months for the entire validation cohort and 12.6 months for the derivation cohort. Median OS in the validation cohort was 30.2 months (95% CI 16.4–44 months) for the low-risk group, 10 months (95% CI 6.4–13.7 months) for the intermediate-risk group and 6.1 months (95% CI 2.9–9.3 months) for the high-risk group ($p<0.001$); this was comparable to the derivation cohort (low risk: 32 months (95% CI 8.1–55.9 months); intermediate risk: 12.6 months (95% CI 8.3–16.9 months); high risk: 5.5 months (95% CI 3.9–7.2 months); $p<0.001$).

The cumulative hazard function for each prognostic category over time is presented in table 2. The hazard of 30-day mortality of the high-risk group was 6.3 times that of the low-risk group, 90-day mortality was 39.5 times higher and 180-day mortality was 17.6 times higher (table 2).

Correlation of the risk categories with 30-day, 90-day and 180-day mortality and OS was consistent with the derivation cohort (area under curve (AUC) for 30-day: 0.717, 95% CI 0.522–0.912, $p=0.05$; 90-day: 0.772, 95% CI 0.707–0.838, $p<0.001$; 180-day: 0.751, 95% CI 0.692–0.809, $p<0.001$; OS: 0.749, 95% CI 0.686–0.811, $p<0.001$; figure 2).

TABLE 1 Characteristics of the patients with UPE

	Validation cohort
Age, years, median (range)	69 (36–91)
Gender	
Male	57.8 (163)
Female	42.2 (119)
Setting	
Radical/adjuvant	28 (79)
Metastatic/incurable	72 (203)
Diagnosis	
Colorectal cancer, early	4.3 (12)
Colorectal cancer, metastatic	17.7 (50)
Oesophagogastric cancer, early	7.1 (20)
Oesophagogastric cancer, metastatic	4.3 (12)
Breast cancer, metastatic	9.2 (26)
Pancreaticobiliary cancer, advanced	5 (14)
NSCLC metastatic/SCLC	10.3 (29)
Other	42.2 (119)
Treatment	
Cytotoxic chemotherapy	68.1 (192)
Biological therapy	14.5 (41)
Hormonal therapy	12.1 (34)
Immunotherapy	4.6 (13)
Risk factors for VTE	
Recent hospitalisation[#]	15.2 (43)
Recent surgery[#]	3.9 (11)
Indwelling CVC	17.4 (49)
Performance status	
0	47.2 (133)
1–2	44.7 (126)
3–4	6 (17)
MD	2.1 (6)
Extent of UPE	
Bilateral	38.3 (100)
Largest vessel: pulmonary artery (main, right, left)	16 (45)
Largest vessel: lobar branch(es)	20.3 (57)
Largest vessel: segmental	49 (138)
Largest vessel: sub-segmental	14.9 (42)
Symptoms (self-reported)	
Any new symptom	25.2 (71)
Worsening pre-existing symptoms	16.3 (46)
PESI group	
I/II	8.9 (25)
III	33.3 (94)
IV	41.8 (118)
V	15.6 (44)
MD	0.4 (1)

Data presented as n (%), unless otherwise indicated. NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; VTE: venous thromboembolism; CVC: central venous catheter; MD: missing data; UPE: unsuspected pulmonary embolism; PESI: Pulmonary Embolism Severity Index. [#]: within 30 days.

UPE has become a frequent presentation, and advances in cancer treatment have resulted in more patients receiving care in an outpatient setting and multiple whole-body multislice CT assessment scans. A validated, easy-to-use CPR would provide safe outpatient management, addressing the detrimental implications on quality of life and healthcare costs from unnecessary hospital admissions [22].

Many CPRs for PE have been developed to assess the suitability of outpatient management in the general population for conventional symptomatic PE patients [23]. However, the generic CPRs such as the Pulmonary Embolism Severity Index (PESI) or simplified PESI are not helpful for risk stratification of cancer-related UPE, especially for 30-day, 90-day and 180-day mortality in ambulatory cancer patients [17].

