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Research Article

CT scoring system to defined thrombus distribution in chronic thromboembolic pulmonary hypertension

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Abstract

Objectives: Characterization of thrombus is important for guiding treatment in chronic thromboembolic pulmonary hypertension (CTEPH). This study presents a novel scoring system for visual assessment of CTEPH on CT pulmonary angiography (CTPA), incorporating both disease location and extent to determine the impact on survival outcomes.

Methods: Patients with CTEPH were identified retrospectively from the Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre registry. The scoring system emphasizes disease based on their predominant location as central, segmental, and distal disease. Survival analysis was conducted using Cox-regression and Kaplan–Meier survival curves.

Results: A total of 208 patients with CTEPH were included (mean age 66 ± 13.6 years, 52.4% female). Mosaic perfusion and infarction were commonly seen in patients with distal disease (92% and 88%). Patients with central and distal disease had more severe pulmonary hemodynamics and lower gas transfer (TLCO) than patients with segmental disease. Central and distal disease showed similar survival, whereas survival was worse in central compared to segmental disease for all patients ($P < .001$), including those undergoing ($P < .04$) and not undergoing endarterectomy ($P < .001$). Central disease was an independent predictor of mortality in those not undergoing endarterectomy (hazard ratio 1.9, $P < .01$).

Conclusions: Our scoring system showed excellent interobserver agreement. Thromboembolic disease location was shown to be a predictor of mortality, with central disease independently associated with shorter survival in patients not undergoing pulmonary endarterectomy.

Advances in knowledge: This is a novel scoring system for characterizing CTEPH on CTPA, considering disease location and extent. It provides disease location as a predictor of survival, introducing a new framework for patient stratification and clinical decision-making.

Keywords: Chronic thromboembolic pulmonary hypertension; computed tomography pulmonary angiography; CTPA; pulmonary hypertension; pulmonary endarterectomy.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) occurs in ∼2% of patients following acute pulmonary embolism (PE) due to incomplete resolution of thrombus within the pulmonary arteries.[1] Accurate and early diagnosis of CTEPH is increasingly important given the growing number of therapeutic options available.[2] Identifying the optimal therapeutic strategy for managing CTEPH poses a significant challenge, and patients often undergo a number of investigations to assess their thrombus burden, severity of pulmonary hypertension, and comorbidities.[3,4] In particular, characterization of thromboembolic disease, including location and extent, is important for determining suitability for and predicting the success of pulmonary endarterectomy and balloon angioplasty.[5] Addressing the precise localization of thromboembolic and the relationship with disease severity may provide essential insights into the pathogenesis of CTEPH, facilitating risk stratification and treatment management.

The current preferred method for confirming suspected CTEPH is CT pulmonary angiography (CTPA), which allows not only for assessment of specific abnormalities in CTEPH—such as intraluminal stenosis, webs, and eccentric thrombus within the pulmonary arteries—but also for evaluation of lung parenchymal and cardiac changes.[6-8] However, assessing chronic thromboembolic disease on CTPA can present significant challenges. CTPA interpretation requires extensive experience due to the potential for misinterpretation of subtle abnormalities, which can result in diagnostic delays or inappropriate management.[9]

The scoring system refers to a standardized tool to quantitatively assess specific findings on imaging evaluations, with the potential to enhance interobserver agreement and ensure

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consistent assessment of CTEPH for accurate clinical decisions. Several widely used scoring systems have previously been developed to characterize thromboembolism on CTPA in acute PE. These have incorporated the number and size of thrombi, their location within the pulmonary vasculature, and their influence on hemodynamics.[10,11] Scoring systems for evaluating CTEPH are infrequently used in routine clinical practice due to their complexity and dependence on modern imaging technology. Dual-energy CT (DECT) scans, eg, are designed to detect and quantify perfusion abnormalities in the lungs, which are frequently associated with hemodynamic parameters to determine disease severity and operability.[12,13] However, to our knowledge, no scoring system has been developed for the characterization of chronic thromboembolic disease on CTPA in CTEPH.

This study aimed to characterize chronic thromboembolic disease features on CTPA in patients with CTEPH and assess their relationship with disease severity and survival outcomes.

Methodology

This retrospective study received ethical approval from our institution with consent waived and the National Research Ethics Service (16/YH/0352).

Study population

Patients were identified from the Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre registry (ASPIRE) database between January 2008 and January 2018.[14] ASPIRE comprises deidentified data obtained during routine clinical care from patients who have undergone evaluation for suspected pulmonary hypertension at the Pulmonary Vascular Disease unit. The research included adult patients aged ≥18 years who underwent CTPA and met guideline criteria for a diagnosis of CTEPH.[15] Patients who underwent pulmonary endarterectomy or received medical therapy were included. Balloon pulmonary angioplasty (BPA) was not nationally commissioned in the United Kingdom until 2018 and therefore no patients underwent this intervention during the conduct of the study. Patients who had external CTPA performed in other institutions and those who had severe artefacts were excluded.

CTPA protocol

CTPA scans were conducted using multidetector scanners (TOSHIBA Aquilion PRIME and GE Medical Systems) with the following standard acquisition parameters: a tube current ranging from 80 to 700 mA with automatic dose reduction, a tube voltage of 120 kV, a pitch of 1, a slice thickness of 0.5 mm, and a rotation speed of 0.275. Intravenous iodinated contrast (Omnipaque 350, GE Healthcare) was administered at a rate of 5 mL/s with a total volume of 60 mL. Bolus tracking was performed in the pulmonary artery utilizing a manual fast start, initiating image acquisition when contrast reached the predefined threshold of 220 Hounsfield units (HU).

