



Enhancing preoperative assessment in chronic thromboembolic pulmonary hypertension: A comprehensive analysis of interobserver agreement and proximity-based CT pulmonary angiography scoring

Grace K. Grafham^a, Marie Bambrick^{b,c}, Christian Houbois^c, Sebastian Mafeld^{c,d},
Laura Donahoe^{e,f}, Marc de Perrot^{e,f}, Micheal C. McInnis^{b,c,*}

^a Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

^b Division of Cardiothoracic and Vascular Imaging, Joint Department of Medical Imaging, Toronto General Hospital, Toronto, Ontario, Canada

^c Department of Medical Imaging, University of Toronto, Toronto, Ontario, Canada

^d Division of Vascular and Interventional Radiology, Joint Department of Medical Imaging, Toronto General Hospital, Toronto, Ontario, Canada

^e Department of Surgery, University of Toronto, Toronto, Ontario, Canada

^f Division of Thoracic Surgery, Department of Surgery, Toronto General Hospital, Toronto, Ontario, Canada

ABSTRACT

Background: Surgical risk in chronic thromboembolic pulmonary hypertension (CTEPH) depends on the proximity of thromboembolism on CT pulmonary angiography (CTPA). We assessed interobserver agreement for the quantification of thromboembolic lesions in CTEPH using a novel CTPA scoring index.

Methods: Forty CTEPH patients (mean age, 58 ± 16 years; 19 men) with preoperative CTPA who underwent pulmonary endarterectomy (PEA) (08/2020-09/2021) were retrospectively included. Three radiologists scored each CTPA for chronic thromboembolism (occlusions, eccentric thickening, webs) using a 32-vessel model of the pulmonary vasculature, with interobserver agreement evaluated using Fleiss' kappa. CT level of disease was determined by the most proximal chronic thromboembolism: level 1 (main pulmonary artery), 2 (lobar), 3 (segmental) and 4 (subsegmental), and compared to surgical level at PEA.

Results: Interobserver agreement for CT level of disease was moderate overall ($\kappa = 0.52$). Agreement was substantial overall at the main/lobar level (κ , mean = 0.71) when excluding the left upper lobe ($\kappa = 0.17$). Though segmental and subsegmental agreement suffered ($\kappa = 0.31$), we found substantial agreement for occlusions ($\kappa = 0.72$) compared to eccentric thickening ($\kappa = 0.45$) and webs ($\kappa = 0.14$). Correlation between CT level and surgical level was strong overall ($\tau_b = 0.73$) and in the right lung ($\tau_b = 0.68$), but weak in the left lung ($\tau_b = 0.42$) ($p < 0.05$). Radiologists often over- and underestimated the proximal extent of disease in right and left lung, respectively.

Conclusions: CT level of disease demonstrated good agreement between radiologists and was highly predictive of the surgical level in CTEPH. Occlusions were the most reliable sign of chronic thromboembolism and are important in assessing the segmental vasculature.

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a progressive pulmonary vascular disease resulting from incomplete resolution and successive organization of obstructive intraluminal pulmonary thromboemboli [1]. In a small but significant proportion

* Corresponding author. Toronto General Hospital, 200 Elizabeth St., 1PMB-298, Toronto, ON, M5G 2C4, Canada.

E-mail address: Micheal.McInnis@uhn.ca (M.C. McInnis).

@imagingtoronto (M.C. McInnis)

<https://doi.org/10.1016/j.heliyon.2023.e20899>

Received 4 August 2023; Received in revised form 28 September 2023; Accepted 10 October 2023

Available online 19 October 2023

2405-8440/© 2023 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Non-standard Abbreviations

CTEPH	chronic thromboembolic pulmonary hypertension
CTPA	computed tomography pulmonary angiography
HU	Hounsfield units
NYHA	New York Heart Association
PEA	pulmonary endarterectomy
UCSD	University of California, San Diego

of patients, chronic thromboembolic material may cause increased pulmonary vascular resistance, pulmonary hypertension, right heart failure and, ultimately, patient death. Recent evidence suggests that CTEPH occurs in approximately 3% of patients following acute pulmonary embolism, however the exact incidence is unknown as CTEPH is largely underdiagnosed and some patients with CTEPH report no history of pulmonary embolism [1]. Pulmonary endarterectomy (PEA) is the preferred treatment for CTEPH, demonstrating superior symptomatic and prognostic improvements compared to conservative management [2,3].

Evaluation of surgical risk is determined in part by the extent of chronic thromboembolism seen on imaging. High quality computed tomography pulmonary angiography (CTPA) directly visualizes chronic thromboembolism and excludes other potential causes of pulmonary hypertension; while digital subtraction angiography remains the gold standard diagnostic imaging modality for CTEPH, CTPA is increasingly preferred due to its non-invasive nature [4,5]. CTPA is also recognized in its ability to measure overall disease severity and predict surgical success in individual patients, particularly those with more proximal disease [6,7]. Although there is extensive data on interobserver agreement in the evaluation of acute pulmonary embolism [8,9], there is limited data in the evaluation of chronic thromboembolism, and the reliability of CT findings in the segmental and subsegmental vasculature has not yet been assessed.

As surgical technique evolves, experienced surgeons are now successfully operating on CTEPH patients with previously inoperable disease restricted to the segmental and subsegmental vasculature. Thus, a closer examination of CTPA findings in CTEPH is required to determine the reliability of signs of chronic thromboembolism in the small vessels. Accordingly, the aims of this retrospective study were to evaluate the interobserver agreement of radiologist-identified features of chronic thromboembolism by lesion type and location.

