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Differences in referral to a chronic thromboembolic pulmonary hypertension center following acute pulmonary embolism: a locoregional experience

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Abstract

Chronic thromboembolic pulmonary hypertension (CTEPH) is a treatable complication of acute pulmonary embolism (PE). Identification of factors that impact referral to a comprehensive CTEPH center may improve disease awareness and patient outcomes. We conducted a study of patients with acute PE. Cases were identified through a natural language processing algorithm. ICD coding was used to assess clinical documentation for dyspnea or CTEPH placed at least 90 days after their acute PE diagnosis. We analyzed characteristics of patients who were referred vs. not referred, as well as referral patterns for "at risk" patients. 2454 patients with acute PE were identified, of which 4.9% (120/2454) were referred for CTEPH evaluation. Patients who were not referred were older (61 vs. 54 years, $p < 0.001$), had higher rates of cancer (28% vs. 10%, $p < 0.001$), and lived further from the referral center (9.1 miles vs. 6.7 miles, $p = 0.03$). Of 175 patients identified as "at risk," 12% (21/175) were referred. In the 'at risk' cohort, distance from referral center among referred and not referred was significant (5.7 miles vs. 8.8 miles, $p = 0.04$). There were low rates of referral to CTEPH center in post-PE patients, and in patients with symptoms who may be at higher risk of CTEPH. Age, co-morbid conditions, distance from comprehensive center, and presence of a primary care provider contribute to differences in referral to a comprehensive CTEPH center. Clinician education about CTEPH is important to ensure optimal care to patients with or at risk for chronic complications of acute PE.

Keywords Referral · Differences · Chronic thromboembolic pulmonary hypertension · Dyspnea · Venous thromboembolic event

Abbreviations

SES	Socioeconomic status
PE	Pulmonary embolism
CTEPH	Chronic thromboembolic pulmonary hypertension
EDW	Electronic data warehouse
NLP	Natural language processing
ICD-10	International classification of diseases—10th revision
MPD	Myeloproliferative disease
MPN	Myeloproliferative neoplasm
COPD	Chronic obstructive pulmonary disease

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CTED Chronic thromboembolic disease
APS Antiphospholipid syndrome

Introduction

Several studies of large national datasets have demonstrated differences in outcomes between gender, race and socioeconomic status (SES) after acute pulmonary embolism (PE) [1, 2]. Using the Nationwide Inpatient Sample (NIS) over a 9-year period, Agarwal et. al demonstrated that women were more likely to suffer in-hospital mortality, have a higher incidence of in-hospital morbidity such as transfusion needs, and are less likely to be discharged home [2]. Recently we demonstrated a national trend of worsening PE mortality since 2008, as well as differences in PE mortality, with black men and women having the highest rates of PE mortality [3]. Furthermore, these differences also exist locoregionally in Illinois, and notably, are more pronounced in the younger population [4].

Chronic thromboembolic pulmonary hypertension (CTEPH) is a known complication of acute PE that occurs in 0.4% to 6.2% of patients, often within the first 2 years after presentation of the acute PE [5–7]. Known risk factors for the development of CTEPH include prior splenectomy, antiphospholipid syndrome, ventriculoatrial shunts among others [8]. If untreated, the 3-year mortality for patients with CTEPH is 30%. The risk of death correlates with the severity of pulmonary hypertension, which may worsen with delayed diagnosis [9]. Fortunately, unlike other forms of pulmonary hypertension, CTEPH may be curable if timely surgical referral is made. Prospective registry data suggest that early surgical referral and treatment with specific pulmonary vasodilators (i.e., soluble guanylate cyclase stimulator) result in better outcomes [10]. Coordination and consideration of advanced treatment strategies including pulmonary thromboendarterectomy, balloon pulmonary angioplasty as well as medical interventions is highly specialized and requires referral to CTEPH centers of excellence to guide care [11].