Data collection

The demographics, clinical, and laboratory information of the patients were collected from an electronic medical database and document reviews. In addition to the CTPA studies, the following data were also retrieved for each included patient where available.

1) Pulmonary function tests (PFTs). Baseline forced vital capacity (FVC), forced expiratory volume (FEV), and transfer factor of the lung for carbon monoxide (TLCO) closest to the date of RHC.
2) Right heart catheterization (RHC) data. RHC was undertaken using a balloon tipped 7.5 F thermodilution catheter (Becton-Dickinson, Franklin Lakes, New Jersey). Mean pulmonary artery pressure (mPAP) and pulmonary arterial wedge pressure (PAWP) were measured by fluid filled pressure. Cardiac output (CO) was measured using the thermodilution technique. PVR was determined as follows: PVR = (mPAP – PAWP)/CO. Cardiac index (CI) was corrected for the patient's body surface area (BSA): CI = CO/BSA. Right heart catheterization was obtained from the ASPIRE registry.
3) Mortality data obtained from the NHS Personal Demographics Service at the time of census. All pulmonary hypertension patients getting treatment are subjected to routine follow-up in accordance with the national service guidance.

Image analysis

Two observers independently evaluated the CTPA images, blinded to clinical information and patient demographic to minimize the risk of interpretation bias. The evaluations were conducted using MIM software, which was employed for clot segmentation and analysis. In addition to disease location, the observers recorded other relevant CTEPH-related features, such as lung parenchymal abnormalities, including mosaic attenuation, bronchial artery changes, and infarction. CT axial plane was used for all CT cardiac measurements including the maximum diameters of the ascending aorta (AO), pulmonary artery (PA), the right and left ventricles (RV and LV). Then, the RV/LV and PA/AO ratios were calculated for each patient as part of the analysis.

The scoring system is designed to classify chronic thromboembolic disease based on their predominant location in the pulmonary arterial tree, providing uniformity and clarity in determining the severity and anatomical extent of CTEPH. The score mainly represents a simplified method for visual assessment of disease distribution and highlights the predominant location of CTEPH involvement. Each location is associated with a score that reflects the number of diseases present within a specific range.

Chronic thromboembolic disease location within the pulmonary vasculature was classified as follows according to conventional anatomical descriptions (Figure 1). "Central" disease was defined as a thromboembolic involvement in the main pulmonary artery, in addition to the proximal segments of the left and right pulmonary arteries (including mid and distal in the main branches). Patients identified as having central disease may also have had disease in segmental and distal arteries, but when central involvement was present, patients were defined as having central disease regardless or extent of clot burden elsewhere. "Segmental" was defined as disease in the branches distal to the central arteries, beginning at the lobar arteries. Patients with segmental disease may also have had distal involvement, but the dominant feature was segmental (higher score than distal). "Distal" involves the smaller, more peripheral subsegmental arteries. Patients with distal disease may also have segmental involvement, but the dominant characteristic is distal.

Step 1 (central arteries): evaluate central based on disease involvement in the 5 main central pulmonary artery locations. Assign 1 point for each thrombus in central, calculate the score as the sum of all involved locations, with a maximum score of 5.