2. Methods

2.1. Study population

This retrospective study included all adult patients who underwent PEA at Toronto General Hospital (Toronto, Ontario, Canada) between August 2020 and September 2021. For each patient, confirmation of diagnosis and surgical eligibility was assessed in a multidisciplinary conference involving thoracic radiologists, thoracic surgeons, respirologists with expertise in pulmonary hypertension, and allied health professionals. Baseline clinical data were obtained from assessments routinely performed during the diagnostic work-up for chronic thromboembolic disease including a 6-minute walk test, pulmonary function testing, echocardiography, right heart catheterization, ventilation-perfusion scintigraphy, and CTPA. Patients were excluded if they underwent concomitant surgery, such as coronary artery bypass grafting at the same time as PEA or had a CTPA greater than 100 days before PEA. This study was approved with waiver of informed patient consent by the institutional review board (22–5343). The study is also in compliance with the International Society for Heart and Lung Transplantation (ISHLT) ethics statement.

2.2. Surgical technique and outcome

All patients underwent PEA with deep hypothermic circulatory arrest using a standard technique previously described [10]. Classification of the extent of thromboembolic disease was defined by the University of California, San Diego (UCSD) [11] level and collected for the left and right lung at the time of surgery. Briefly, surgical level 1 was defined as the most proximal disease in the main pulmonary arteries, including patients with complete occlusion of one lung; level 2 by disease in the lobar or intermediate pulmonary arteries; level 3 by disease in the segmental arteries only; and level 4 by disease restricted to the subsegmental vasculature.

2.3. CTPA technique

Although CT technique varies, generally, CT imaging was performed during suspended respiration after the injection of 70 cm³ of iodinated contrast (Ultravist 370; Bayer Healthcare, Berlin, Germany) at 5 cc/s via an 18-gauge antecubital intravenous catheter. The acquisition was triggered at 200–250 HU using bolus tracking software with the region of interest placed over the main pulmonary artery. In most patients, a standard voltage was set to 120 kV with automated exposure control determining the current. CT images were reconstructed into 0.5-mm thick axial slices using a mediastinal kernel, with coronal and sagittal reformats performed with 1-mm thick slices.

The CTPA study closest to the date of PEA was chosen for review. CTPA exams were performed both at our institution and

externally for patients who were referred from other hospital centres. A fellowship trained thoracic radiologist reviewed all internal and external CTPA studies for technical adequacy. Studies with poor opacification of the pulmonary arteries (e.g., <300 HU measured over the main pulmonary artery) and those with motion artifacts obscuring the segmental or proximal vasculature were excluded.

2.4. Image analysis

Images were independently analyzed by radiologists with varying levels of expertise: two fellowship trained thoracic radiologists with seven years (reader 1, M.M.) and two years (reader 2, C.H.) of experience, and one board certified thoracic radiology fellow (reader 3, M.B.). All readers were blinded to patients' preoperative clinical assessment and surgical findings. The pulmonary vasculature was divided into a total of 32-named pulmonary arteries (main, left and right main; interlobar; 5 lobar; lingular; 2 descending branches; and 20 segmental vessels) which were each assessed per patient. Each pulmonary artery segment was defined as having either (1) no disease, (2) a web, (3) eccentric thickening, or (4) a complete occlusion [12]. If there was no lesion identified in the segmental vessel but there was a subsegmental lesion peripherally then this was noted in the applicable segment. If two or more findings of chronic thromboembolism were present in a single vessel, the most obstructive finding was recorded (i.e. occlusion > eccentric thickening > web > subsegmental disease).

2.5. CT level of disease

The CT level of disease was assigned for each reader using a model analogous to the UCSD surgical scoring system, with scores based on the most proximal pulmonary artery level of thromboembolic disease present on CTPA [6]. Level 1 was defined as any disease in the main, left or right main pulmonary artery; level 2 by disease in the interlobar or lobar pulmonary vessels; level 3 by disease starting in the segmental pulmonary arteries, including disease in the descending branch of the lower lobes; and level 4 by disease located in the subsegmental vessels only.

Table 1
Clinical characteristics of included patients.

Baseline parameters	Patients (n = 40)
Age, years	58 ± 16
Sex, female	21 (53)
BMI, kg·m ⁻²	31 ± 7.6
6MWD, m (n = 36)	365 ± 141
BNP, pg·L ⁻¹	214 ± 307
NYHA Class	
1	4 (10)
2	11 (27.5)
3	21 (52.5)
4	4 (10)
Right heart catheter	
Mean PAP, mmHg	43 ± 12
PVR, wood units (n = 36)	7.4 ± 4.06
PCWP, mmHg (n = 37)	13 ± 9.3
Cardiac output, L·min ⁻¹ (n = 39)	4.7 ± 1.1
Cardiac index, L·min ⁻¹ ·m ⁻² (n = 39)	2.3 ± 0.6
Echocardiogram	
RV size	
Normal	0
Mild	12 (30)
Moderate	6 (15)
Severe	14 (35)
RV function (n = 37)	
Normal	9 (24.3)
Mild	10 (27)
Moderate	8 (21)
Severe	10 (27)
^a RVSP, mmHg (n = 33)	80 ± 28

Data is presented as n (%) for categorical variables and mean ± SD for continuous variables, unless otherwise stated. ^aRight ventricular systolic pressure was not obtained for technical reasons in n = 3 patients and was missing in n = 4 patients. 6MWD: 6-min walk distance; BMI: body mass index; BNP: b-type natriuretic peptide; NYHA: New York Heart Association; PAP: pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; RV: right ventricular; RVSP: right ventricular systolic pressure.

