BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-067579
Article Type:	Original research
Date Submitted by the Author:	19-Aug-2022
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Keywords:	Thromboembolism < CARDIOLOGY, RESPIRATORY MEDICINE (see Thoracic Medicine), Thoracic medicine < INTERNAL MEDICINE

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Clinical Relevance of Pulmonary Infarction Following Acute Pulmonary Embolism

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Word count: 2312 words

Keywords: pulmonary embolism, pulmonary infarction, venous thromboembolism, shortness of breath, pleuritic chest pain

Abbreviations: BNP= B-type natriuretic peptide; CDT= catheter-directed thrombolysis; CKD= chronic kidney disease; CT= computed tomography; CTPA= computed tomography pulmonary angiography; PA= pulmonary artery; PE= Pulmonary embolism; RV= Right ventricular; sPESI= simplified pulmonary embolism severity index

Abstract

Objective: Pulmonary infarction is a common clinical and radiographic finding in acute pulmonary embolism (PE), yet the clinical relevance and prognostic significance of pulmonary infarction remain unclear. The study aims to investigate the clinical features, radiographic characteristics, impact of reperfusion therapy, and outcomes of patients with pulmonary infarction.

Design, **setting and participants**: A retrospective cohort study of 496 adult patients (≥ 18 years of age) diagnosed with PE who were evaluated by the pulmonary embolism response team (PERT) at a tertiary academic referral center in the US. We collected baseline characteristics, laboratory, radiographic, and outcome data. Statistical analysis was performed by Student t-test, Mann-Whitney U test, Fischer's exact or X^2 test where appropriate. Multivariate logistic regression was used to evaluate potential risk factors for pulmonary infarction.

Results: We identified 143 (29%) cases of pulmonary infarction in 496 patients with PE. Patients with infarction were significantly younger (52 ± 15.9 vs. 61 ± 16.6 years, $p<0.001$) and with fewer comorbidities. Most infarction occurred in the lower lobes (60%) and involved a single lobe (64%). The presence of right ventricular (RV) strain on computed tomography (CT) imaging was significantly higher in patients with infarction (21% vs 14%, $p=0.031$). There was no significant difference in advanced reperfusion therapy, in-hospital mortality, length of stay, and readmission between groups. In multivariate analysis, age, and evidence of RV strain on CT and hemoptysis increased the risk of infarction.

Conclusions: Radiographic evidence of pulmonary infarction was demonstrated in nearly one-third of patients with acute PE. There was no difference in the rate of reperfusion therapies and the presence of infarction did not correlate with poorer outcomes.

Strengths and limitations of this study:

- Acute pulmonary embolism (PE) is a leading cause of cardiovascular death globally, this study assessed the clinical characteristics and prognostic significance of pulmonary infarction, which is a common complication following PE.
- Our study highlighted the potential role of pulmonary infarction in the risk stratification of acute PE, since the presence of infarction was not associated with poorer outcomes, it should not be considered a supporting factor nor a contraindication for advanced reperfusion therapy for PE.
- Limitations: Cases of pulmonary infarction were identified based on CT findings and there was no histological correlation to differentiate between true necrosis (infarction) versus alveolar hemorrhage. Due to the retrospective nature of this study, not all patients underwent CT imaging post-discharge and thus we were unable to comment on the precise timing of resolution of infarction and its long-term significance.

Introduction

Acute pulmonary embolism (PE) is the third leading cause of cardiovascular death following myocardial infarction and stroke, with approximately 100,000 annual deaths in the United States (1, 2). Pulmonary infarction is a common complication of acute PE with a reported radiographic prevalence of up to 36% (3). The dual blood supply of lungs has been thought to be protective against ischemic insults, with the bronchial circulation and other collateral vessels undergoing hypertrophy or remodeling to maintain blood flow to ischemic lung tissues through anastomoses at the level of alveoli and respiratory bronchioles (4, 5). Nevertheless, obstruction of the pulmonary artery by acute PE can cause infarction. In the past, the presence of infarction has been regarded as a sign of poor outcomes due to its association with compromised cardiac function, which leads to increased pulmonary venous pressure and impairment of forwarding flow through the bronchial circulation (6, 7). Contrarily, recent studies have suggested that younger, healthier patients are at the highest risk for infarction, because of their less robust collateral blood supply (8, 9). The clinical relevance and prognostic significance of pulmonary infarction remain unclear. The aim of this study is to investigate the clinical features, radiographic characteristics, impact of reperfusion therapy, and outcomes of patients with pulmonary infarction.

Methods

Study population

We conducted a single-center retrospective review of all patients between January 2017 and June 2020 at Temple University Hospital who underwent evaluation by the pulmonary embolism response team (PERT) and included all cases of acute PE diagnosed by computed tomography pulmonary angiography (CTPA). Cases of acute PE diagnosed by other imaging modalities were

excluded from the study. Cases of pulmonary infarction were identified by review of the final CT reports by board-certified thoracic radiologists. Our study met approval by the Institutional Review Board (Protocol #26021) and informed consent was waived due to the retrospective nature of the study. Figure 1 demonstrates patient selection.

Data Collection

Clinical data

Patient demographic, clinical features, laboratory data, echocardiographic data, radiographic characteristics, and patient outcomes were extracted from electronic medical records. Demographics included age, gender, race, and body mass index (BMI). Clinical features included symptoms at presentation, comorbid conditions, calculated simplified pulmonary embolism severity index (sPESI), and PE severity per the European Society of Cardiology (ESC) guideline at the time of diagnosis (i.e., low, intermediate-low, intermediate-high, and high risk).(10) Laboratory data included B-type natriuretic peptide (BNP; positive if ≥100pg/ml) and troponin I (positive if ≥ 0.1ng/ml). Data regarding treatment modalities, length of stay, in-hospital mortality, readmission within 30 days, new oxygen on discharge, complications including major and minor bleeding using the International Society on Thrombosis and Haemostasis (ISTH) criteria(11), need for transfusion, access site hematoma, and pulmonary follow-up were recorded.

Radiographic data

All CTPAs performed at the time of acute PE diagnosis were retrieved. A central PE was defined as the presence of thrombus in the main trunk of pulmonary artery (PA) or the left or the right main PA. A peripheral PE was defined as thrombus in the lobar, segmental, or subsegmental PA. Signs of right ventricular (RV) strain were defined as the presence of one, or a combination of

the following signs: 1) right-to-left ventricular ratio >0.9; 2) pulmonary artery enlargement; 3) abnormal interventricular septum (flattening of septum or leftward septal bowing); and 4) inferior vena caval contrast reflux. Parameters including PE distribution (central vs distal), infarct location and burden, signs of RV strain, and other parenchymal abnormalities were collected. All available follow-up CT chest imaging up to 1-year post-discharge were reviewed by board-certified thoracic radiologists to determine the resolution of infarctions or residual abnormalities on available scans. All echocardiograms were reviewed, and data regarding left ventricular ejection fraction (LVEF), RV dilation, and RV dysfunction were collected.