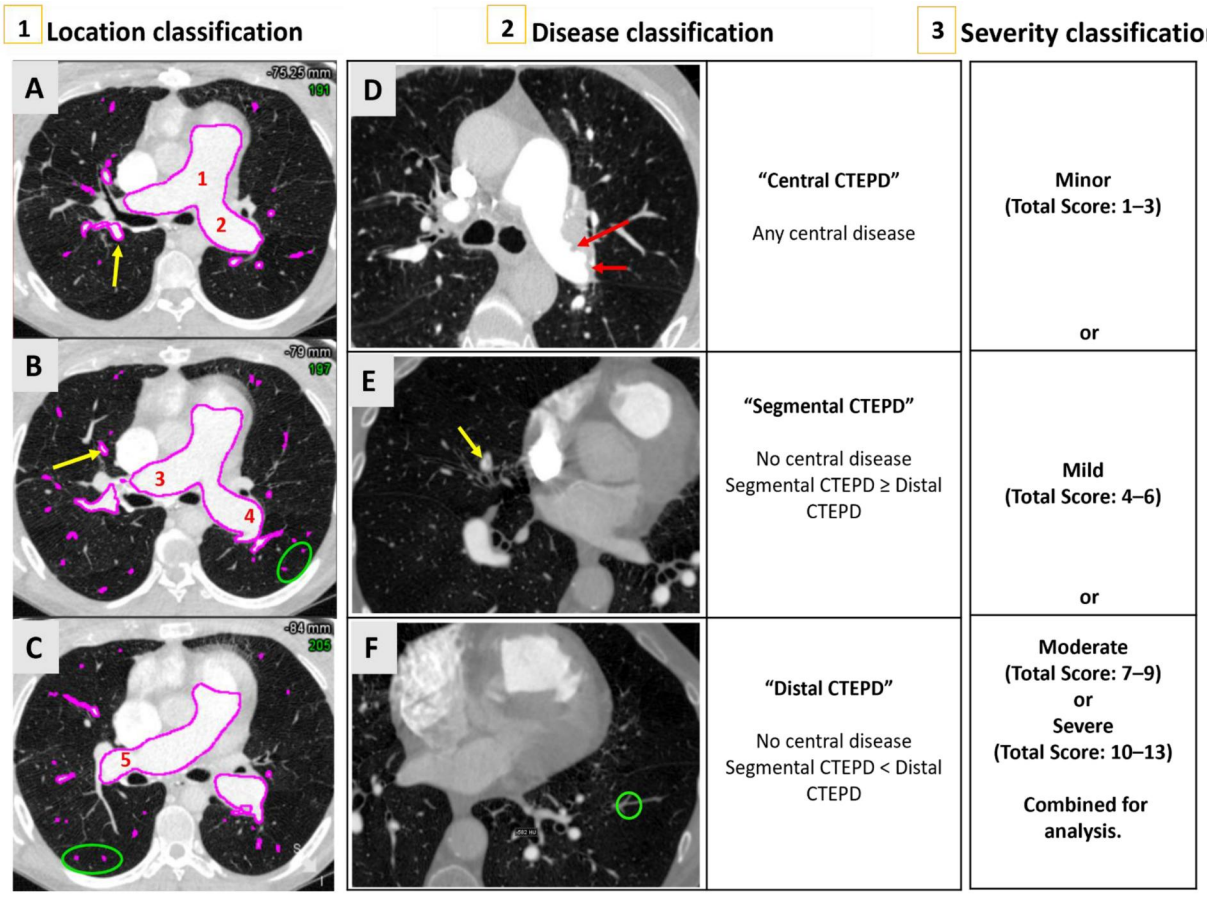

Figure 1. Axial chest CTPA slices illustrate chronic thromboembolic disease location, disease and severity classifications into central, segmental, and distal subgroups (each column includes 3 different slices from a single patient). (A) In location classification, central included the main pulmonary artery (1) as well as the midsection of the main pulmonary artery (2 and 3) and distal aspect of the main pulmonary artery (4 and 5) of both the left and right main pulmonary arteries. (B) Segmental location, 10 segments on the right and 9 on the left (yellow arrows). (C) The presence of distal was assessed at distal segmental locations 10 segments on the right and 9 on the left (green circle). In disease classification, (D) there is extensive central mural disease present involving both main pulmonary arteries and extending primarily into the lower lobe arteries bilaterally (red arrow). (E) In the right middle lobe, there is complex web formation at the origin of the lateral segmental branches (yellow arrow). (F) On the left side there are subsegmental attenuated vessels showing chronic thromboembolic disease (green circle). If any central disease is identified the patient is classified as having "central" chronic thromboembolic disease. In the absence of central disease, segmental and distal are classified by the score weighting towards either category.

Step 2 Determine the predominant non-central classification: evaluate the segmental and distal scores if there is no central disease involvement (central score = 0). Segmental and distal classifications were simplified using 19 pulmonary arteries for each location. This approach simplifies the original scheme (19 segmental and 19 distal branches) into a more standardized framework. The scoring system for chronic thrombi operates on a simple quantitative categorization, by assessing the number of thrombi within a specific range and assigning a corresponding score based on predefined intervals:

1) **Score of 1:** Assigned when the thrombi count is between 1 and 5.
2) **Score of 2:** Assigned when the thrombi count is between 6 and 10.
3) **Score of 3:** Assigned when the thrombi count is between 11 and 14.
4) **Score of 4:** Assigned when the thrombi count is between 15 and 19.

Then, assess the differences between the segmental and distal scores, using the higher score as the predominant score.

Step 3 Calculate the Total Score: Combine all 3 locations to calculate the total score:

Total Score = Central Score + Segmental Score + Distal Score.

Maximum Total Score: 5 (Central) + 4 (Segmental) + 4 (Distal)=13 (predominant location)

Clinical example

- Central disease in 0 locations → **Central Score = 0.**
- Segmental disease in 15 arteries → **Segmental Score = 4.**
- Distal disease in 5 arteries → **Distal Score = 1.**
- **Total Score = 0 (Central) + 4 (Segmental) + 1 (Distal) = 5 (segmental).**
- The classification as segmental overall based on segmental disease having the higher score (4) than distal disease (1), which prioritizes the location with the higher score if no central disease.

The total score can be grouped into 4 categories based on severity and extent of the chronic thromboembolic disease: Minor (Total Score: 1–3) reflects minimal disease involvement. Mild (Total Score: 4–6) represents a moderate disease distribution. Moderate (Total Score: 7–9) indicates significant disease involvement affecting multiple regions. Finally, Severe (Total Score: 10–13) highlights extensive disease widespread distribution. All patients within the severe group by definition have central disease in addition to segmental and distal disease in order for their total score to be 10 or more. This is due to the fact that segmental and distal disease is unable to achieve the threshold score of 10 under the scoring methodology employed in this study. If central involvement is absent (Central Score = 0), classification is based on the higher score between segmental and distal disease. When both are present, their combined score (eg, 4 + 4 = 8) places the patient in the severe category (Total Score: 10–13) if central disease is present; otherwise, a total score of 8 categorized into moderate (Total Score: 7–9). This system provides a structured way to evaluate and grade disease presence and severity, offering a standardized method for categorization in clinical research settings.

In a blinded sub-study, the CTPA of 20 patients with CTEPH was assessed by 2 observers with different levels of CT imaging experience (AS, 13 years as a cardiothoracic radiologist and LA, a radiographer with 8 years of experience). This sub-study, as part of the overall research, aimed to evaluate interobserver agreement and validate the robustness and consistency of the scoring system across different levels of imaging expertise.