2.6. Statistical analysis

Categorical variables were described by counts and proportions. Continuous variables were described using mean and standard deviation. Cohen's weighted kappa was applied to evaluate pairwise interobserver agreement, while Fleiss' kappa and percentage concordance were used to evaluate overall interobserver agreement for CT level of disease. Interobserver agreement for findings of chronic thromboembolism in individual pulmonary arteries was also assessed using Fleiss' kappa. Kappa values were interpreted as follows: poor (<0), slight (0.0–0.2), fair (0.21–0.4), moderate (0.41–0.6), substantial (0.61–0.8), almost perfect (0.81–1.0) [13]. Sensitivity and specificity of radiologists' interpretations were calculated by relating them to the consensus score for 200 (out of a total possible 1280) randomly selected pulmonary vessel segments. The correlation between CT level of disease and UCSD surgical level were assessed using Kendall's tau-b. A two-sided p-value of <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS version 29 software (Chicago, IL, USA).

3. Results

3.1. Patient characteristics and operative findings

There were 56 PEAs performed between August 2020 and September 2021. Eight cases were excluded for CT imaging greater than 100 days before surgery, five cases for concomitant surgeries, two cases for respiratory motion obscuring the segmental vasculature, and one case for incomplete surgical data. The mean patient age was 58 years (range, 22–81 years) with near equal numbers of women and men ($n = 21$ and 19 , respectively). Most patients were NYHA functional class 3 or 4 and 27% ($n = 10$) had severe right heart dysfunction on echocardiogram (Table 1). At surgery, 23 patients had overall UCSD surgical level 1 or 2 and 17 had level 3 or 4.

3.2. Lesion distribution

The distribution of findings of chronic thromboembolism across all readers is presented in Fig. 1. On average, the readers identified 596 out of a total of 1280 possible vessel segments as being involved by chronic thromboembolic disease (mean \pm SD = 14.9 ± 7.2 lesions per case). The frequency of lesion types varied significantly per case, reflecting the diverse presentation of chronic thromboembolism in CTEPH ($p = 0.029$). Arterial webs were the most common lesion type identified (mean \pm SD = 4.6 ± 4.3 lesions per case) followed by occlusions (mean \pm SD = 3.7 ± 4.3), eccentric thickening (mean \pm SD = 3.7 ± 3.6), and subsegmental disease only (mean \pm SD = 2.9 ± 2.9).

Regarding the location of chronic thromboembolic lesions, most patients were found to have disease in the right lower lobe (94%) while the right middle lobe was least involved (78%) (Table S1). The most frequently involved pulmonary vessel segments, as assessed by any reader, were the lateral basal right lower lobar (74%), posterior basal right lower lobar (73%), superior right lower lobar (72%), and the posterior and lateral basal left lower lobar vessels (68%) (Table S2).

3.3. Interobserver agreement

At the main and lobar level, interobserver agreement for the presence of chronic thromboembolism ranged from moderate to near perfect (κ , mean [range] = 0.71 [0.57 – 0.89]) when excluding the left upper lobe where agreement was slight ($\kappa = 0.17$) (Fig. 2). At the

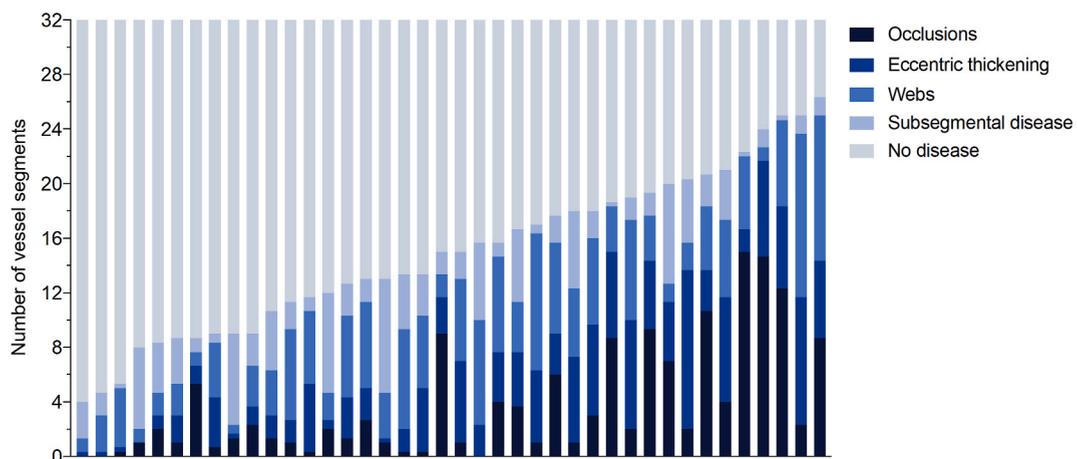


Fig. 1. Distribution of signs of chronic thromboembolism (occlusions, eccentric thickening, webs, subsegmental disease). Each bar represents one patient, with the number of individual lesions displayed as an average between the 3 readers. A one-way ANOVA was performed which revealed a significant difference between the frequency of occlusions, eccentric thickening, webs, and subsegmental disease per patient ($p = 0.029$). Statistical significance, two-sided $p < 0.05$.

segmental level, mean interobserver agreement for grouped segmental vessels was overall fair (κ , mean [range] = 0.31 [0.22–0.42]). Agreement differed by lesion type with substantial agreement for pulmonary artery occlusions (κ , mean [range] = 0.72 [0.41–1]) and consistently lower agreement scores for the remaining lesion types: eccentric thickening (κ , mean [range] = 0.45 [0.12–0.89]), subsegmental disease only (κ , mean [range] = 0.15 [0.07–0.20]), and webs (κ , mean [range] = 0.14 [–0.01–0.40]).