Statistical analysis

All continuous variables were tested for normality and presented as mean with a standard deviation (SD), or median with an interquartile range (IQR) if distribution was skewed. Categorical variables were presented as absolute number (percentage). Comparisons between patients with and without infarction were performed using Student t-test or Mann-Whitney U for continuous variables, or Fischer's exact or X^2 test for categorical variables, as appropriate. Univariable and multivariable logistic regression models were used to evaluate risk factors associated with pulmonary infarction. The software SPSS Statistics for Mac, version 26.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. P-values of <0.05 (two-sided) were considered statistically significant.

Results

Patient characteristics

Twenty-nine percent (143 of 496) of patients had evidence of pulmonary infarction on CTPA. Patients with pulmonary infarction were younger (52 ± 15.9 vs. 61 ± 16.6 years, $p<0.001$) and with a significantly lower prevalence of comorbidities including cardiac disease (30% vs 42%,

p=0.014), chronic kidney disease (CKD) (5% vs 42%, p=0.018), diabetes mellitus (17% vs 26%, p=0.032), hypothyroidism (4% vs 9%, p=0.039) and malignancy (16% vs 25%, p= 0.032). Although results did not reach statistical significance, chronic obstructive pulmonary disease (COPD) was less prevalent in the infarction group. Patients with infarction were more likely to present with pleuritic chest pain (32% vs 20%, p=0.004) and hemoptysis (8% vs 3%, p= 0.04), while patients without infarction were more likely to present with syncope (6% vs 11%, p=0.05). The baseline characteristics and symptoms of presentation of the study population are reported in Table 1.

Table 1. Baseline characteristics and symptoms of presentation.

	All (496)	Without infarction (353)	With infarction (143)	P-value
Gender (female)	238 (48%)	168 (48%)	70 (49%)	0.784
Age, mean (±SD)	58 ±16.9	61 ± 16.6	52 ± 15.9	<0.001
Race, n (%)				0.017
Black	249 (50%)	168 (48%)	81 (57%)	
White	98 (20%)	81 (23%)	17 (12%)	
Other	149 (30%)	104 (30%)	45 (32%)	
BMI, mean (±SD)	31.8 ± 9.3	31.8 ± 9.5	32.0 ± 8.7	0.421
Symptoms at presentation, n (%)				
Dyspnea	297 (60%)	207 (59%)	90 (63%)	0.376
Hypoxia	237 (49%)	173 (50%)	64 (46%)	0.371
Pleuritic chest pain	114 (23%)	69 (20%)	45 (32%)	0.004
DVT symptoms	50 (10%)	40 (11%)	10 (7%)	0.146
Syncope	48 (10%)	40 (11%)	8 (6%)	0.05
Hemoptysis	21 (4%)	9 (3%)	12 (8%)	0.04
Altered mental status	38 (8%)	28 (8%)	10 (7%)	0.722
Cardiac arrest	22 (4%)	15 (4%)	7 (5%)	0.752
Comorbidities, n (%)				
Cardiac diseases	191 (39%)	148 (42%)	43 (30%)	0.014
COPD/asthma	71 (14%)	54 (15%)	17 (12%)	0.326
CKD	49 (10%)	42 (12%)	7 (5%)	0.018
Diabetes mellitus	115 (23%)	91 (26%)	24 (17%)	0.032
Hypothyroidism	36 (7%)	31 (9%)	5 (4%)	0.039
Malignancy	111 (22%)	88 (25%)	23 (16%)	0.032
Recent surgery	68 (14%)	52 (15%)	16 (11%)	0.299
Current anticoagulation	59 (12%)	41 (12%)	18 (13%)	0.762

COPD= chronic obstructive pulmonary disease; CKD= chronic kidney disease; BMI= body mass index; DVT= deep vein thrombosis; SD= standard deviation.

Risk stratification of PE

Troponin elevation (>0.1ng/ml) was less frequently observed in patients with infarction (39% vs 49%, p= 0.031). The presence of RV strain on CT was significantly higher in patients with infarction (58% vs 45%, p=0.009), although no differences in signs of RV dilation or dysfunction on echocardiogram between infarction and non-infarction group were noted. There was no significant difference in sPESI score, BNP elevation, PE severity, or evidence of RV dysfunction on electrocardiography and echocardiogram between groups. Table 2 describes factors associated with PE severity.

Table 2. PE severity indices.

	All (496)	Without infarction (353)	With infarction (143)	P-value
sPESI score, mean	1.43	1.46	1.36	0.339
Elevated BNP	242 (54%)	169 (53%)	73 (55%)	0.629
Elevated troponin	228 (46%)	173 (49%)	55 (39%)	0.031
Evidence of RV strain on EKG	77 (16%)	48 (14%)	29 (21%)	0.137
PE severity				
Low risk	132 (27%)	93 (26%)	39 (27%)	0.994
Intermediate low risk	173 (35%)	124 (35%)	49 (34%)	
Intermediate high risk	144 (29%)	103 (29%)	41 (29%)	
High risk	47 (10%)	33 (9%)	14 (10%)	
Elevated BNP	242 (54%)	169 (53%)	73 (55%)	0.629
Elevated troponin	228 (46%)	173 (49%)	55 (39%)	0.031
EKG evidence of RV strain	77 (16%)	48 (14%)	29 (21%)	0.137
CT evidence of RV strain	242 (49%)	159 (45%)	83 (58%)	0.009
Echocardiogram				
RV dilation	251 (54%)	173 (52%)	78 (57%)	0.302
RV dysfunction	235 (50%)	162 (49%)	73 (54%)	0.338
LVEF	38 (8%)	23 (7%)	15 (11%)	0.306
LE DVT	227 (50%)	161 (51%)	66 (50%)	0.928
UE DVT	39 (22%)	27 (22%)	12 (21%)	0.916

BNP= B-type natriuretic peptide; CT= computed tomography; DVT= deep vein thrombosis; EKG= electrocardiography; LE= lower extremity; LVEF= left ventricular ejection function; sPESI= simplified pulmonary embolism severity index; RV= right ventricular; LVEF= left ventricular ejection fraction; PE= pulmonary embolism; UE= upper extremity

Radiographic characteristics

There was no difference in PE distribution and clot burden between groups and 50% of patients with infarction had thrombus located at the main PAs including those who had saddle PE. Most infarction occurred in lower lobe (60%) and involved single lobe (64%). Patients with infarction were more likely to have parenchymal abnormalities including consolidation (21% vs 12%, p= 0.007), pulmonary edema (13% vs 7%, p= 0.036), pleural effusion (33% vs 24%, p=0.038) and ground glass opacity (20% vs 13%, p= 0.042). Table 3a demonstrates the radiographic characteristics of patients with acute PE. Table 3b demonstrates the radiographic characteristics of pulmonary infarction. Fifty-eight (41%) patients had follow-up CT-chest imaging for variety of reasons performed up to 1-year post-discharge, resolution of pulmonary infarction was observed in 53% (17 out of 32), 85% (12 out of 14), and 92% (11 out of 12) of patients who had imaging at 3-month, 6-month and 1-year interval.

Table 3a. Radiographic characteristics of patients with acute pulmonary embolism.