Current guidelines suggest consideration of CTEPH in patients experiencing continued dyspnea or functional limitation despite 3 months of effective anticoagulation therapy following an acute PE [11]. Expected versus observed rates of CTEPH suggests under recognition of this potentially curable disease [12]. Unlike well documented outcome differences apparent in the acute PE population, there is a paucity of data addressing other potential differences that may impact referral to CTEPH centers and subsequently outcomes for patients with CTEPH [6, 12–15]. Our objective was to examine clinical, demographic and socioeconomic factors that may impact referral to a major locoregional CTEPH center in an at risk patient population.

Methods

We conducted a retrospective observational cohort study of adult patients at a single academic center who were diagnosed with acute PE from January 2018 through December 2021. Patients were identified as having an acute PE by means of an electronic data warehouse (EDW) query employing a natural language processing (NLP) algorithm to bin contrasted chest computed tomography radiology narrative reports as positive, negative, or indeterminate for acute PE (described in detail below). Excluded from the analysis were radiology reports from non-contrast enhanced images. We collected baseline demographic (including home address distance from CTEPH center), clinical, insurance type (categorized into Medicaid, Medicare, Private, and other), comorbid, and referral characteristics of each patient with a PE diagnosis. Owing to consensus on the time-frame for the definition of CTEPH, we identified patients who had *International Classification of Diseases*, tenth revision (ICD-10) clinical documentation coding for dyspnea (R06) or CTEPH (I27.24) placed greater than 90 days from acute PE diagnosis; patients with a diagnosis code for dyspnea or CTEPH were categorized into "at risk" cohort (Fig. 1) [11]. We categorized patients who were referred to our CTEPH center as "referral cohort" and those without a referral to a CTEPH provider as "non-referral cohort" (Fig. 1). Our institution does not utilize an automatic electronic health record trigger for CTEPH referrals or consultations.

Microsoft SQL Server Management Studio 18 was used to generate the acute PE NLP algorithm, employing start phrases followed by select target phrases, skip phrases, absolute negative assertions, and absolute positive assertions. See Appendix 1 for a full list of phrases. Methods of previous NLP generation for acute venous thromboembolism have been described previously [16]. This NLP tool was then applied to a training set of 276 computed tomography scans. Two reviewers (RM & MJC) manually coded for the presence or absence of PE on this training set. Using the reviewers coding as the gold standard, three successive iterations of target and skip phrases, and the