Cases of discordance in radiologists' classification of signs of chronic thromboembolism are shown in Fig. 3. The mean sensitivity to detect chronic thromboembolism in the main and lobar vessels was 81% and the specificity was 99% (Table S3). The mean sensitivity and specificity for segmental disease was comparable at 80% and 88%, respectively. CT detection of chronic subsegmental thromboembolism was lowest with a mean sensitivity of 57% and specificity of 43%.

3.4. CT level of disease

The distribution of scores for CT level of disease is presented in Table S4. For all readers, most cases were scored as CT level 1 or 2, and this was also true when examining the right lung alone. In the left lung, all readers identified most cases as being CT level 3 or 4. The agreement between the three readers for CT level of disease was moderate overall ($\kappa = 0.51$ [95% CI = 0.39–0.63]), with similar ranges for the right ($\kappa = 0.43$ [95% CI = 0.32–0.55]) and left lung alone ($\kappa = 0.46$ [95% CI = 0.35–0.56]) (Table 2). For all paired comparisons, agreement ranged from moderate to substantial with the greatest agreement between reader 1 and reader 3 ($\kappa = 0.67$ [95% CI = 0.48–0.86]). Overall agreement was strongest for scoring of chronic thromboembolism in the main pulmonary arteries, CT level 1 ($\kappa = 0.69$ [95% CI = 0.51–0.87]), and declined distally: level 2, $\kappa = 0.48$, 95% CI = 0.30–0.67; level 3, $\kappa = 0.49$, 95% CI = 0.31–0.67; level 4, $\kappa = -0.03$, 95% CI = –0.21–0.14 (Table S5).

3.5. Radiological-surgical correlation

There was a strong, positive correlation between each radiologist's interpretation of CT level of disease and the UCSD level at surgery (R1, $\tau_b = 0.74$; R2, $\tau_b = 0.78$; R3, $\tau_b = 0.72$) ($p < 0.0001$ for all) (Table 3, Fig. 4). As a whole, the CT level of disease over- and underestimated the UCSD surgical level at a similar rate. In the left lung, there was a greater number of cases where the CT level of

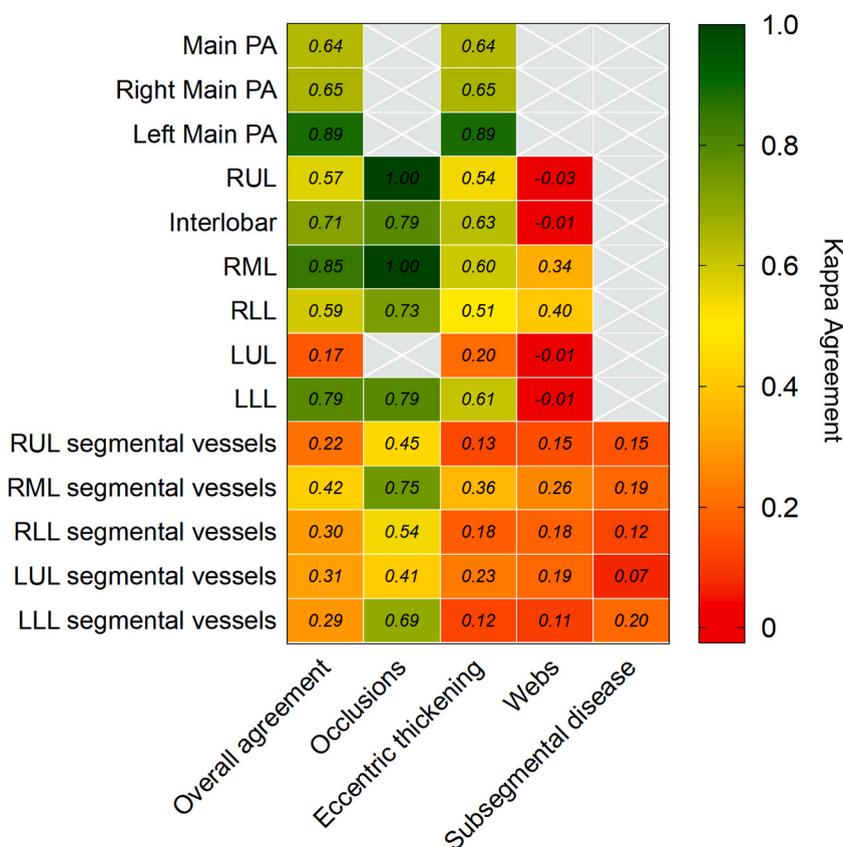


Fig. 2. Interobserver agreement for CT signs of chronic thromboembolism for individual pulmonary vessel segments. Fleiss' kappa was calculated per lesion type per pulmonary artery, and overall, for the presence of any disease. Segmental vessels were grouped per lobe. The heat map colour corresponds to the degree of kappa agreement with the associated numerical kappa values labelled in each cell. Abbreviations: LLL, left lower lobe; LUL, left upper lobe; PA, pulmonary artery; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