Statistical analysis

Statistical analyses were performed using SPSS Statistics (version 27, IBM) and GraphPad Prism (v8; GraphPad, La Jolla, CA, USA), with a significance threshold of $P < .05$. The main goal of the study was to examine a disease location for CTEPH assessment. To achieve this, we examined the correlations between chronic thromboembolic disease location and several clinical and hemodynamic metrics using Spearman's correlation coefficient with 95% CIs. Descriptive statistics are presented as the mean ± SD or median and interquartile range (IQR) for continuous variables, and as percentages and frequencies for categorical data. Comparison of total scoring disease severity groups (ie, minor, mild, and moderate-severe) were performed using a 1-way ANOVA with *post hoc* Bonferroni correction. Due to the small number of patients in the severe group ($n = 7$), they were merged with the moderate group for analysis, forming a combined "moderate-severe" category. Interobserver agreement was measured using Cohen's weighted κ (linear weights) for categorical variables, and intraclass correlation coefficient (ICC) for continuous variables. Kappa value was interpreted using the thresholds defined by McHugh (2012)[16]: as (0.01–0.20) slight agreement, (0.21–0.40) fair agreement, (0.41–0.60) moderate agreement, (0.61–0.80) substantial agreement, and (0.81–0.99) almost perfect agreement. The ICC values were interpreted as follows according to established thresholds: (<0.50) indicated poor agreement, (0.50–0.75) fair or moderate agreement, (0.75–0.90) moderate to good agreement, (>0.90) indicated excellent agreement.[17] Correlations between disease location and severity were assessed using Cox regression and Kaplan–Meier analysis.

Results

Patient population

A total of 208 patients with CTEPH were included in the study (mean age 66 ± 13.6, 52.4% female) (Figure 2). Of these 195 patients (94%) had available RHC data and 185 patients (89%) had available PFT data. Their clinical

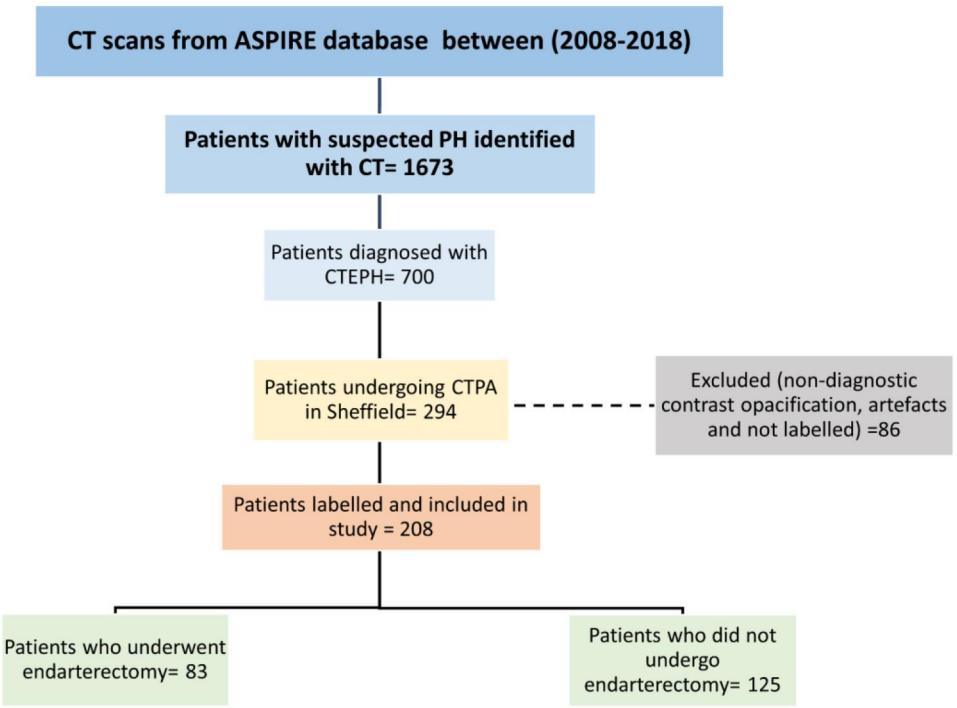

Figure 2. Study flow diagram.

Table 1. Characteristics of patients who underwent right heart catheterization and pulmonary function tests, comparing those who had pulmonary endarterectomy (PEA) *versus* those who did not (no PEA), as well as comparing patients with central, segmental, and distal CTEPD.