	All (496)	Without infarction (353)	With infarction (143)	P-value
RV strain on CT	242 (49%)	159 (45%)	83 (58%)	0.009
RV to LV ratio ≥1	155 (31%)	106 (30%)	49 (34%)	0.640
Dilated PA	99 (20%)	59 (17%)	40 (28%)	0.011
Septal position Rightward bowing Flattened Leftward bowing	 131 (27%) 112 (23%) 50 (10%)	 102 (29%) 66 (19%) 32 (9%)	 29 (20%) 46 (32%) 18 (13%)	0.030
PE distribution Central PE Distal PE	 216 (44%) 280 (57%)	 144 (41%) 209 (59%)	 72 (50%) 71 (50%)	0.052
Clot burden Main, saddle or proximal Interlobar to lobar Segmental Subsegmental	 215 (43%) 124 (25%) 150 (30%) 7 (1%)	 143 (41%) 94 (27%) 110 (31%) 6 (2%)	 72 (50%) 30 (21%) 40 (28%) 1 (1%)	0.200

Parenchymal abnormalities				
Pulmonary edema	42 (9%)	24 (7%)	18 (13%)	0.036
Consolidation	71 (14%)	41 (12%)	30 (21%)	0.007
Emphysema	65 (13%)	48 (14%)	16 (11%)	0.469
Fibrosis	42 (9%)	30 (9%)	12 (8%)	0.969
Pleural effusion	128 (26%)	84 (24%)	47 (33%)	0.038
Atelectasis	161 (33%)	113 (32%)	48 (34%)	0.738
Ground glass opacity	72 (15%)	44 (13%)	28 (20%)	0.042

CT= computed tomography; LV= left ventricular; RV= right ventricular; PA= pulmonary artery; PE= pulmonary embolism

Table 3b. Radiographic characteristics of pulmonary infarction.

	Infarcts, number (%)
Infarct location	
Upper lobe	31 (22%)
Middle lobe	8 (6%)
Lower lobe	86 (60%)
Multiple	18 (12%)
Infarct burden	
Single lobe	91 (64%)
Multiple lobes	52 (36%)

Treatment and outcomes

There was no significant difference in the number of patients receiving advanced reperfusion therapy between groups. Most patients with pulmonary infarction received anticoagulation alone (69%), followed by catheter-directed thrombolysis (12%), and systemic thrombolysis (11%). There were more patients with infarction who received antimicrobial therapy compared to those without infarction (15% vs 5%, $p<0.001$). Among the 47 patients who had concomitant infarction and pleural effusion, six patients (13%) underwent diagnostic and/or therapeutic thoracocentesis and five had an exudative pleural effusion. Patients with infarction were less likely to require oxygen on discharge (11% vs 19%, $p= 0.031$), and those who required oxygen on discharge were more likely to have multiple lobe infarctions than single lobe infarction (19% vs 7%, $p= 0.032$). There was no significant difference between patients with infarction and without infarction regarding length of stay (10.7±14.7 vs 9.5±12.3, $p=0.698$), in-hospital death

(7% vs 8%, p= 0.801), disposition (home: 78% vs 75%, p=0.759), bleeding complications (24% vs 12%, p=0.089) and readmission within 30 days (18% vs 16%, p=0.584) (Supplemental material online, table 1).

Patients with infarction who underwent CDT had a longer length of stay (15± 24.4 vs 7±8.4, p=0.044) and a higher rate of readmission within 30 days (18% vs 2%, p= 0.047), compared to those without infarction. Readmission diagnoses of patients with infarction who underwent CDT were as follows: one patient developed vaginal bleeding from anticoagulant use, one patient developed acute hypoxic respiratory failure due to multifocal pneumonia, and one patient was admitted for chest pain. There was no significant difference in in-hospital mortality (6% vs 6%, p= 0.973) and complications including minor and major bleeding (24% vs 21%, p=0.676), access site hematoma (13% vs 2%, p= 0.134) and need for transfusion (18% vs 13%, p=0.649) between those with and without infarction (Supplemental material online, table 2).

In univariable regression analyses, we identified several factors independently associated with pulmonary infarction. These included age, history of cardiac diseases, malignancy, hypothyroidism, diabetes mellitus, CKD, elevated troponin, pleuritic chest pain, hemoptysis, and RV strain on CT. A multivariable regression analysis was subsequently performed, and four factors remained significant: Both hemoptysis (OR, 3.034; 95% CI, 1.162-7.924) and presence of RV strain on CT (OR, 2.142; 95% CI 1.365-3.360) significantly increased the risk of infarction, while age (OR, 0.973, 95% CI, 0.959-0.987) and presence of elevated troponin (OR, 0.629; 95% CI 0.398-0.993) decreased risk (Table 4).

Table 4. Univariate and multivariate analysis of potential risk factors.

Variables			Univariate analysis			Multivariate analysis		
	Without infarction (353)	With infarction (143)	Odds ratio	P-value	95% CI	Odds ratio	P-value	95% CI
Age, years	61 ± 16.6	52 ± 15.9	0.968	<0.001	0.956-0.980	0.973	<0.001	0.959-0.987
Cardiac diseases	148 (42%)	43 (30%)	0.596	0.014	0.393-0.902			
CKD	42 (12%)	7 (5%)	0.381	0.022	0.167-0.870			

DM	91 (26%)	24 (17%)	0.581	0.033	0.352-0.957			
Malignancy	88 (25%)	23 (16%)	0.577	0.034	0.348-0.958			
Hypothyroidism	31 (9%)	5 (4%)	0.375	0.047	0.143-0.985			
Elevated troponin	173 (49%)	55 (39%)	0.647	0.032	0.435-0.962	0.629	0.047	0.398-0.993
Pleuritic CP	69 (20%)	45 (32%)	1.890	0.005	1.217-2.935			
Hemoptysis	9 (3%)	12 (8%)	3.491	0.006	1.437-8.479	3.034	0.023	1.162-7.924
RV strain on CT	159 (45%)	83 (58%)	1.688	0.009	1.140-2.500	2.142	<0.001	1.365-3.360

CP= chest pain; CKD= chronic kidney disease; CT= computed tomography DM= diabetes mellites; RV= right ventricular

Discussion

In this study, the estimated prevalence of pulmonary infarction was 29%. Patients with infarction were more likely to present with pleuritic chest pain and hemoptysis. Additionally, those with pulmonary infarction were younger and had a lower prevalence of comorbidities. While the presence of RV strain on CT imaging was more common in patients with pulmonary infarction, the rate of reperfusion therapies, complications, and outcomes was similar in both groups. The presence of hemoptysis and RV strain on CT significantly increased the risk of infarction, whereas age and elevated troponin decreased the risk. Pulmonary infarction resolved in the majority of patients for whom follow-up imaging was available, which is in concordance with newer studies (8, 9, 12).

The prevalence of pulmonary infarction in our cohort is in keeping with previously reported rates ranging from 9% to 36% (3, 12). Regarding clinical presentation, the higher presence of pleuritic chest pain and hemoptysis in patients with infarction likely represents a result of alveolar hemorrhage, leading to pleural inflammation, irritation, and necrosis. In addition, the presence of pleural effusion was more prevalent in patients with infarction due to pleural inflammation following infarction, however, most of these effusions were not intervened upon and had resolved on follow-up imaging. Interestingly, patients with pulmonary infarction were more likely to be treated with antimicrobial therapy than those without. One possible explanation is that other lung processes, such as pneumonia, pulmonary edema, or atelectasis can produce

consolidative changes similar to infarction on CT imaging (13), and as a result, pneumonia cannot be excluded especially when combined with a clinically compatible presentation.