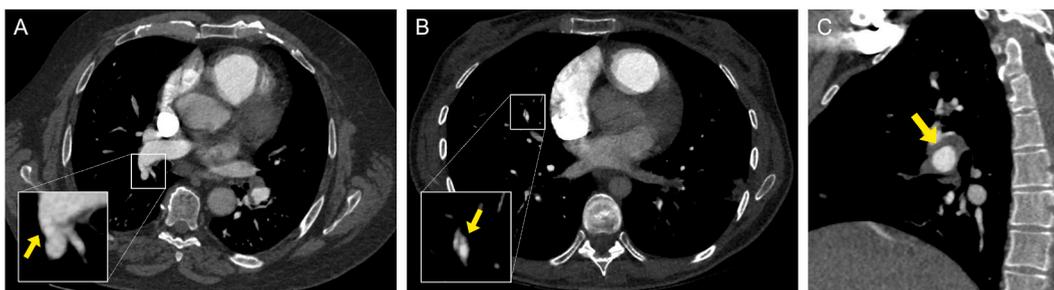


Fig. 3. Representative cases of discordance between radiologists for signs of chronic thromboembolism. (A) Axial CTPA in a 70-year-old male with CTEPH. On initial reading, reader 1 identified an arterial web in the right lower lobe superior segmental artery (arrow) where readers 2 and 3 identified none. The consensus reading agreed with the presence of a web. (B) Axial CTPA in a 43-year-old female with CTEPH. On initial reading, readers 1 and 3, but not reader 2, identified chronic thromboembolic disease in the subsegmental branches of the right middle lobar medial segmental artery (arrow). The consensus reading agreed with the presence of subsegmental disease. (C) Sagittal CTPA in a 34-year-old female with CTEPH. On initial reading, only readers 1 and 2 identified eccentric irregularities in the wall of the right lower lobar pulmonary artery (arrow). The consensus reading agreed.

Table 2

Kappa agreement and percent concordance for CT level of disease for each lung and for the whole lung.

CT level of disease	Reader pair comparisons, Cohen's Kappa (95% CI)			Percent concordance (%)	Overall agreement, Fleiss' Kappa (95% CI)
	R1:R2	R1:R3	R2:R3		
Right lung	0.45 (0.28, 0.63)	0.64 (0.45, 0.84)	0.52 (0.36, 0.68)	61.67	0.43 (0.32, 0.55)
Left lung	0.58 (0.40, 0.76)	0.60 (0.40, 0.80)	0.53 (0.34, 0.72)	65.83	0.46 (0.35, 0.56)
Whole lung	0.56 (0.39, 0.74)	0.67 (0.48, 0.86)	0.61 (0.46, 0.77)	66.67	0.51 (0.39, 0.63)

Statistical significance, two-sided $p < 0.001$ for all comparisons. CI: confidence interval; R1: reader 1; R2: reader 2; R3: reader 3.

disease was scored more distal than the UCSD surgical level reflecting a weaker correlation (R1, $\tau_b = 0.47$; R2, $\tau_b = 0.59$; R3, $\tau_b = 0.41$) ($p < 0.01$ for all) (Table S6). Most of these errors in underestimation pertained to the radiologists scoring UCSD surgical level 2 cases as CT level 3. Conversely, in the right lung there were more cases where the CT level of disease was more proximal than the UCSD surgical level with the correlation remaining strong (R1, $\tau_b = 0.71$; R2, $\tau_b = 0.65$; R3, $\tau_b = 0.68$) ($p < 0.0001$ for all) (Table S7). Many of these errors in overestimation are attributed to perceived webs or eccentric thickening in the right lower lobe pulmonary artery which was classified as CT level 2 but surgical level 3.

4. Discussion

Our study demonstrated good agreement between radiologists in the scoring of CT level of disease in CTEPH and a strong correlation with surgical findings at PEA. Compared to the surgical classification, radiologists more commonly overestimated the proximal extent of disease in the right lung and underestimated the proximal extent of disease in the left. Radiologists' agreement in the main and lobar vasculature was moderate but suffered at the segmental and subsegmental levels. We identified the left upper lobe as the location with the greatest discordance among radiologists and an area where CT level of disease does not perform well. Furthermore, we found that although there was limited agreement among radiologists distally, there was moderate agreement for pulmonary artery occlusions and this sign was more reliable than eccentric thickening or webs.

Pulmonary endarterectomy represents a potentially curative option for patients with CTEPH. More recently, balloon pulmonary angiography has been implemented as an alternative for CTEPH patients who are ineligible for PEA, further underscoring the significance of high-quality imaging for treatment decision making in CTEPH [14]. Yet, a validated scoring index for chronic

Table 3

Correlation matrices for whole lung surgical level and CT level of disease.

	CT level of disease											
	Reader 1				Reader 2				Reader 3			
Surgical level	1	2	3	4	1	2	3	4	1	2	3	4
1	8	1	0	0	7	2	0	0	7	2	0	0
2	0	13	1	0	0	11	3	0	1	11	2	0
3	0	3	11	0	0	2	10	2	1	2	10	1
4	0	2	1	0	0	0	2	1	0	0	3	0
Kendall's tau-b (p-value)	0.74 ($p < 0.0001$)				0.78 ($p < 0.0001$)				0.72 ($p < 0.0001$)			

Statistical significance, two-sided $p < 0.05$.