Patient characteristics	Full cohort 208 (100%)	PEA 83 (40%)	No PEA 125 (60%)	*P* value	Central 77 (37%)	Segmental 80 (38%)	Distal 51 (25%)	*P* value
Age (years)	66 ± 13.6	62 ± 13.01	68 ± 13.6	**.002**	67.2 ± 12.8	64.7 ± 13.2	65.5 ± 15.5	.51
Sex (female)	109 (52%)	46 (55%)	63 (50%)	.48	36 (47%)	42 (53%)	31 (61%)	.3
WHO FC	II (18), III (165), IV (21)	II (3), III (70), IV (8)	II (15), III (95), IV (13)	.16	II (3), III (62), IV (11)[a]	II (12), III (67), IV (1)[b,c]	II (3), III (36), IV (9)[a]	**<.001**
Mosaic perfusion	177 (85%)	77 (93%)	100 (80%)	**.01**	66 (86%)	64 (80%)	47 (92%)	.16
Infarction	159 (76%)	67 (81%)	92 (74%)	.23	63 (82%)[a]	51 (64%)[b,c]	45 (88%)[a]	**.002**
Lung disease	57 (27%)	16 (19%)	41 (33%)	**.03**	24 (31%)	25 (31%)	8 (16%)	.09
Coronary artery disease	140 (67%)	51 (61%)	89 (71%)	.14	56 (73%)	51 (64%)	33 (65%)	.44
RHC	**195 (94%)**	**78 (94%)**	**117 (94%)**	***P* value**	**69 (90%)**	**77 (96%)**	**49 (96%)**	***P* value**
PVR (wood unit)	8.5 ± 5.4	9.07 ± 5.4	8.1 ± 5.4	.22	9.9 ± 5.9[a]	6.3 ± 3.7[b,c]	10 ± 6.06[a]	**<.001**
mPAP (mmHg)	46 ± 12.01	47.4 ± 11.2	45 ± 12.4	.15	47.4 ± 12.6	44.6 ± 12.7	45.8 ± 9.5	.34
PAWP (mmHg)	12.1 ± 4.6	12.2 ± 4.4	12.1 ± 4.8	.89	12.5 ± 4.5	12.5 ± 5	11.09 ± 4	.29
SVO_2 (%)	61.5 ± 8.7	62 ± 8.3	61.3 ± 9	.62	58.5 ± 9.3[a]	65 ± 6.4[b,c]	60.3 ± 9.4[a]	**<.001**
SaO_2 (%)	93.2 ± 3.8	92.7 ± 4.1	93.5 ± 3.5	.2	93 ± 4	93.4 ± 3.6	92.9 ± 3.8	.73
CI (L/min/m^2)	2.5 ± 0.87	2.5 ± 0.85	2.6 ± 0.89	.3	2.4 ± 0.95[a]	2.9 ± 0.83[b,c]	2.3 ± 0.66[a]	**<.001**
PFT	**185 (89%)**	**77 (93%)**	**108 (86%)**	***P* value**	**70 (91%)**	**69 (86%)**	**46 (90%)**	***P* value**
Predicted FEV1 (%)	76.8 ± 20.2	80.5 ± 18.7	74.1 ± 20.8	**.03**	75.8 ± 21.5	76.5 ± 18.8	78.7 ± 20.5	.73
Predicted FVC (%)	90.2 ± 22.5	93.5 ± 21.3	87.9 ± 23.1	.09	89.5 ± 23.3	89.4 ± 22.2	92.3 ± 22	.75
Predicted TLCO (%)	61 ± 18.5	61.3 ± 15.9	60.2 ± 20.3	.69	56.5 ± 21[a]	65.9 ± 15.4[b]	59 ± 17.2	**.009**

Data are expressed as mean ± standard deviation or counts (percentage). Hemodynamic parameters include pulmonary vascular resistance (PVR), mean pulmonary arterial pressure (mPAP), pulmonary artery wedge pressure (PAWP), venous oxygen saturation (SVO_2), arterial oxygen saturation (SaO_2), cardiac index (CI), and cardiac output (CO). Pulmonary function measures include predicted forced expiratory volume in 1 second (FEV1), predicted forced vital capacity (FVC), and predicted transfer factor of the lung for carbon monoxide (TLCO). *P* values ($P < .05$) indicate statistically significant differences between the PEA and no PEA groups and between the 3 groups of CTEPD, respectively. Bold values for P indicate statistical significance ($P < .05$).

[a]A significant difference from the "segmental" reference.

[b]A result is significantly different from the "central" reference.

[c]A significant difference from the "distal" reference.

Abbreviations: CI = cardiac index; CO = cardiac output; FEV1 = predicted forced expiratory volume in 1 second; FVC = predicted forced vital capacity; mPAP = mean pulmonary arterial pressure; PAWP = pulmonary artery wedge pressure; PFT = pulmonary function tests; PVR = pulmonary vascular resistance; RHC = right heart catheterization; SaO_2 = arterial oxygen saturation; SVO_2 = venous oxygen saturation; and TLCO = predicted transfer factor of the lung for carbon monoxide.

characteristics are summarized in full in Table 1. Thirty-seven percent (77/208) had central chronic thromboembolic disease, 38% (80/208) had segmental disease, and 25% (51/208) had distal disease. Of the patients, 18 (9%) were categorized as WHO Functional Class (FC) II, 165 (79%) as WHO FC III, and 21 (10%) as WHO FC IV.

The chronic thromboembolic disease scores were categorized into 4 groups based on the severity of the disease. The distribution of patients across these groups was as follows: 64 (31%) patients were classified as minor, 92 (44%) as mild, 45 (22%) as moderate, and 7 (3%) as severe. By combining the moderate and severe groups, a total of 52 (25%) patients were classified as moderate-severe disease ($45 + 7 = 52$). When grouped by severity score, patients with moderate-severe disease demonstrated significantly higher PVR ($P < .001$) and lower cardiac index ($P < .001$).

Interobserver agreement

The agreement among observers for the detection of 20 patients with CTEPH was 89% for central location, 80% for segmental, and 66% distal. Interobserver agreement, assessed using kappa values and intraclass correlation coefficients for disease location and extent assessment, are presented in Table 2.

CT, RHC, and lung function measurements

Table 3 presents the correlations found between chronic thromboembolic location with CT measurements (RV/LV and PA/AO ratios), mosaic perfusion, and infarction.

Patients with central and distal disease had more severe pulmonary hemodynamics and lower TLCO but similar spirometry to those with segmental disease ($P < .001$), Table 1.

Table 2. Interobserver reliability kappa (κ) and ICC between observers (R1 and R2) in CT imaging to determine the number and location of CTEPH.