In our study, patients with infarction were significantly younger and with fewer comorbid conditions, specifically a lower prevalence of cardiac disease and malignancy that have traditionally been regarded as major risk factors for infarction. This discrepancy may be due to a lack of efficient collateral circulation to lung tissues, which presumably develops in the setting of longstanding local tissue hypoxia (8, 14), and is unlikely to happen in otherwise healthy, young individuals in absence of cardiopulmonary diseases.

Our cohort also found that patients with infarction did have higher rates of RV strain, dilated PA, and flattened or leftward bowing of interventricular septum, although signs of RV strain were not reproducible on echocardiography. A potential explanation for this finding is that patients with infarction were younger with less comorbid diseases, thus without pre-existing RV hypertrophy allowing for tolerance of acute RV afterload elevation. Regarding the discrepancy between CT and echocardiographic findings, unlike CTPA which is often the first diagnostic and confirmatory modality for PE, most echocardiography is performed after the initial diagnosis and potentially after reperfusion therapy. Thus, it is possible that the initial signs of RV strain shown on CTPA could have improved or resolved through several potential mechanisms; administration of supplemental oxygen leading to a reversal of hypoxic vasoconstriction, clot burden reduction using reperfusion therapy, or intrinsic thrombolytic activity with anticoagulation support alone.

Importantly, we demonstrated no differences in complication rates and in-hospital mortality in patients who underwent CDT with pulmonary infarction compared to those without, although patients with infarction had a longer length of stay and a higher rate of 30-day readmission for non-PE or CDT-related diagnoses. There remains a theoretical risk of increased bleeding

complications in the area of pulmonary infarction during catheter manipulation and local installation of thrombolytics, however, this was not demonstrated in our cohort.

To the best of our knowledge, this study represented the largest cohort of patients with acute PE complicated by pulmonary infarction, however, there are several limitations in our study. Cases of pulmonary infarction were identified based on CT findings and there was no histological correlation to differentiate between true necrosis versus alveolar hemorrhage. Owing to the retrospective nature of this study, not all patients underwent CT imaging post-discharge, thus we were unable to comment on the precise timing of resolution of pulmonary infarction. We acknowledge the fact that not all patients in our cohort performed echocardiography, in particular patients with low-risk PE when echocardiography was not deemed necessary to change management or patients with high-risk PE who expired prior to completion of echocardiography.

In conclusion, pulmonary infarction was demonstrated on CT in nearly one-third of acute PE, and patients with infarction were younger, with fewer comorbidities, and more likely to present with pleuritic chest pain and hemoptysis. Overall, there was no difference in length of stay, in-hospital death, bleeding complication, and readmission rate between patients with and without infarction, and patients with infarction were less likely to require oxygen on discharge. The presence of pulmonary infarction did not correlate with poorer outcomes and should not be considered a supporting factor nor a contraindication for advanced reperfusion therapy for PE.

Author contributions: KUL is the primary author, collected and analyzed the data, and is the guarantor of the article, taking responsibility for the integrity of the work as a whole from inception to published article. OO and PR are responsible for the study concept and helped write the manuscript. RB, GC, VL, and JP reviewed the imaging studies and treated the patients who underwent catheter-directed thrombolysis. SB and BRL helped write the manuscript.

Conflict of interest: There are no financial or other conflicts of interest to disclose.

Ethics approval: This study was approved by the Institutional Review Board (Protocol #26021) at Temple University Hospital and informed consent was waived due to the retrospective nature of the study.

Patient consent for publication: Not required.

Funding statement: This study received no funding.

Data sharing statement: Data used to produce this manuscript are available on request from the corresponding author.

Patient and public involvement: Patients or the public were not involved in the design, recruitment, conduct, reporting, or dissemination of our research.

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Figure 1. Patient selection flow diagram.

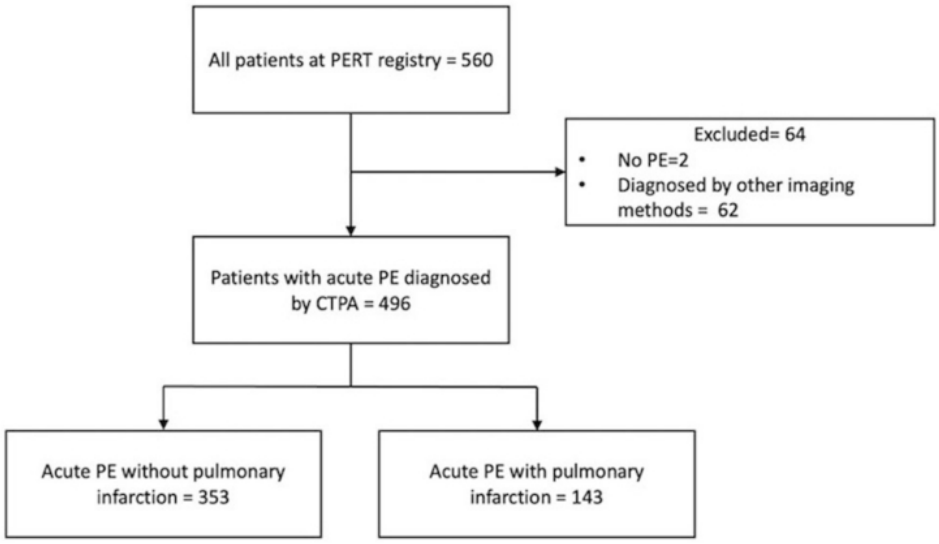

Figure 1. Patient selection flow diagram.

32x19mm (600 x 600 DPI)

Supplemental material, table 1. Treatment and outcomes between patients with and without infarction.

	All (496)	Without infarction (353)	With infarction (143)	P-value
Anticoagulation alone	357 (72%)	259 (73%)	98 (69%)	0.545
CDT	70 (14%)	53 (15%)	17 (12%)	0.365
Thrombolysis				0.212
Half dose	25 (5%)	15 (4%)	10 (7%)	
Full dose	14 (3%)	8 (2%)	6 (4%)	
Mechanical thrombectomy	19 (4%)	10 (3%)	9 (6%)	0.069
Surgical thrombectomy	9 (2%)	6 (2%)	3 (2%)	0.763
ECMO	11 (2%)	6 (2%)	5 (4%)	0.218
Mechanical ventilation	48 (10%)	30 (9%)	18 (13%)	0.163
Antimicrobials	39 (8%)	19 (5%)	22 (15%)	<0.001
In-hospital death	37 (8%)	27 (8%)	10 (7%)	0.801
Disposition				0.759
Home	349 (76%)	245 (75%)	104 (78%)	
ECF	100 (22%)	74 (23%)	26 (20%)	
Hospice	10 (2%)	7 (2%)	3 (2%)	
Length of stay, days	10±13.0	9.5±12.3	10.7±14.7	0.698
Bleeding complication				0.089
Minor bleeding	31 (6%)	25 (7%)	6 (4%)	
Major bleeding	32 (7%)	18 (5%)	14 (10%)	
Need for transfusion	63 (13%)	41 (12%)	22 (16%)	0.253
Readmission within 30 days	76 (16.6%)	52 (16%)	24 (18%)	0.584
New O2 on discharge	75 (16%)	61 (19%)	14 (11%)	0.031
Pulmonary follow-up	199 (42%)	144 (44%)	55 (40%)	0.610

CDT= catheter-directed thrombolysis; ECMO= extracorporeal membrane oxygenation; ECF= extended care facility

Supplemental material, table 2. Outcomes and complication rates in CDT.