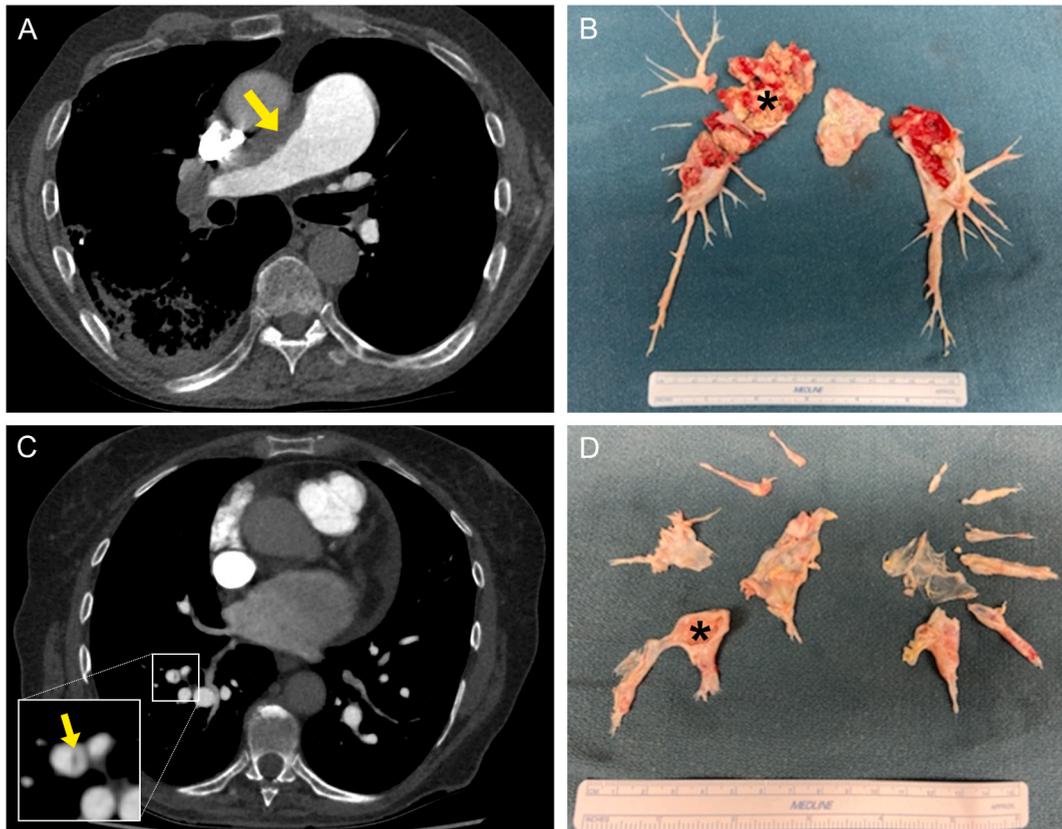


Fig. 4. Representative cases of concordance between the level of disease on CT and the UCSD surgical level determined at PEA. (A) CTPA in a 59-year-old male with CTEPH demonstrating eccentric thickening of the main pulmonary artery (arrow) with the corresponding (B) surgical specimen (asterisk). This case was universally scored as CT and UCSD level 1. (C) CTPA in a 75-year-old female with CTEPH showing a distal web in the anterior basal right lower lobar segmental artery (arrow) with the corresponding (D) surgical specimen (asterisk). This case was universally scored as CT and UCSD level 3.

thromboembolic disease does not exist. Here, we observed moderate interobserver agreement between radiologists for CT level of disease, comparable to that reported by Eberhard et al. ($\kappa = 0.55$) [15] and McInnis et al. ($\kappa = 0.64$) [6]. While similar in findings, a further and important step in this study was the extension of the agreement analysis on a per-segment basis to explore the distribution of lesions and determine where interobserver agreement is strongest and conversely, the weakest. While exact kappa coefficients vary between studies, we identified a consistent trend with interobserver agreement being highest at the main level (CT level 1) and lowest at the subsegmental level (CT level 4) [16]. Lower detection of subsegmental disease is often attributed to limited visualization of distal arteries on CTPA, however this may be improved with concomitant perfusion imaging [17].

Evaluation of interobserver agreement for individual pulmonary arteries provided insight into areas where radiologists had the most difficulty in their analysis. We found a high rate of discordance in the left upper lobar pulmonary artery and its anterior segmental branch, similar to work from others in acute pulmonary embolism [18,19]. The left upper lobe anatomy is distinct in that there is often not a single common origin for the pulmonary vessels, as such the segmental branches arise directly from the left main pulmonary artery. Most commonly, these branches include an apico-posterior (or apico-anterior) trunk and anterior (or posterior) segmental branch. In the present study, we used a lung model with separate anterior, apical, and posterior segmental vessels which could explain some of the discrepancies in the left upper lobe. Another possible explanation is the increased detection of false pulmonary emboli from partial volume averaging of adjacent bronchi. Gotway et al. reports that this pitfall is most common in the left upper lobar anterior segmental vessel but may occur in any obliquely oriented vessel on axial CT, such as the lower lobar superior segment vessels which we also found to be highly discordant [20].

One of the proposed reasons for the underdiagnosis of CTEPH is inadequate awareness of the condition among the medical imaging community and this reflects our experience in evaluating referrals to our program. Rogberg et al. found that the sensitivity to correctly diagnose CTEPH from CT scans performed at initial pulmonary embolism diagnosis was only 26%. For mention of specific pulmonary arterial abnormalities, the sensitivity was 63% with radiologists demonstrating limited knowledge of CTEPH findings beyond eccentric thickening [21]. Ende-Verhaar et al. showed that if evaluated by expert radiologists, CTEPH could be correctly diagnosed in 72% of patients based on initial CT scans [22]. In our study, sensitivity was most disparate among radiologists in the distal vasculature, with the most experienced radiologist having the highest sensitivity (Table S3). The use of multiple imaging modalities, like V/Q scanning,

in the initial workup for CTEPH favours correct interpretation of such distal disease by non-expert radiologists. Additional discrepancies may be resolved using DSA [23,24]. Despite this, we found that the right lower lobe was the most common location for chronic thromboembolism and this lobe should be closely evaluated in cases of suspected CTEPH. Furthermore, although we found limited interobserver agreement for webs and eccentric thickening similar to Hrdlicka et al. [25], our findings demonstrate pulmonary artery occlusions as a reliable sign even in the distal vasculature among radiologists with different experience levels.