Disease location	R1-R2 _ K(95%CI)
Central clot ICC	0.97 (0.92-0.98)
Weighted kappa	0.89 (0.74-1)
Segmental ICC	0.93 (0.83-0.97)
Weighted kappa	0.8 (0.62-0.99)
Distal ICC	0.88 (0.63-0.96)
Weighted kappa	0.66 (0.46-0.86)
Total abnormal ICC	0.92 (0.82-0.97)
Weighted kappa	0.78 (0.58-0.98)

In all 208 patients, highly significant statistical differences were demonstrated between the score system (disease severity) and the hemodynamic parameters (PVR, Svo2, and cardiac index), with ($P < .001$). Patients with moderate-severe disease demonstrated significantly higher PVR and lower cardiac index (Figure 3).

Survival of patients according to disease location

Endarterectomy was performed in 40% (83/208) patients, at a median time of 7 months (IQR 0–11) from CTPA. Notably, there were no instances of patients being lost to follow-up during the study period.

The results of the Kaplan–Meier survival analyses are shown in Figure 4. Patients with central and distal disease demonstrated similar survival rates. Survival rates were worse for patients with central disease compared to segmental disease for all patients ($P < .001$), those undergoing endarterectomy ($P < .04$) and those not undergoing endarterectomy ($P < .001$).

Table 3. Spearman's correlations between disease locations severity and CT measurements, including RV/LV and PA/AO ratios, as well as the presence of mosaic perfusion or infarction.

Disease location	RV/LV ratio	PA/AO ratio	Mosaic perfusion	Infarction
Central	$r = -0.07$, $P = .27$	**$r = 0.19$, $P = .009$**	$r = 0.85$, $P = .08$	$r = 0.09$, $P = 0.21$
Segmental	**$r = -0.1$, $P = .01$**	$r = 0.05$, $P = .43$	$r = -0.1$, $P = .09$	**$r = -0.2$, $P < .001$**
Distal	$r = 0.1$, $P = .12$	$r = -0.07$, $P = .28$	**$r = 0.27$, $P < .001$**	**$r = 0.17$, $P = .01$**
Total	**$r = 0.14$, $P = .04$**	$r = 0.06$, $P = .36$	**$r = 0.19$, $P = .009$**	**$r = 0.22$, $P = .003$**

Bold values for P indicate statistical significance ($P < .05$)

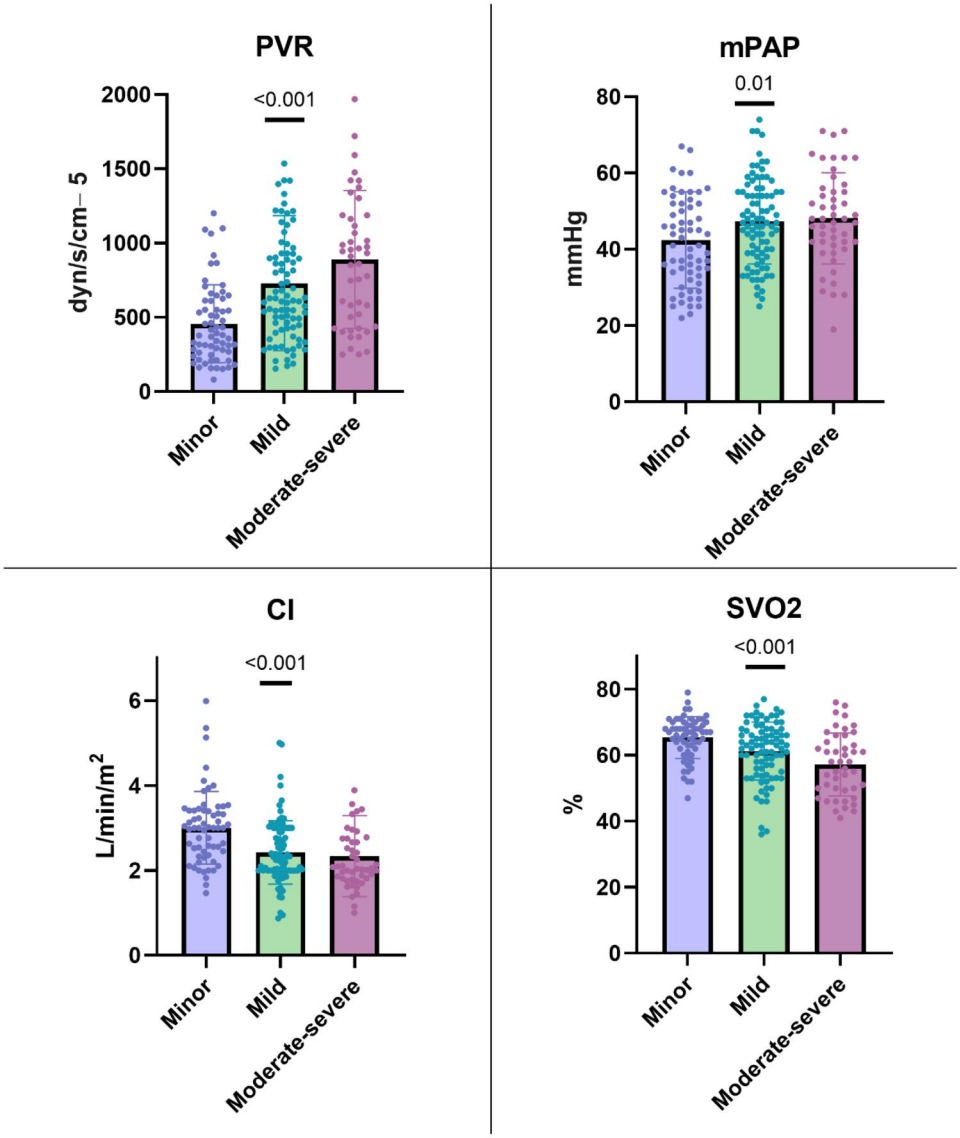

Figure 3. Group comparison of the right heart catheterization with total abnormal CTEPD using 1-way ANOVA. Minor: low clot burden, mild: a slightly higher clot burden, moderate-severe: high clot burden. Abbreviations: CI = cardiac index; mPAP = mean pulmonary arterial pressure; PVR = pulmonary vascular resistance; and SVO_2 = venous oxygen saturation.