	All (70)	Without infarction (53)	With infarction (17)	P-value
In-hospital death	4 (6%)	3 (6%)	1 (6%)	0.973
Disposition Home ECF	 57 (86%) 9 (14%)	 42 (84%) 8 (16%)	 15 (94%) 1 (7%)	0.436
Length of Stay	9±14.2	7±8.4	15±24.4	0.044
Readmission within 30 days	4 (6%)	1 (2%)	3 (18%)	0.047
New O2 on discharge	10 (16%)	8 (17%)	2 (12%)	0.609
Pulmonary follow-up	47 (72%)	38 (76%)	9 (56%)	0.166
Complications				
Bleeding Minor Major	 10 (14%) 5 (7%)	 8 (15%) 3 (6%)	 2 (12%) 2 (12%)	0.676
RBC transfusion	10 (14%)	7 (13%)	3 (18%)	0.649
Access site hematoma	3 (5%)	1 (2%)	2 (13%)	0.134

ECF= extended care facility; RBC= red blood cell

BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-067579.R1
Article Type:	Original research
Date Submitted by the Author:	15-Nov-2022
Complete List of Authors:	Lio, Ka U; Lewis Katz School of Medicine at Temple University, Department of Medicine O'Corragain, Oisin; Lewis Katz School of Medicine at Temple University, Department of Thoracic Medicine and Surgery Bashir, Riyaz ; Lewis Katz School of Medicine at Temple University, Cardiology Brosnahan, Shari; NYU Langone Health, Pulmonary, Critical Care and Sleep Medicine Cohen, Gary; Lewis Katz School of Medicine at Temple University, Radiology Lakhter, Vladimir; Lewis Katz School of Medicine at Temple University, Cardiology Panaro, Joseph; Lewis Katz School of Medicine at Temple University, Radiology Rivera-Lebron, B; University of Pittsburgh School of Medicine, Pulmonary and Critical Care Medicine Rali, Parth; Lewis Katz School of Medicine at Temple University, Thoracic Medicine and Surgery
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Cardiovascular medicine, General practice / Family practice, Intensive care, Radiology and imaging
Keywords:	Thromboembolism < CARDIOLOGY, RESPIRATORY MEDICINE (see Thoracic Medicine), Thoracic medicine < INTERNAL MEDICINE

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Clinical Outcomes and Factors Associated with Pulmonary Infarction Following Acute Pulmonary Embolism: A Retrospective Observational Study at a US Academic Center

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Word count: 2643 words

Keywords: pulmonary embolism, pulmonary infarction, venous thromboembolism, shortness of breath, pleuritic chest pain

Abbreviations: BNP= B-type natriuretic peptide; CDT= catheter-directed thrombolysis; CKD= chronic kidney disease; CT= computed tomography; CTPA= computed tomography pulmonary angiography; PA= pulmonary artery; PE= Pulmonary embolism; RV= Right ventricular; sPESI= simplified pulmonary embolism severity index

Abstract

Objective: Pulmonary infarction is a common clinical and radiographic finding in acute pulmonary embolism (PE), yet the clinical relevance and prognostic significance of pulmonary infarction remain unclear. The study aims to investigate the clinical features, radiographic characteristics, impact of reperfusion therapy, and outcomes of patients with pulmonary infarction.

Design, **setting and participants**: A retrospective cohort study of 496 adult patients (≥ 18 years of age) diagnosed with PE who were evaluated by the pulmonary embolism response team (PERT) at a tertiary academic referral center in the US. We collected baseline characteristics, laboratory, radiographic, and outcome data. Statistical analysis was performed by Student t-test, Mann-Whitney U test, Fischer's exact or X^2 test where appropriate. Multivariate logistic regression was used to evaluate potential risk factors for pulmonary infarction.

Results: We identified 143 (29%) cases of pulmonary infarction in 496 patients with PE. Patients with infarction were significantly younger (52 ± 15.9 vs. 61 ± 16.6 years, $p<0.001$) and with fewer comorbidities. Most infarctions occurred in the lower lobes (60%) and involved a single lobe (64%). The presence of right ventricular (RV) strain on computed tomography (CT) imaging was significantly more common in patients with infarction (21% vs 14%, $p=0.031$). There was no significant difference in advanced reperfusion therapy, in-hospital mortality, length of stay, and readmissions between groups. In multivariate analysis, age, and evidence of RV strain on CT and hemoptysis increased the risk of infarction.

Conclusions: Radiographic evidence of pulmonary infarction was demonstrated in nearly one-third of patients with acute PE. There was no difference in the rate of reperfusion therapies and the presence of infarction did not correlate with poorer outcomes.

Strengths and limitations of this study:

- This study represents the largest cohort describing the clinical characteristics and outcomes of patients with pulmonary infarction.
- This study highlights the potential role of pulmonary infarction in the risk stratification of acute PE.
- Cases of pulmonary infarction were identified based on CT findings and there was no histological correlation to differentiate between true necrosis (infarction) versus alveolar hemorrhage.
- Not all patients underwent CT imaging post-discharge and thus unable to comment on the precise timing of the resolution of infarction and its long-term significance.

Introduction

Acute pulmonary embolism (PE) is the third leading cause of cardiovascular death following myocardial infarction and stroke, with approximately 100,000 annual deaths in the United States (1, 2). Pulmonary infarction is a common complication of acute PE with a reported radiographic prevalence of up to 36% (3). The dual blood supply of lungs has been thought to be protective against ischemic insults, with the bronchial circulation and other collateral vessels undergoing hypertrophy or remodeling to maintain blood flow to ischemic lung tissues through anastomoses at the level of alveoli and respiratory bronchioles (4, 5). Nevertheless, obstruction of the pulmonary artery by acute PE can cause infarction. In the past, the presence of infarction has been regarded as a sign of poor outcomes due to its association with compromised cardiac function, which leads to increased pulmonary venous pressure and impairment of forwarding flow through the bronchial circulation (6, 7). Contrarily, recent studies have suggested that younger, healthier patients are at the highest risk for infarction, because of their less robust collateral blood supply (8, 9). The clinical relevance and prognostic significance of pulmonary infarction remain unclear. The aim of this study is to investigate the clinical features, radiographic characteristics, impact of reperfusion therapy, and outcomes of patients with pulmonary infarction.