In recent years, a revised surgical classification for CTEPH has been developed based on the level of chronic thromboembolism seen intraoperatively [11]. McInnis et al. [6] and Eberhard et al. [15] showed that CT level of disease had moderate agreement with the surgical level but tended to classify more patients as having proximal disease. Likewise, our data shows a strong correlation between CT level of disease and surgical level. When divided per lung, we found that radiologists often over- and underestimated the proximal extent of disease in right and left lung, respectively. While our scoring index focuses on the proximity of disease, we appreciate that radiologists frequently underestimate total thromboembolic burden, in that radiologists may identify an isolated proximal web on CT where the surgeon will find an entire cast of chronic thromboembolism along the vessel wall (Fig. 4).

There are several limitations to the present study in addition to the single-centre, retrospective design. First, our study population comprised a small number of patients, in keeping with CTEPH being a rare condition but also because we required cases with the revised UCSD classification for both right and left lung limiting our ability to leverage the bulk of cases at our centre. Second, our analysis was restricted to patients who had undergone PEA thus excluding the subset of patients who were deemed ineligible for surgery and the distribution of chronic thromboembolism reported here may not be consistent with that of chronic thromboembolism overall. However, this is unlikely to have significantly impacted our segmental analysis as this was calculated per lesion versus per case. Third, we compared CT level of disease to findings at surgery, yet the UCSD surgical level only describes the most proximal extent of disease and not the entire disease distribution. We did obtain a surgical level for each individual lung, and this is the first study to describe differences between the right and left. Regardless, we demonstrated that the areas of greatest disagreement between radiologists were at the segmental and subsegmental level and there were very few surgical level 4 cases where identification of a segmental lesion would alter the final classification.

From our discussion, several questions remain unanswered. What is the comparative utility of CTPA in relation to DSA, and under what circumstances might DSA be circumvented? What are the disparities in interobserver agreement within proximal vessels in cases where our statistical power was lacking? Is there a discernible correlation between lesion type and distribution, patient characteristics, and clinical phenotype? And what associations can be established between these and hemodynamic parameters? Our current work establishing interobserver agreement represents an important preliminary step in exploring these future questions.

5. Conclusion

Our results show that CT level of disease has overall good interobserver agreement among radiologists in the evaluation of CTEPH, with the greatest concordance at the main and lobar levels. Moreover, CT level of disease was highly predictive of the surgical level at PEA and may be used in the assessment of surgical candidacy at expert centres.

Data availability statement

Data associated with this study has not been deposited into a publicly available repository. Data is included in the article and referenced therein.

CRedit authorship contribution statement

Grace K. Grafham: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Marie Bambrick:** Writing – review & editing, Investigation, Formal analysis. **Christian Houbois:** Writing – review & editing, Investigation, Formal analysis. **Sebastian Mafeld:** Writing – review & editing. **Laura Donahoe:** Writing – review & editing. **Marc de Perrot:** Writing – review & editing. **Micheal C. McInnis:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Micheal McInnis reports speaker fees from Bayer. Marc de Perrot reports consulting fees from AstraZeneca, BMS, Merck, Roche and honoraria from Bayer, BMS, Merck, AstraZeneca. All other authors declare no relevant relationship.

Acknowledgements

G.K.G. was supported by the Comprehensive Research Experience for Medical Students (CREMS) award. We would like to thank Fatemeh Zaeimi (MSc) for assistance with the CTEPH Research Program database.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.heliyon.2023.e20899>.