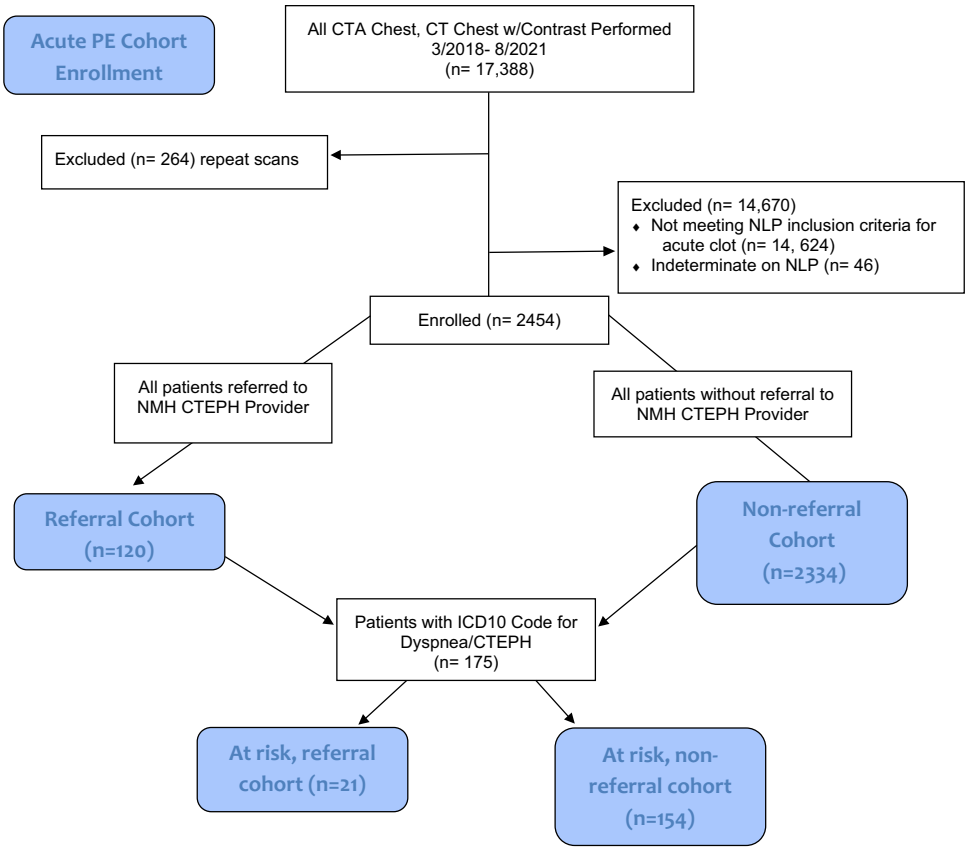

Fig. 1 Enrollment. *PE* pulmonary embolism, *CTA* Computed tomography angiography, *CT* computed tomography, *NLP* natural language processing, *CTEPH* chronic thromboembolic pulmonary hypertension, *ICD*-10 international classification of diseases, 10th revision

positive and negative assertions, were used to generate an improvement in test characteristics, to a specificity of 99% and a sensitivity of 98%, from an original specificity and sensitivity of 78% and 69%, respectively. Three of the 276 scans (1%) were incorrectly identified as both positive and negative with the NLP algorithm.

The primary outcome was referral to CTEPH center. The null hypothesis is that the characteristics of referred and non-referred patients are uniform. Data are summarized as median (interquartile range) for continuous variables, and number of subjects (%) for categorical variables. Comparisons between groups were performed using Mann–Whitney U test for continuous variables, or by chi-square test for categorical variables. Results were considered significant when p-values were < 0.05. A multivariable analysis was planned, but after finding one significant variable in univariate analysis, the logistic regression analysis was abandoned. All analyses were completed using Graph Pad Prism Version 8.0. The study was approved by the Institutional Review Board of Northwestern University.

Results

We identified 2454 unique patients diagnosed with acute PE during the study period, as determined from the NLP algorithm (Fig. 1). Of these, 120 (4.9%) were referred to our CTEPH center. As compared to the referral cohort, patients who were not referred were older (61 vs. 54 years, $p < 0.001$), had a lower BMI (28 vs. 29 kg/m2, $p = 0.02$), had a higher comorbid cancer rate (28% vs. 10%, $p < 0.001$), and had a higher rate of Medicare insurance (42% vs. 31%, $p = 0.01$) and private insurance (43 vs. 40%, $p < 0.001$) (Table 1). Patients who were referred were more likely to have described risk factors for CTEPH such as antiphospholipid syndrome (APS) (3% vs. 1%, $p = 0.03$), myeloproliferative disorders/myeloproliferative neoplasms (MPD/MPN) (10% vs. 4%, $p < 0.001$), and osteomyelitis (8% vs. 3%, $p = 0.03$). There were no significant differences with regard to sex, race, ethnicity, and median household income among the referral and non-referral cohort. As compared to the referral cohort, patients who were not referred were less likely to be admitted to an inpatient ward at time of diagnosis (47% vs. 74%, $p < 0.001$), lived further away

Table 1 Baseline demographic and clinical characteristics of referral and non-referral acute PE cohorts between 2018 and 2021