Methods

Study population

We conducted a single-center retrospective review of all patients between January 2017 and June 2020 at Temple University Hospital who underwent evaluation by the pulmonary embolism response team (PERT) and included all cases of acute PE diagnosed by computed tomography pulmonary angiography (CTPA). Cases of acute PE diagnosed by other imaging modalities were

excluded from the study. Cases of pulmonary infarction were identified by review of the final CT reports by board-certified thoracic radiologists. Our study met approval by the Institutional Review Board (Protocol #26021) and informed consent was waived due to the retrospective nature of the study.

Patient and public involvement

Patients or the public were not involved in the design, recruitment, conduct, reporting, or dissemination of our research.

Data Collection

Clinical data

Patient demographic, clinical features, laboratory data, echocardiographic data, radiographic characteristics, and patient outcomes were extracted from electronic medical records. Demographics included age, gender, race, and body mass index (BMI). Clinical features included symptoms at presentation, comorbid conditions, calculated simplified pulmonary embolism severity index (sPESI), and PE severity per the European Society of Cardiology (ESC) guideline at the time of diagnosis (i.e., low, intermediate-low, intermediate-high, and high risk).(10) Laboratory data included B-type natriuretic peptide (BNP; positive if ≥100pg/ml) and troponin I (positive if ≥ 0.1ng/ml). Data regarding treatment modalities, length of stay, in-hospital mortality, readmission within 30 days, new oxygen requirement on discharge, complications including major and minor bleeding using the International Society on Thrombosis and Haemostasis (ISTH) criteria(11), need for transfusion, access site hematoma, and pulmonary follow-up were recorded.

Radiographic data

All CTPAs performed at the time of acute PE diagnosis were retrieved. The diagnosis of infarction was based on a generally accepted criteria with the presence of a peripheral wedge-consolidation within the region of an obstructed vessel, with or without the presence of the other suggestive findings including: (i) central lucency; (ii) vessel signs; (iii) air bronchogram (12). In case of discrepancies, a final decision was reached by consensus. A central PE was defined as the presence of thrombus in the main trunk of the pulmonary artery (PA) or the left or the right main PA. A peripheral PE was defined as thrombus in the lobar, segmental, or subsegmental PA. Signs of right ventricular (RV) strain were defined as the presence of one, or a combination of the following signs: 1) right-to-left ventricular ratio >0.9; 2) pulmonary artery enlargement; 3) abnormal interventricular septum (flattening of septum or leftward septal bowing); and 4) inferior vena caval contrast reflux. Parameters including PE distribution (central vs distal), infarct location and burden, signs of RV strain, and other parenchymal abnormalities were collected. All available follow-up CT chest imaging up to 1-year post-discharge were reviewed by board-certified thoracic radiologists to determine the resolution of infarctions or residual abnormalities on available scans. All echocardiograms were reviewed, and data regarding left ventricular ejection fraction (LVEF), RV dilation, and RV dysfunction were collected.

Statistical analysis

All continuous variables were tested for normality and presented as mean with a standard deviation (SD), or median with an interquartile range (IQR) if distribution was skewed. Categorical variables were presented as absolute number (percentage). Comparisons between patients with and without infarction were performed using Student t-test or Mann-Whitney U for continuous variables, or Fischer's exact or X^2 test for categorical variables, as appropriate. Univariable and multivariable logistic regression models were used to evaluate risk factors

associated with pulmonary infarction. The software SPSS Statistics for Mac, version 26.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. P-values of <0.05 (two-sided) were considered statistically significant.

Results

Patient characteristics

Out of 560 patients in the PERT registry, 62 cases were excluded due to diagnosis by other imaging modalities, and 2 cases were excluded after diagnosis of PE was ruled out. Hence, 496 patients were included in the study with a mean age of 58 years and 48% were female. Twenty-nine percent (143 of 496) of patients had evidence of pulmonary infarction on CTPA. Patients with pulmonary infarction were younger (52 ± 15.9 vs. 61 ± 16.6 years, p<0.001) and with a significantly lower prevalence of comorbidities including cardiac disease (30% vs 42%, p=0.014), chronic kidney disease (CKD) (5% vs 42%, p=0.018), diabetes mellitus (17% vs 26%, p=0.032), hypothyroidism (4% vs 9%, p=0.039) and malignancy (16% vs 25%, p= 0.032). Although results did not reach statistical significance, chronic obstructive pulmonary disease (COPD) was less prevalent in the infarction group. Patients with infarction were more likely to present with pleuritic chest pain (32% vs 20%, p=0.004) and hemoptysis (8% vs 3%, p= 0.04), while patients without infarction were more likely to present with syncope (6% vs 11%, p=0.05). The baseline characteristics and symptoms of presentation of the study population are reported in Table 1.

Table 1. Baseline characteristics and symptoms of presentation.

	All (496)	Without infarction (353)	With infarction (143)	P-value
Gender (female)	238 (48%)	168 (48%)	70 (49%)	0.784
Age, mean (±SD)	58 ±16.9	61 ± 16.6	52 ± 15.9	<0.001
Race, n (%) Black	249 (50%)	168 (48%)	81 (57%)	0.017

White Other	98 (20%) 149 (30%)	81 (23%) 104 (30%)	17 (12%) 45 (32%)	
BMI, mean (±SD)	31.8 ± 9.3	31.8 ± 9.5	32.0 ± 8.7	0.421
Symptoms at presentation, n (%)				
Dyspnea	297 (60%)	207 (59%)	90 (63%)	0.376
Hypoxia	237 (49%)	173 (50%)	64 (46%)	0.371
Pleuritic chest pain	114 (23%)	69 (20%)	45 (32%)	0.004
DVT symptoms	50 (10%)	40 (11%)	10 (7%)	0.146
Syncope	48 (10%)	40 (11%)	8 (6%)	0.05
Hemoptysis	21 (4%)	9 (3%)	12 (8%)	0.04
Altered mental status	38 (8%)	28 (8%)	10 (7%)	0.722
Cardiac arrest	22 (4%)	15 (4%)	7 (5%)	0.752
Comorbidities, n (%)				
Cardiac diseases	191 (39%)	148 (42%)	43 (30%)	0.014
COPD/asthma	71 (14%)	54 (15%)	17 (12%)	0.326
CKD	49 (10%)	42 (12%)	7 (5%)	0.018
Diabetes mellitus	115 (23%)	91 (26%)	24 (17%)	0.032
Hypothyroidism	36 (7%)	31 (9%)	5 (4%)	0.039
Malignancy	111 (22%)	88 (25%)	23 (16%)	0.032
Recent surgery	68 (14%)	52 (15%)	16 (11%)	0.299
Current anticoagulation	59 (12%)	41 (12%)	18 (13%)	0.762

COPD= chronic obstructive pulmonary disease; CKD= chronic kidney disease; BMI= body mass index; DVT= deep vein thrombosis; SD= standard deviation.

Risk stratification of PE

Troponin elevation (>0.1ng/ml) was less frequently observed in patients with infarction (39% vs 49%, p= 0.031). The presence of RV strain on CT was significantly higher in patients with infarction (58% vs 45%, p=0.009), although no differences in signs of RV dilation or dysfunction on echocardiogram between infarction and non-infarction group were noted. There was no significant difference in sPESI risk group, BNP elevation, PE severity, or evidence of RV dysfunction on electrocardiography and echocardiogram between groups. Table 2 describes factors associated with PE severity.