Predictors of using univariate and multivariate cox regression

Multivariate Cox-regression adjusting for age, sex, and hemodynamics parameters (mPAP, PVR) is shown in Table 4. Whereas central disease remained an independent predictor or a worse outcome in those not undergoing endarterectomy (hazard ratio [HR] 1.9, $P < .01$), its presence did not impact on survival in those having endarterectomy.

Discussion

This study aimed to address how chronic thromboembolic disease location in CTEPH is assessed on CTPA and relates to key clinical outcomes. We developed a scoring system for the categorization of chronic thromboembolic disease location on visual assessment of CTPA studies. The scores showed high kappa and ICC values, indicating excellent interobserver agreement between 2 observers. Central disease

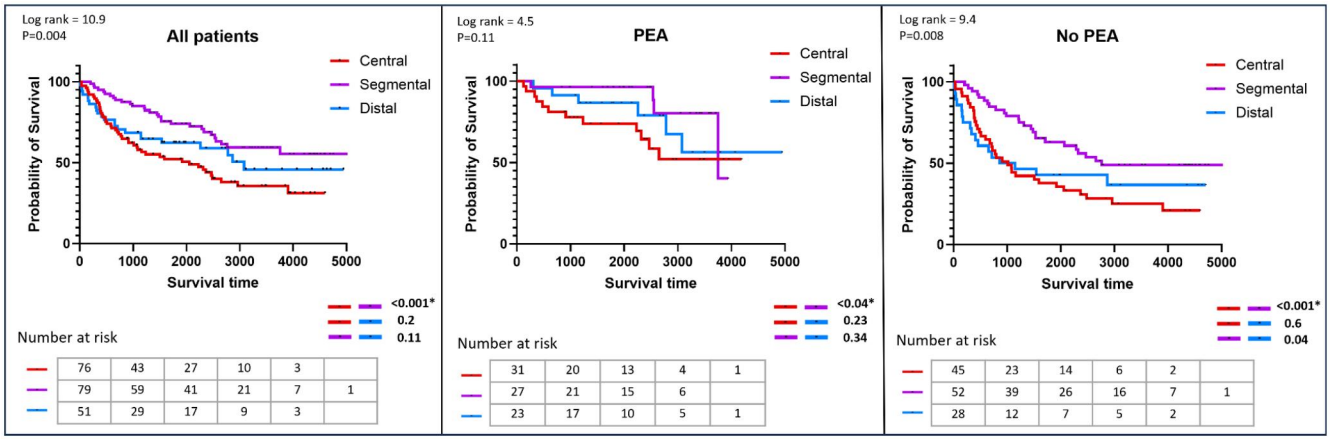

Figure 4. Kaplan–Meier survival curves for each location (central, segmental, and distal) in CTEPH patients, comparing the pulmonary endarterectomy (PEA) group with the non-surgical (no PEA) group. *P* values ($P < .05$) indicate statistically significant differences between the subgroups of CTEPD, respectively. (Red-purple) indicates that "central" is significantly different from the "segmental," (purple-blue) indicates a significant difference between "segmental" and "distal" CTEPD, and (red-blue) indicates the difference between "central" and "distal."

Table 4. Univariate and multivariate cox-regression analysis for CT assessed vessels, cardiac changers and parenchymal change in patients undergoing and not undergoing PEA.

Variables	Univariate analysis			Multivariate adjusting for age, sex, mPAP, and PVR		
Endarterectomy	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Central disease	2.64	0.9-7.08	**.05**	NA		
Segmental disease	0.37	0.12-1.12	.08	NA		
Distal disease	0.8	0.18-3.5	.77	NA		
No endarterectomy	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Central disease	1.91	1.19-3.05	**.007**	1.9	1.1-3.1	**.01**
Segmental disease	0.47	0.29-0.77	**.003**	NA		
Distal disease	1.2	0.65-2.3	.49	NA		

Bold values for *P* indicate statistical significance ($P < .05$) association with mortality. PVR group (<400 = 1, 400-800 = 2, 800-1200 = 3, >1200 = 4).
Abbreviations: 95% CI = confidence intervals; HR = hazard ratio; mPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance.

was an independent predictor of outcome in patients not undergoing pulmonary endarterectomy. While in patients who underwent endarterectomy the pattern was less clear with no independent predictive value identified.

Prior studies have assessed the severity of CTEPH including clinical, hemodynamic, and imaging investigations.[18-20] A prior study used DECT to assess changes in lung perfused blood volume based on the extent of pulmonary hypoperfusion; highlighting the value of assessing lung parenchymal tissue and perfusion in the setting of suspected chronic thromboembolic.[12] Another study proposed a CT scoring system in 145 patients with CTEPH, based on CTEPH radiological signs and hemodynamic changes, which includes mosaic perfusion, tricuspid regurgitation, pulmonary artery diameter, and unilateral/bilateral thrombus.[21] However, we are unaware of prior studies that have assessed disease location in the pulmonary artery tree compared with hemodynamics, surgical intervention and mortality in CTEPH.