References

- [1] Y.M. Ende-Verhaar, S.C. Cannegieter, A.V. Noordegraaf, et al., Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature, *Eur. Respir. J.* 49 (2017), 1601792, <https://doi.org/10.1183/13993003.01792-2016>.
- [2] M. Delcroix, I. Lang, J. Pepke-Zaba, et al., Long-term outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry, *Circulation* 133 (9) (2016) 859–871, <https://doi.org/10.1161/CIRCULATIONAHA.115.016522>.
- [3] M. Newnham, K. Bunclark, N. Abraham, et al., CAMPHOR score: patient-reported outcomes are improved by pulmonary endarterectomy in chronic thromboembolic pulmonary hypertension, *Eur. Respir. J.* 56 (4) (2020), 1902096, <https://doi.org/10.1183/13993003.02096-2019>.
- [4] F. Aluja Jaramillo, F.R. Gutierrez, F.G. Diaz Telli, S. Yevenes Aravena, C. Javidan-Nejad, S. Bhalla, Approach to pulmonary hypertension: from CT to clinical diagnosis, *Radiographics* 38 (2) (2018) 357–373, <https://doi.org/10.1148/rg.2018170046>.
- [5] A. Grosse, C. Grosse, I.M. Lang, Distinguishing chronic thromboembolic pulmonary hypertension from other causes of pulmonary hypertension using CT, *Am. J. Roentgenol.* 209 (6) (2017) 1228–1238, <https://doi.org/10.2214/AJR.17.17871>.
- [6] M.C. McInnis, D. Wang, L. Donahoe, et al., Importance of computed tomography in defining segmental disease in chronic thromboembolic pulmonary hypertension, *ERJ Open Res* 6 (4) (2020), <https://doi.org/10.1183/23120541.00461-2020>, 00461-02020.
- [7] M. Heinrich, M. Uder, D. Tscholl, A. Grgic, B. Kramann, H.J. Schäfers, CT scan findings in chronic thromboembolic pulmonary hypertension: predictors of hemodynamic improvement after pulmonary thromboendarterectomy clinical investigations, *Chest* 127 (2005) 1606–1613. www.chestjournal.org.
- [8] C. Zhou, H.P. Chan, A. Chughtai, et al., Variabilities in reference standard by radiologists and performance assessment in detection of pulmonary embolism in CT pulmonary angiography, *J. Digit. Imag.* 32 (6) (2019) 1089–1096, <https://doi.org/10.1007/s10278-019-00228-w>.
- [9] The Pioped Investigators, Value of the ventilation/perfusion scan in acute pulmonary embolism: results of the prospective investigation of pulmonary embolism diagnosis (PIOPED), *JAMA* 263 (20) (1990) 2753–2759, <https://doi.org/10.1001/jama.1990.03440200057023>.
- [10] M. de Perrot, K. McRae, L. Donahoe, E. Abdelnour-Berchtold, J. Thenganatt, J. Granton, Pulmonary endarterectomy in severe chronic thromboembolic pulmonary hypertension: the Toronto experience, *Ann. Cardiothorac. Surg.* 11 (2) (2022) 133–142, <https://doi.org/10.21037/acs-2021-pte-14>.
- [11] M.M. Madani, Surgical treatment of chronic thromboembolic pulmonary hypertension: pulmonary thromboendarterectomy, *Methodist DeBakey Cardiovasc J* 12 (4) (2016) 213, <https://doi.org/10.14797/MDCJ-12-4-213>.
- [12] E. Castañer, X. Gallardo, E. Ballesteros, et al., CT diagnosis of chronic pulmonary thromboembolism, *Radiographics* 29 (1) (2009) 31–33, <https://doi.org/10.1148/rg.291085061>.
- [13] J.R. Landis, G.G. Koch, The measurement of observer agreement for categorical data, *Biometrics* 33 (1) (1977) 159–174, <https://doi.org/10.2307/2529310>.
- [14] L. Zhang, Y. Bai, P. Yan, et al., Balloon pulmonary angioplasty vs. pulmonary endarterectomy in patients with chronic thromboembolic pulmonary hypertension: a systematic review and meta-analysis, *Heart Fail. Rev.* 26 (4) (2021) 897–917, <https://doi.org/10.1007/s10741-020-10070-w>.
- [15] M. Eberhard, M. McInnis, M. de Perrot, et al., Dual-energy CT pulmonary angiography for the assessment of surgical accessibility in patients with chronic thromboembolic pulmonary hypertension, *Diagnostics* 12 (2) (2022), <https://doi.org/10.3390/diagnostics12020228>.
- [16] C. Dong, M. Zhou, D. Liu, X. Long, T. Guo, X. Kong, Diagnostic accuracy of computed tomography for chronic thromboembolic pulmonary hypertension: a systematic review and meta-analysis, *PLoS One* 10 (4) (2015), e0126985, <https://doi.org/10.1371/journal.pone.0126985>.
- [17] J. le Faivre, A. Duhamel, S. Khung, et al., Impact of CT perfusion imaging on the assessment of peripheral chronic pulmonary thromboembolism: clinical experience in 62 patients, *Eur. Radiol.* 26 (11) (2016) 4011–4020, <https://doi.org/10.1007/s00330-016-4262-1>.
- [18] S. Brunot, O. Corneloup, V. Latrabe, M. Montaudon, F. Laurent, Reproducibility of multi-detector spiral computed tomography in detection of sub-segmental acute pulmonary embolism, *Eur. Radiol.* 15 (10) (2005) 2057–2063, <https://doi.org/10.1007/s00330-005-2844-4>.
- [19] S.J. Kligerman, J.W. Mitchell, J.W. Sechrist, A.K. Meeks, J.R. Galvin, C.S. White, Radiologist performance in the detection of pulmonary embolism: features that favor correct interpretation and risk factors for errors, *J. Thorac. Imag.* 33 (6) (2018). https://journals.lww.com/thoracicimaging/Fulltext/2018/11000/Radiologist_Performance_in_the_Detection_of_4.aspx.
- [20] M.B. Gotway, R.A. Patel, W.R. Webb, Helical CT for the evaluation of suspected acute pulmonary embolism: diagnostic pitfalls, *J. Comput. Assist. Tomogr.* 24 (2) (2000). https://journals.lww.com/jcat/Fulltext/2000/03000/Helical_CT_for_the_Evaluation_of_Suspected_Acute.16.aspx.
- [21] A.N. Rogberg, D. Gopalan, E. Westerlund, P. Lindholm, Do radiologists detect chronic thromboembolic disease on computed tomography? *Acta Radiol.* 60 (11) (2019) 1576–1583, <https://doi.org/10.1177/0284185119836232>.
- [22] Y.M. Ende-Verhaar, L.J. Meijboom, L.J.M. Kroft, et al., Usefulness of standard computed tomography pulmonary angiography performed for acute pulmonary embolism for identification of chronic thromboembolic pulmonary hypertension: results of the InShape III study, *J. Heart Lung Transplant.* 38 (7) (2019) 731–738, <https://doi.org/10.1016/j.healun.2019.03.003>.
- [23] S. Higuchi, H. Ota, N. Yaoita, et al., Update on the roles of imaging in the management of chronic thromboembolic pulmonary hypertension, *J. Cardiol.* 81 (3) (2023) 297–306, <https://doi.org/10.1016/j.jjcc.2022.03.001>.
- [24] M. McInnis, Imaging advances in chronic thromboembolic pulmonary hypertension, *Semin. Roentgenol.* 57 (4) (2022) 324–334, <https://doi.org/10.1053/j.ro.2022.07.003>.
- [25] J. Hrdlicka, M. Jurka, B. Bircakova, et al., Even non-expert radiologists report chronic thromboembolic pulmonary hypertension (CTEPH) on CT pulmonary angiography with high sensitivity and almost perfect agreement, *Eur. Radiol.* Published online (2023), <https://doi.org/10.1007/s00330-023-10098-0>.