	Referral cohort (n = 120)	Non-referral cohort (n = 2334)	p value
Age, years (IQR)	54 (40–66)	61 (47–72)	**< 0.001**
Female sex, (%)	59 (49)	1118 (51)	0.71
Race			
Black or African American	40 (33)	734 (31)	0.66
Caucasian	65 (54)	1291 (55)	0.80
Native American or Alaskan Native	1 (1)	11 (0.5)	
Asian	1 (1)	50 (2)	0.33
Hawaiian or Pacific Islander	0 (0)	2 (0)	n/a
Other	6 (5)	145 (6)	n/a
Declined	7 (5)	100 (4)	n/a
Ethnicity (%)			
Hispanic	8 (7)	198 (8)	0.48
Non-Hispanic	107 (89)	2039 (87)	
Median Weight (kg)	90 (68–99)	82 (68–99)	**< 0.001**
Body mass index (kg/m^2)	29 (25–36)	28 (24–33)	**0.02**
Comorbidities (%)			
Obesity	42 (35)	616 (26)	**0.04**
Smoking	2 (2)	42 (2)	0.91
COPD	9 (8)	220 (9)	0.48
Cancer	12 (10)	649 (28)	**< 0.001**
HRT use	12 (10)	245 (10)	0.86
CHF	42 (35)	510 (22)	**< 0.001**
CTEPH risk factors			
Splenectomy	2 (2)	37 (2)	0.94
APLS	3 (3)	16 (1)	**0.03**
Hypothyroidism	19 (16)	342 (15)	0.72
MDS/MPN	12 (10)	101 (4)	**< 0.001**
Osteomyelitis	9 (8)	69 (3)	**0.01**
Pacemaker	4 (3)	45 (2)	0.28
Admission status[a]			
Inpatient	89 (74)	1102 (47)	**< 0.001**
Insurance type			
Medicare	37 (31)	989 (42)	**0.01**
Medicaid	13 (11)	287 (12)	0.63
Private	69 (40)	1001 (43)	**< 0.001**
Other	1 (0)	5 (0)	
Distance from center (mi)	6.7 (4–23)	9.1 (3–14)	**0.03**
Median household income[b] (range)	78,859 (48,297–100,313)	74,403 (49,688–100,425)	0.54
PCP on file	105 (88)	1770 (76)	**< 0.001**

Significant p values are given in bold

All values are reported as no. (%) or median (IQR). n/a—frequency insufficient for analysis

PE pulmonary embolism, *CTEPH* chronic thromboembolic pulmonary hypertension, *COPD* Chronic obstructive pulmonary disease, *HRT* hormone replacement therapy, *CHF* congestive heart failure, *APLS* antiphospholipid syndrome, *MDS* myelodysplastic syndrome, *MPN* myeloproliferative neoplasm, *PCP* primary care provider