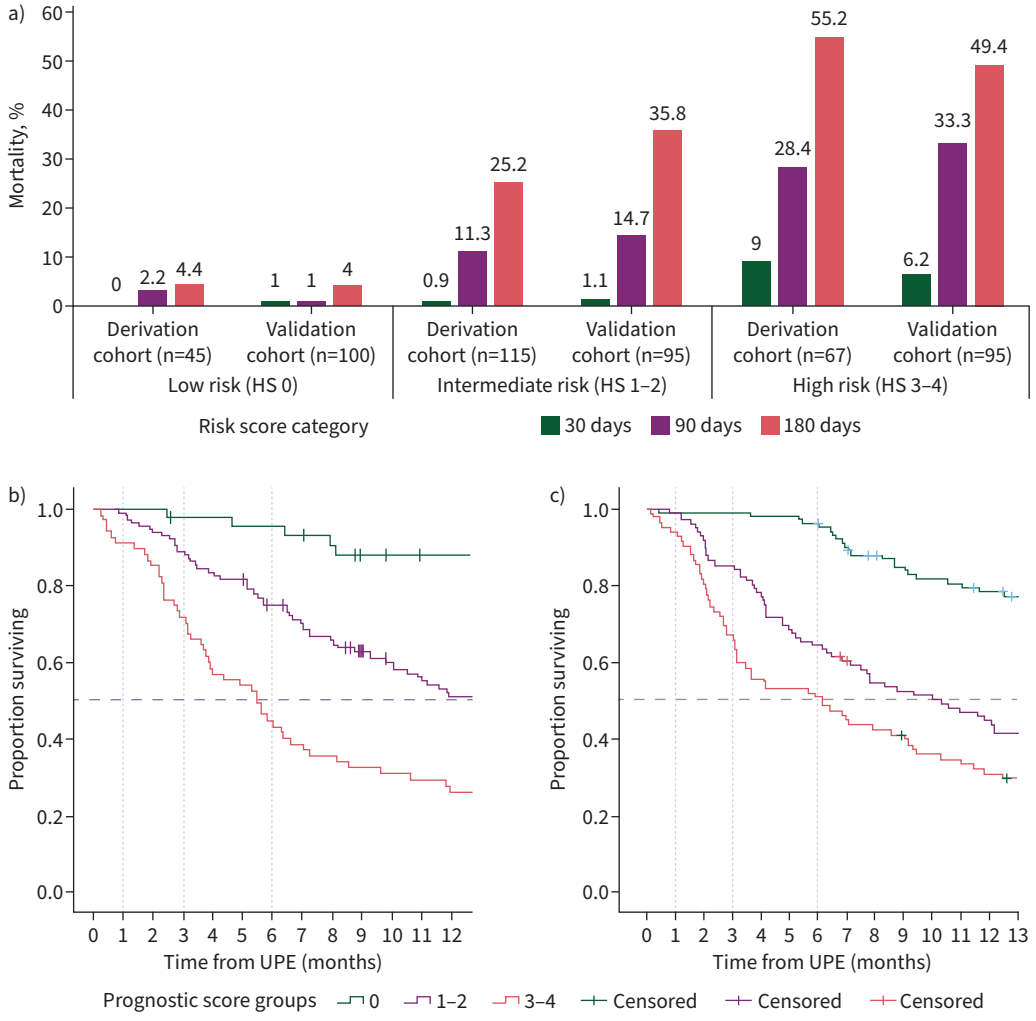

FIGURE 1 a) Mortality by HULL Score clinical prediction rule (CPR) in derivation (2010–2014) and validation (2015–2020) cohorts. b, c) Kaplan–Meier survival curves for the HULL Score CPR categories for the first 12 months of follow-up for derivation (b) and validation (c) cohorts. Line separators for the 30-day, 90-day and 180-day cut-offs and the median for survival are included. HULL Score (HS) categorised as follows: low risk: 0 (green); intermediate risk: 1–2 (purple); high risk: 3–4 (red). UPE: unsuspected pulmonary embolism.

Furthermore, scoring systems like the Computerised Registry of Patients with Venous Thromboembolism (RIETE) [18] or POMPE-C [19] developed from cancer patient cohorts with suspected PE have a limited role in discriminating between low-risk and high-risk categories for proximate mortality in ambulatory cancer patients with UPE.