Grafham et al[22] established a proximity-based CT pulmonary angiography scoring system, exhibiting moderate interobserver agreement among 40 patients with CTEPH and demonstrating the value of extensive pulmonary artery location evaluation. The highest degree of agreement was found at the main and lobar levels, but as expected decreased agreement was found distally. Interestingly the authors evaluated different vessel appearances such as webs, eccentric thickening, and occlusions and showed variable agreement demonstrating the challenge of accurate evaluation in chronic thromboembolic disease. In contrast, Hrdlicka et al[23] found that radiologists, even non-experts, had good sensitivity and inter-reader agreement when diagnosing CTEPH on CTPA; however, in our experience of clinical practice, such high agreement may not be consistently reproducible. These findings emphasize the importance of comprehensive scoring systems and the necessity for standardized methods to assess disease impact and distribution. In the present study, the interobserver agreement demonstrated good consistency between the 2 observers in determining the extent of disease. However, inaccurate results may arise due to subtle or small thrombi, vessel wall thickening or luminal irregularity, alterations in the surrounding lung tissue, or artefacts.[8] The lowest level of agreement was found in patients with distal disease, likely due to the fact that distal arteries are smaller, and the disease is more challenging to interpret in the distal regions.

Overall, the results indicate that broad classes of disease location showed clear clinical value, central location is independently associated with mortality and distal location with PVR. The more detailed scoring system provided may be useful for therapeutic intervention planning, but further work is needed to determine if there is incremental clinical value in the hemodynamic assessment or mortality prediction.

Distal disease presents a significant challenge in the management of CTEPH due to a lower accessibility for endarterectomy and an association with worse outcomes.[24] In our

study, distal disease was associated with mortality rates comparable to central disease. A study by Gan et al[25] found that distal disease was a significant predictor of mortality compared to proximal CTEPH in both endarterectomy and non-endarterectomy groups. Several factors could indicate the reason why distal disease outcomes are similar to central disease. Distal disease, *albeit* affecting smaller arteries, can cause severe pulmonary hypertension due to the cumulative impact of many blockages, leading to a hemodynamic impact comparable to that of central disease. In this study, PVR was similarly high in distal and central disease, for both of these chronic embolic disease locations, PVR was higher than that found in segmental disease, suggesting similarly severe vascular obstruction in distal and central disease. This is consistent with previous study, demonstrating the significance of identifying distal disease as a high-risk characteristic in chronic thromboembolic disease, which has been associated with high PVR and severe pulmonary hypertension.[25]

The lack of effectiveness of existing scoring systems to precisely evaluate distal disease demonstrates the importance of accurately characterizing the hemodynamics and parenchymal alterations, associated with distal disease in patients with CTEPH. Additionally, our study also highlights the important relationship between distal disease with lung parenchymal abnormalities such as mosaic attenuation (indicating abnormal perfusion) and infarction. Distal disease may indirectly affect lung parenchyma through alterations in regional blood flow dynamics and subsequent tissue ischemia.[26,27] The presence of mosaic perfusion and lung infarction may indeed aid the diagnosis of CTEPH when distal diseases are not clearly identified.[6]

This study demonstrated that higher chronic thromboembolic disease scores are associated with higher PVR and mPAP, indicating a relationship between greater thrombus burden and more severe hemodynamic abnormalities in CTEPH. Previous studies have shown that CTEPH scoring systems significantly correlate with PVR and mPAP, these associations are either determined by visually assessing hemodynamic changes in CT imaging,[21] or by quantifying pulmonary blood volume using DECT.[19] Thrombus impedes flow, and it is unsurprising that a greater burden is associated with larger alterations in the hemodynamics of the pulmonary circulation.

We acknowledge the limitations of our research. Eligible patients were identified from a single-centre registry and only 2 observers assessed scans. This could affect the generalizability of our findings. Additionally, intraobserver variability when using the scoring system was not assessed. Patients were identified retrospectively, which limited the ability to control for potential confounders. While CTPA was performed on all patients, contemporaneous PFT and RHC data were not fully complete. Results can be impacted by a variety of factors, including treatment efficacy, comorbidities, and the overall condition of the patient. Future research could focus on using AI to better characterize the location and burden of chronic thromboembolic disease, potentially improving diagnosis accuracy in patients with CTEPH.[28] AI algorithms, utilizing deep learning models, may analyse CTPA images with more accuracy, detecting subtle patterns and estimating disease burden more reliably than conventional approaches.

Conclusion

This study presents a scoring system for chronic thromboembolic disease location and extent in CTEPH on CTPA. The scoring system correlated strongly with hemodynamic severity; central thromboembolic disease was independently associated with worse survival in patients not undergoing endarterectomy. While the score provides clinical value, further research is warranted to assess its incremental benefit in hemodynamic evaluation and mortality prediction. Distal disease was associated with elevated PVR and lung parenchymal abnormalities. Our results confirm the effectiveness of determining the chronic thromboembolic disease location and extent in the assessment of CTEPH severity and risk prediction.

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Conflicts of interest

D.G.K., S.A. and A.J.S. are investigators within the National Institute for Health Research (NIHR) Sheffield Cardiovascular Biomedical Research Unit. A.J.S. is part of research grants and speaker fees from Janssen, Wellcome trust, and BHF. M.J.J.S. is funded by the Wellcome Trust 223521/Z/21/Z and NIHR Sheffield Biomedical Research Centre NIHR203321. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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