[a]Admission status at time of Acute PE diagnosis

[b]Median Income derived from patient's zip code and 2019 national census data

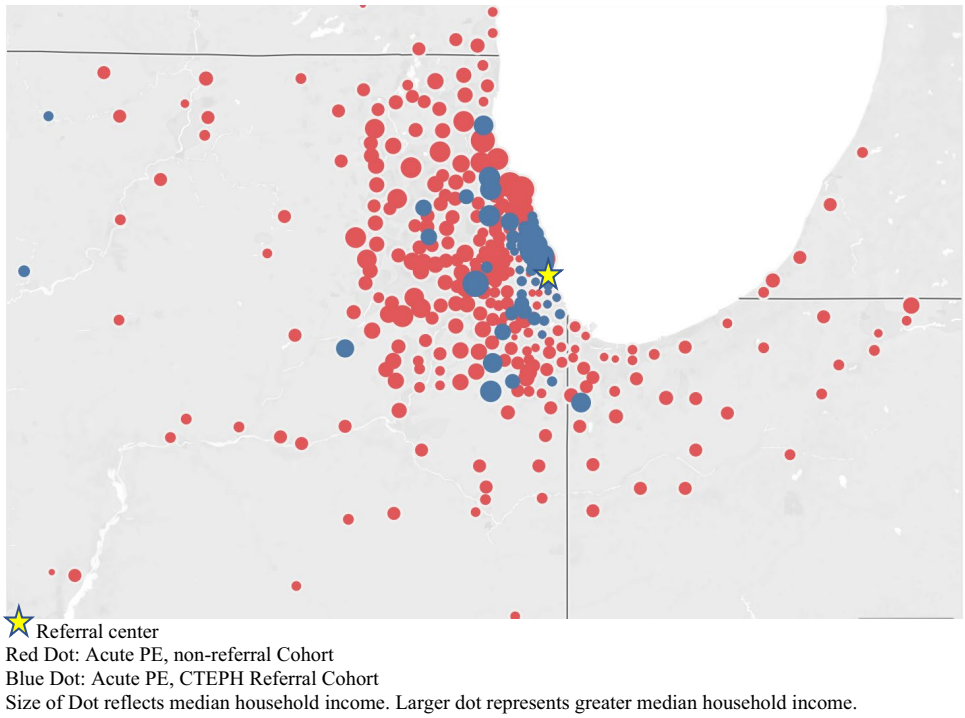

Fig. 2 Geographic/income distribution of acute pe referral and non-referral cohorts

from the referral center (9.1 miles vs. 6.7 miles, $p=0.03$), and were less likely to have a primary care provider (76% vs. 88%, $p<0.001$) (Table 1, Fig. 2).

Of 175 subjects identified as "at risk" for CTEPH, 12% (21/175) were referred for CTEPH evaluation. In this "at risk" cohort, distance from referral center was significantly different between those referred and those not referred (5.7 miles vs. 8.8 miles, $p=0.04$). Although not meeting statistical significance, not referred patients in the "at risk" cohort, compared to those referred, were older (59 vs. 52 years), had a lower BMI (27 vs. 32 kg/m^2), higher comorbid cancer diagnosis (38 vs. 10%), and were less likely to be admitted at time of Acute PE diagnosis (55 vs. 81%)) (Table 2).

Discussion

Between 2018 and 2021, 4.9% (120/2454) of patients diagnosed with acute PE were referred for further CTEPH evaluation, which included only 12% (21/175) of patients considered "at risk" for CTEPH. Our comprehensive CTEPH center represents the locoregional center for CTEPH referral and care and for reference completed 59 pulmonary thromboendarterectomy surgeries and 120 BPA interventions in 37 patients during this study period. Similar to the data obtained from the United Kingdom, distance to the locoregional comprehensive CTEPH center remains a consistent factor contributing to differences in patient referral [15]. Additionally, older age, comorbid conditions such as cancer, the absence of a primary care physician as part of the care team, as well as outpatient management of acute PE episodes are associated with lower likelihood of referral differences.

Although CTEPH occurs in up to 6.2% of patients following acute PE, it remains an underrecognized long-term complication of PE in clinical practice [17]. Persistent dyspnea and/or functional limitations after an episode of acute PE are common, occurring in up to 50% of patients, and may be related to deconditioning, post-PE syndrome, chronic thromboembolic disease (CTED), or CTEPH [18, 19]. For this reason, referral to a dedicated CTEPH center is recommended to help navigate multiple complex diagnostic considerations needed in this patient population to distinguish the underlying pathologic process and guide advanced interventions that improve morbidity and mortality after PE.