TABLE 2 Prognostic risk category (HULL Score CPR category) for mortality

Validation cohort HULL Score CPR category	Proximate mortality					
	30 days[#]		90 days[¶]		180 days[+]	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Low risk (HS 0)	1		1		1	
Intermediate risk (HS 1–2)	1.05 (0.07–16.1)	0.973	15.7 (2.1–119.8)	0.008	10.5 (3.7–29.7)	<0.001
High risk (HS 3–4)	6.3 (0.7–54.1)	0.092	39.5 (5.4–290.9)	<0.001	17.6 (6.3–49.2)	<0.001

CPR: clinical prediction score; HS: HULL Score. [#]: overall p=0.0066; [¶]: overall p<0.001; [+]: overall p<0.001.

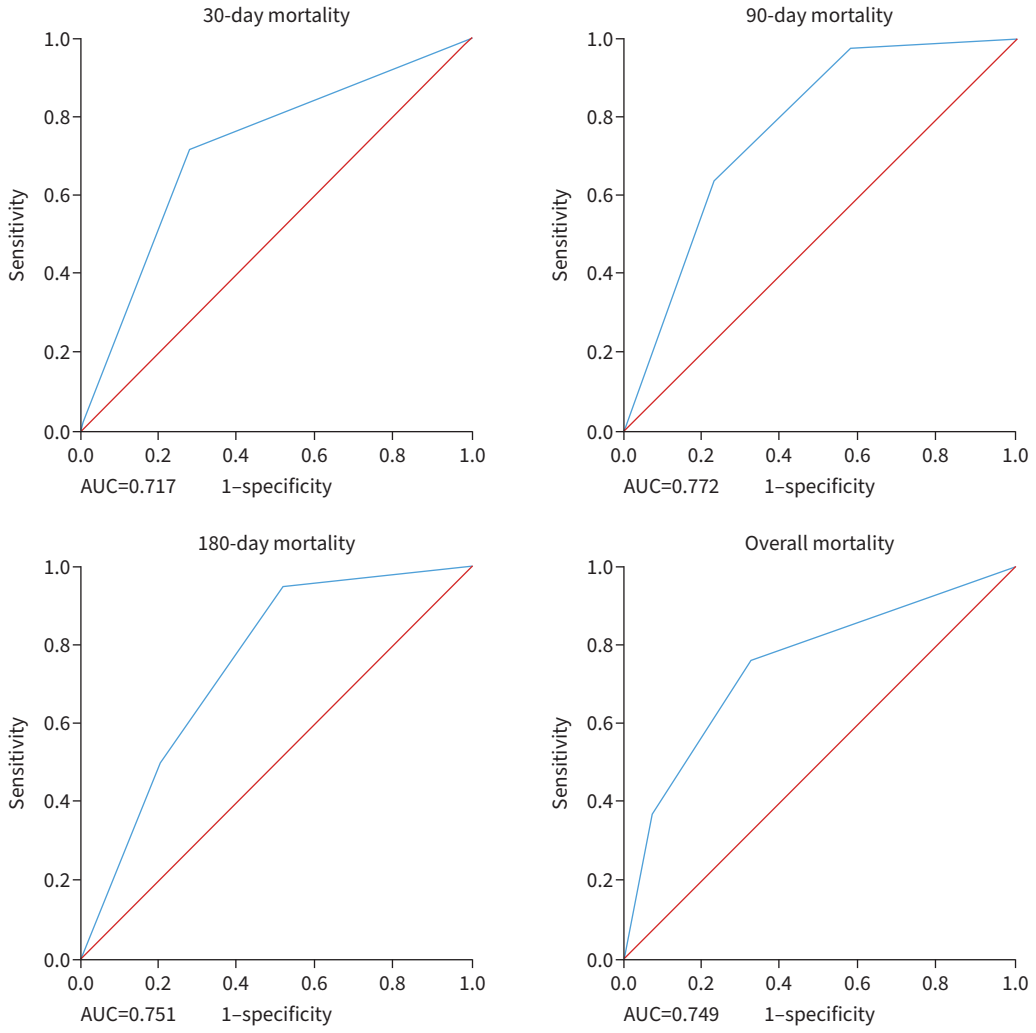

FIGURE 2 Receiver operating characteristic curve analysis on the prognostic performance of the HULL Score clinical prediction rule. AUC: area under the curve.