Table 2. PE severity indices.

	All (496)	Without infarction (353)	With infarction (143)	P-value
sPESI score Low risk (0 points)	89 (21%)	57 (19%)	32 (26%)	0.108

High risk (≥1 points)	327 (79%)	238 (81%)	89 (74%)	
Elevated BNP	242 (54%)	169 (53%)	73 (55%)	0.629
Elevated troponin	228 (46%)	173 (49%)	55 (39%)	0.031
Evidence of RV strain on EKG	77 (16%)	48 (14%)	29 (21%)	0.137
PE severity				
Low risk	132 (27%)	93 (26%)	39 (27%)	0.994
Intermediate low risk	173 (35%)	124 (35%)	49 (34%)	
Intermediate high risk	144 (29%)	103 (29%)	41 (29%)	
High risk	47 (10%)	33 (9%)	14 (10%)	
Elevated BNP	242 (54%)	169 (53%)	73 (55%)	0.629
Elevated troponin	228 (46%)	173 (49%)	55 (39%)	0.031
EKG evidence of RV strain	77 (16%)	48 (14%)	29 (21%)	0.137
CT evidence of RV strain	242 (49%)	159 (45%)	83 (58%)	0.009
Echocardiogram				
RV dilation	251 (54%)	173 (52%)	78 (57%)	0.302
RV dysfunction	235 (50%)	162 (49%)	73 (54%)	0.338
LVEF	38 (8%)	23 (7%)	15 (11%)	0.306
LE DVT	227 (50%)	161 (51%)	66 (50%)	0.928
UE DVT	39 (22%)	27 (22%)	12 (21%)	0.916

BNP= B-type natriuretic peptide; CT= computed tomography; DVT= deep vein thrombosis; EKG= electrocardiography; LE= lower extremity; LVEF= left ventricular ejection function; sPESI= simplified pulmonary embolism severity index; RV= right ventricular; LVEF= left ventricular ejection fraction; PE= pulmonary embolism; UE= upper extremity

Radiographic characteristics

There was no difference in PE distribution and clot burden between groups and 50% of patients with infarction had thrombus located at the main PAs including those who had saddle PE. Most infarctions occurred in the lower lobe (60%) and involved a single lobe (64%). Patients with infarction were more likely to have parenchymal abnormalities including consolidation (21% vs 12%, p= 0.007), pulmonary edema (13% vs 7%, p= 0.036), pleural effusion (33% vs 24%, p=0.038) and ground glass opacity (20% vs 13%, p= 0.042). Table 3a demonstrates the radiographic characteristics of patients with acute PE. Table 3b demonstrates the radiographic characteristics of pulmonary infarction. Fifty-eight (41%) patients had follow-up CT-chest imaging for a variety of reasons performed up to 1-year post-discharge. Resolution of pulmonary infarction was observed in 53% (17 out of 32), 85% (12 out of 14), and 92% (11 out of 12) of patients who had imaging at 3-month, 6-month, and 1-year intervals.

Table 3a. Radiographic characteristics of patients with acute pulmonary embolism.

	All (496)	Without infarction (353)	With infarction (143)	P-value
RV strain on CT	242 (49%)	159 (45%)	83 (58%)	0.009
RV to LV ratio ≥1	155 (31%)	106 (30%)	49 (34%)	0.640
Dilated PA	99 (20%)	59 (17%)	40 (28%)	0.011
Septal position				0.030
Rightward bowing	131 (27%)	102 (29%)	29 (20%)	
Flattened	112 (23%)	66 (19%)	46 (32%)	
Leftward bowing	50 (10%)	32 (9%)	18 (13%)	
PE distribution				0.052
Central PE	216 (44%)	144 (41%)	72 (50%)	
Distal PE	280 (57%)	209 (59%)	71 (50%)	
Clot burden				0.200
Main, saddle or proximal	215 (43%)	143 (41%)	72 (50%)	
Interlobar to lobar	124 (25%)	94 (27%)	30 (21%)	
Segmental	150 (30%)	110 (31%)	40 (28%)	
Subsegmental	7 (1%)	6 (2%)	1 (1%)	
Parenchymal abnormalities				
Pulmonary edema	42 (9%)	24 (7%)	18 (13%)	0.036
Consolidation	71 (14%)	41 (12%)	30 (21%)	0.007
Emphysema	65 (13%)	48 (14%)	16 (11%)	0.469
Fibrosis	42 (9%)	30 (9%)	12 (8%)	0.969
Pleural effusion	128 (26%)	84 (24%)	47 (33%)	0.038
Atelectasis	161 (33%)	113 (32%)	48 (34%)	0.738
Ground glass opacity	72 (15%)	44 (13%)	28 (20%)	0.042

CT= computed tomography; LV= left ventricular; RV= right ventricular; PA= pulmonary artery; PE= pulmonary embolism

Table 3b. Radiographic characteristics of pulmonary infarction.

	Infarcts, number (%)
Infarct location	
Upper lobe	31 (22%)
Middle lobe	8 (6%)
Lower lobe	86 (60%)
Multiple	18 (12%)
Infarct burden	
Single lobe	91 (64%)
Multiple lobes	52 (36%)

Treatment and outcomes

There was no significant difference in the number of patients receiving advanced reperfusion therapy between groups. Most patients with pulmonary infarction received anticoagulation alone (69%), followed by catheter-directed thrombolysis (12%), and systemic thrombolysis (11%). There were more patients with infarction who received antimicrobial therapy compared to those without infarction (15% vs 5%, p<0.001). Among the 47 patients who had concomitant infarction and pleural effusion, six patients (13%) underwent diagnostic and/or therapeutic thoracocentesis and five had an exudative pleural effusion. Patients with infarction were less likely to require oxygen on discharge (11% vs 19%, p= 0.031), and those who required oxygen on discharge were more likely to have multiple lobe infarctions than single lobe infarction (19% vs 7%, p= 0.032). There was no significant difference between patients with infarction and without infarction regarding length of stay (10.7±14.7 vs 9.5±12.3, p=0.698), in-hospital death (7% vs 8%, p= 0.801), disposition (home: 78% vs 75%, p=0.759), bleeding complications (24% vs 12%, p=0.089) and readmission within 30 days (18% vs 16%, p=0.584) (Supplemental material online, table 1).

Patients with infarction who underwent CDT had a longer length of stay (15± 24.4 vs 7±8.4, p=0.044) and a higher rate of readmission within 30 days (18% vs 2%, p= 0.047), compared to those without infarction. Readmission diagnoses of patients with infarction who underwent CDT were as follows: one patient developed vaginal bleeding from anticoagulant use, one patient developed acute hypoxic respiratory failure due to multifocal pneumonia, and one patient was admitted for chest pain. There was no significant difference in in-hospital mortality (6% vs 6%, p= 0.973) and complications including minor and major bleeding (24% vs 21%, p=0.676), access site hematoma (13% vs 2%, p= 0.134) and need for transfusion (18% vs 13%, p=0.649) between those with and without infarction (Supplemental material online, table 2).