Distance from the local referral center appears to represent a barrier to 'best' care in both the overall cohort and in those considered at "increased risk" following PE. This finding suggest patients may have difficulties reaching referral centers or there is an inadequate awareness of specialty center services amongst providers practicing further from the center. However, as the difference in median distance

Table 2 Demographic and clinical characteristics of referred and non-referred at risk patients between 2018 and 2021

	Referred at risk cohort (n = 21)	Non-referred at risk cohort (n = 154)	
Age, years (IQR)	52 (44–66)	59 (44–69)	0.32
Female sex, (%)	15 (71)	86 (55)	0.05
Race			
Black or African American	9 (43)	50 (32)	0.40
Caucasian	12 (57)	93 (60)	0.80
Native American or Alaskan Native	0 (0)	1 (0)	n/a
Asian	0 (0)	4 (3)	n/a
Hawaiian or Pacific Islander	0 (0)	0 (0)	n/a
Other	0 (0)	145 (6)	n/a
Declined	0 (0)	1 (0)	n/a
Ethnicity			
Hispanic	1 (5)	9 (6)	0.71
Non-Hispanic	20 (96)	145 (94)	
Weight (kg)	86 (76–114)	82 (69–98)	0.31
Body mass index (kg/m^2)	32 (25–39)	27 (24–33)	0.15
Comorbidities			
Obesity	10 (48)	51 (33)	0.27
Smoking	0 (0)	4 (3)	0.55
COPD	1 (5)	28 (18)	0.65
Cancer	2 (10)	59 (38)	0.95
HRT use	3 (15)	21 (14)	0.56
CHF	6 (29)	40 (26)	0.56
CTEPH risk factors			
Splenectomy	0 (0)	5 (3)	0.55
APLS	1 (5)	3 (2)	0.53
Hypothyroidism	5 (24)	30 (19)	0.37
MDS/MPN	0 (0)	11 (7)	0.13
Osteomyelitis	0 (0)	7 (5)	0.19
Pacemaker	0 (0)	3 (2)	0.40
Admission status[a]			
Inpatient	17 (81)	85 (55)	0.50
Insurance type			
Medicare	6 (29)	63 (42)	0.84
Medicaid	1 (5)	18 (12)	0.39
Private	14 (66)	73 (49)	0.43
Other			
Distance from center (mi)	5.7 (1.9–11.7)	8.8 (3–22)	**0.04**
Median household income[b] (range)	75,657 (57,221–106,906)	78,704 (54,554–101,161)	0.70
PCP on file	20 (95)	145 (96)	0.48

Significant p value is given in bold

All values are reported as no. (%) or median (IQR). n/a—frequency insufficient for analysis

PE pulmonary embolism, *CTEPH* chronic thromboembolic pulmonary hypertension, *COPD* Chronic obstructive pulmonary disease, *HRT* hormone replacement therapy, *CHF* congestive heart failure, *APLS* antiphospholipid syndrome, *MDS* myelodysplastic syndrome, *MPN* myeloproliferative neoplasm, *PCP* primary care provider

[a]Admission status at time of Acute PE diagnosis

[b]Median Income derived from patient's zip code and 2019 national census data

between referred and non-referred is around three miles, it is also important to explore additional confounders of care. We found that subjects who were treated as inpatients for their acute PE and those with a primary care physician on file were more likely to be referred. This may suggest that direct inpatient attention and/or outpatient follow-up in the healthcare system improves access to specialized care. Furthermore, comorbid conditions that increase the likelihood of requiring access to healthcare such as congestive heart failure or conditions that are associated with increased risk for CTEPH (antiphospholipid syndrome, myelodysplastic syndrome, infections/inflammatory conditions) were associated with an increased rate of referral.

The presence of cancer was associated with lower likelihood of referral. Although the comparison of cancer comorbidity in the at-risk referral and at-risk non-referred cohort did not reach statistical significance, there was a much higher rate of cancer in the non-referred (38%) than the referred (10%) cohort ($p = 0.95$). Given the important intersection between cancer and venous thromboembolic disease, this finding raises several important questions that warrant further exploration. Although we are limited by access to information on the types and severity of cancer which would impact the decision to refer for specialized care, it is important to note that the presence of cancer does not preclude medical or even surgical intervention for chronic thromboembolic disease. Interventions for CTEPH could significantly reduce the morbidity and mortality of patients with cancer.