The EPIPHANY index [20] was developed from a mixed cohort of cancer patients with suspected PE and UPE and validated externally in cancer patients. Though the EPIPHANY index predicts mortality, it does so based on very high mortality in the UPE cohort, suggesting that many of these patients were not ambulatory [21]. The variation in the characteristics of the EPIPHANY and HULL Score CPR cohorts is exemplified by the observed differences in the mortality (2-fold) of the symptomatic UPE EPIPHANY cohort compared to the sickest patients of the HULL Score CPR derivation and validation cohorts (HS 3–4). 30-day mortality rates were 9% and 6.2% in the high-risk groups of the derivation and validation cohorts, respectively, but 20% for the symptomatic UPE group of the EPIPHANY cohort. Likewise, 90-day mortality was significantly higher in the symptomatic UPE EPIPHANY patients. This suggests that unwell inpatients with UPE were enrolled in the EPIPHANY study.

The prognostic value of new respiratory symptoms and PS status in ambulatory cancer patients with UPE was studied in the UPE registry, an international, prospective, observational cohort study, and the discriminatory value of the HULL Score CPR has been confirmed [21]. The most consistent predictors of mortality were patient-reported respiratory symptoms within 14-days before and ECOG-PS at the time of UPE. When applied to the HULL Score CPR, the UPE cohort produced consistent results with the derivation cohort of the HULL Score CPR. Consistent correlation was found with 30-day mortality (AUC 0.70, 95% CI 0.63–077), 90-day mortality (AUC 0.65, 95% CI 0.60–070), 180-day mortality (AUC 0.64, 95% CI 0.59–068) and OS (AUC 0.61, 95% CI 0.57–0.65).

A recent *post hoc* analysis of the Hokusai VTE cancer study also showed the importance of ECOG-PS in predicting VTE-related outcomes, including recurrent VTE, major bleeding and all-cause mortality [24]. This may guide decision-making regarding anticoagulation therapy during follow-up in patients with cancer-associated PE.

Our study has some limitations. First, the long period over which cases were collected may have resulted in some differences in the baseline demographic traits of the two tandem derivation (supplementary table S2) and validation cohorts (table 1). We highlight the reduced frequency of metastatic disease, the greater use of systemic anticancer treatment, including biologicals such as tyrosine kinase inhibitors and immunotherapy, and the reduced frequency of some cancers for which thromboprophylaxis is becoming common (*e.g.* pancreatic ductal adenocarcinoma and gastro-oesophageal cancer). Nevertheless, the very similar median and overall OS for the two cohorts suggests that these cohorts are well matched for this analysis.

It is also notable that the external validation study happened before the follow-on validation cohort data could be collected. This was due to the faster accrual rate of a multicentre study and, to the best of our knowledge, the absence of other cohorts with ambulatory cancer patients and UPE that have prospectively collected the relevant data.

Strengths of our study include the prospective design from the same clinical setting with a uniform management protocol and a large study group. To avoid selection bias, we recruited consecutive patients from January 2015 to March 2020 to form this cohort. Further potential ways of improving the HULL Score CPR are being investigated, such as considering the granularity of the "symptoms" and including other biochemical parameters at UPE diagnosis.

This study validates the capacity of the HULL Score CPR to stratify proximate mortality risk in ambulatory cancer patients with UPE. The HULL Score CPR is composed of practical clinical parameters that are easy to obtain and use in an acute oncology setting and can guide appropriate decision-making in these patients.

Provenance: Submitted article, peer reviewed.

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Data statement: Data are available from the corresponding author on demand, at the discretion of the Hull University Teaching Hospitals NHS Trust Governance bodies, who are the legal guardians.

Ethics approval and consent to participate: This study was conducted under the UK Health Research Authority regulations as an audit/quality improvement project, not requiring ethics approval. This is an anonymised cohort collected as part of an audit process. Patient consent for anonymised data collection for audit purposes is not required. Regulatory compliance (as per the Data Protection Act (1998), the Caldicott principles (1997) and the NHS Confidentiality code of practice (2003)) was overseen by the Hull University Teaching Hospitals NHS Trust Governance bodies (audit registration number 2013.287).

Conflict of interest: All authors declared that they have no competing financial or personal interests relevant to this manuscript.

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