Strengths of our study include the use of the unbiased NLP algorithm which allows for robust and more encompassing identification of an acute PE population in the electronic medical record and obviated issues that arise when relying on clinical coding documentation for building the patient cohort. However, identification of our "at risk" cohort was reliant on clinical documentation for identification of dyspnea or chronic disease which likely misses patients with ongoing symptoms that can be attributed to persistent clot. Future iterations of this model will need to build on both known risk factors and direct review of clinical and diagnostic data attributed to chronic thromboembolic disease to better identify the "at risk" patient population. Another limitation of our study is the inability to determine if CTEPH referrals or CTEPH care were ultimately provided outside of our institution. Although possible, the risk of this is minimized in this case as we are the largest provider of comprehensive CTEPH care in the geographic region. Importantly, the study period also included the COVID-19 pandemic, and while the impact of this is unmeasurable, it is important to note that our program's clinical volume for CTEPH care increased during the pandemic. Finally, while the nature of this research highlights associations between distinct groups that are ultimately hypothesis generating, firm conclusions about causation cannot be reliably drawn from this data.

Conclusion

We found a low rate of referral to CTEPH center for patients "at risk" or CTEPH. Equity in referral practices of PE patients who may be at risk for the development of CTEPH is an important step in the effort to provide fair, comprehensive care to both acute and chronic thromboembolic disease patients. The differences highlighted in this paper including age, chronic co-morbid conditions, distance from comprehensive CTEPH center, and presence of a primary care provider, suggest that targeted clinician and patient education related to long term PE complications and available therapies should be available to help minimize referral differences. With the creation of a comprehensive CTEPH center offering lifesaving interventions for this disease, it is incumbent on CTEPH clinicians to provide educational outreach to both patients and physicians and address any and all barriers to access to ensure equitable care.

Appendix 1: Natural language processing logic for computed tomography results

Logic for CT Results:

Positive Cases:

Target phrases:

'%there%pulm% emb%'
or '%filling defect%'
or '%pulm% emb%'
or '%Acute%clot%'
or '%segmental%clot%'
or '%lobar%clot%'
or '%occlusive%clot%'
or '%Acute%thromb%'
or '%segmental%thromb%'
or '%lobar%thromb%'
or '%occlusive%thromb%'
or ('%arter%' and one of the following

'%Acute%filling defect%'
'%segmental%filling defect%'
'%lobar%filling defect%'
'%occlusive%filling defect%'

Skip phrases:

'% no %'
'%no %'
'%negative%'
'%no filling%'
'%without filling%'
'%sequela%'

Absolute positive assertions:

These usually contain the words “exam”, “examination”, “evaluation”, etc. after the word "positive"

'%POSITIVE %FOR PULMONARY EMBOLISM'
'%Positive %for pulmonary thromboembolism'

Negative cases:

Target phrases:

'%negative%'
or '%sequela%'
or '%no filling%'
or '%without filling%'
or '% no %' but doesn't contain '% no other%'
or 'no %' but doesn't contain 'no other%'

Skip phrases:

'%evaluate%'
or '%evaluation%'
or '%history%'
or '%indication%'
or '%technique%'
or '%comparison%'
or '%assessment%'
or '%nondiagnostic%'
or '%uninterpretable%'
or '%artifact%'
or '%artifactual%'
or '%repeat%'
or '%resolved%'

Absolute negative assertions**:**

'%No evidence of acute pulmonary embolism%'
'%No acute pulmonary embolism%'
'%No acute pulmonary embolus%'
'%No pulmonary emboli%'
'%No pulmonary embolism%'
'%No evidence of pulmonary embolism%'
'%Negative evaluation for acute pulmonary thromboembolism%'

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by RM and MJC. The first draft of the manuscript was written by RM and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declarations

Conflict of interest The authors declare that there is no conflict of interest and the authors did not receive any funds, grants or support from any organization for the submitted work. The authors have no relevant financial or non-financial interests to disclose.

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