In univariable regression analyses, we identified several factors independently associated with pulmonary infarction. These included age, history of cardiac diseases, malignancy, hypothyroidism, diabetes mellitus, CKD, elevated troponin, pleuritic chest pain, hemoptysis, and RV strain on CT. A multivariable regression analysis was subsequently performed, and four factors remained significant: Both hemoptysis (OR, 3.034; 95% CI, 1.162-7.924) and presence of RV strain on CT (OR, 2.142; 95% CI 1.365-3.360) significantly increased the risk of infarction, while age (OR, 0.973, 95% CI, 0.959-0.987) and presence of elevated troponin (OR, 0.629; 95% CI 0.398-0.993) decreased risk (Table 4).

Table 4. Univariate and multivariate analysis of potential risk factors.

Variables			Univariate analysis			Multivariate analysis		
	Without infarction (353)	With infarction (143)	Odds ratio	P-value	95% CI	Odds ratio	P-value	95% CI
Age, years	61 ± 16.6	52 ± 15.9	0.968	<0.001	0.956-0.980	0.973	<0.001	0.959-0.987
Cardiac diseases	148 (42%)	43 (30%)	0.596	0.014	0.393-0.902			
CKD	42 (12%)	7 (5%)	0.381	0.022	0.167-0.870			
DM	91 (26%)	24 (17%)	0.581	0.033	0.352-0.957			
Malignancy	88 (25%)	23 (16%)	0.577	0.034	0.348-0.958			
Hypothyroidism	31 (9%)	5 (4%)	0.375	0.047	0.143-0.985			
Elevated troponin	173 (49%)	55 (39%)	0.647	0.032	0.435-0.962	0.629	0.047	0.398-0.993
Pleuritic CP	69 (20%)	45 (32%)	1.890	0.005	1.217-2.935			
Hemoptysis	9 (3%)	12 (8%)	3.491	0.006	1.437-8.479	3.034	0.023	1.162-7.924
RV strain on CT	159 (45%)	83 (58%)	1.688	0.009	1.140-2.500	2.142	<0.001	1.365-3.360

CP= chest pain; CKD= chronic kidney disease; CT= computed tomography DM= diabetes mellites; RV= right ventricular

Discussion

In this study, the estimated prevalence of pulmonary infarction was 29%. Patients with infarction were more likely to present with pleuritic chest pain and hemoptysis. Additionally, those with pulmonary infarction were younger and had a lower prevalence of comorbidities. While the presence of RV strain on CT imaging was more common in patients with pulmonary infarction, the rate of reperfusion therapies, complications, and outcomes was similar in both groups. The presence of hemoptysis and RV strain on CT significantly increased the risk of infarction, whereas age and elevated troponin decreased the risk. Pulmonary infarction resolved in the

majority of patients for whom follow-up imaging was available, which is in concordance with newer studies (8, 9, 13).

The prevalence of pulmonary infarction in our cohort is in keeping with previously reported rates ranging from 9% to 36% (3, 13). Regarding clinical presentation, the higher presence of pleuritic chest pain and hemoptysis in patients with infarction likely represents a result of alveolar hemorrhage, leading to pleural inflammation, irritation, and necrosis. In addition, the presence of pleural effusion was more prevalent in patients with infarction due to pleural inflammation following infarction, however, most of these effusions were not intervened upon and had resolved on follow-up imaging. Although patients with infarction were more likely to present with pleuritic chest pain and hemoptysis, these symptoms were only present in 32% and 8% of patients with infarction respectively. Thus, it is important to note that the majority remained asymptomatic, and thus the presence of these symptoms may not be useful in identifying pulmonary infarction. Interestingly, patients with pulmonary infarction were more likely to be treated with antimicrobial therapy than those without. One possible explanation is that other lung processes, such as pneumonia, pulmonary edema, or atelectasis can produce consolidative changes similar to infarction on CT imaging (14), and as a result, pneumonia cannot be excluded especially when combined with a clinically compatible presentation.

In our study, patients with infarction were significantly younger and with fewer comorbid conditions, specifically a lower prevalence of cardiac disease and malignancy that have traditionally been regarded as major risk factors for infarction. This discrepancy may be due to a lack of efficient collateral circulation to lung tissues, which presumably develops in the setting of longstanding local tissue hypoxia (8, 15), and is unlikely to happen in otherwise healthy, young individuals in the absence of cardiopulmonary diseases.

Our cohort also found that patients with infarction did have higher rates of RV strain, dilated PA, and flattened or leftward bowing of the interventricular septum, although signs of RV strain were not reproducible on echocardiography. A potential explanation for this finding is that patients with infarction were younger with less comorbid diseases, thus without pre-existing RV hypertrophy allowing for tolerance of acute RV afterload elevation. This may also explain our finding that troponin elevation was less likely to be observed in patients with infarction. While troponin elevation is indicative of RV strain, RV myocardium might not necessarily be its only source (16). A mismatch between oxygen demand and supply (demand ischemia) and a decrease in renal clearance could contribute to the higher rates of troponin elevation observed in patients without infarction, as evidenced by their higher prevalence of comorbidities.

Regarding the discrepancy between CT and echocardiographic findings, unlike CTPA which is often the first diagnostic and confirmatory modality for PE, most echocardiography is performed after the initial diagnosis and potentially after reperfusion therapy. In our study, the mean and median time lapse between the availability of CT results to echocardiogram results was 29 hours 40 minutes and 20 hours 11 minutes respectively. Thus, it is possible that the initial signs of RV strain shown on CTPA could have improved or resolved through several potential mechanisms; administration of supplemental oxygen leading to a reversal of hypoxic vasoconstriction, clot burden reduction using reperfusion therapy, or intrinsic thrombolytic activity with anticoagulation support alone.

Importantly, we demonstrated no differences in complication rates and in-hospital mortality in patients who underwent CDT with pulmonary infarction compared to those without, although patients with infarction had a longer length of stay and a higher rate of 30-day readmission for non-PE or CDT-related diagnoses. There remains a theoretical risk of increased bleeding

complications in the area of pulmonary infarction during catheter manipulation and local installation of thrombolytics, however, this was not demonstrated in our cohort.

Study Limitations

To the best of our knowledge, this study represented the largest cohort of patients with acute PE complicated by pulmonary infarction, however, there are several limitations in our study. Cases of pulmonary infarction were identified based on CT findings and there was no histological correlation to differentiate between true necrosis versus alveolar hemorrhage. Patients with conditions that led to pulmonary hypertension could have pre-existing parenchymal changes that resemble acute RV strain caused by PE. In those scenarios, it would be technically difficult to differentiate whether these CT features are related to pre-existing pulmonary hypertension itself, or the combination. Owing to the retrospective nature of this study, not all patients underwent CT imaging post-discharge, thus we were unable to comment on the precise timing of the resolution of pulmonary infarction. We acknowledge the fact that not all patients in our cohort had echocardiography, in particular, patients with low-risk PE when echocardiography was not deemed necessary to change management or patients with high-risk PE who expired prior to the completion of echocardiography. Other limitations included the retrospective, single-center nature of the data, which may be prone to selection bias.

In conclusion, pulmonary infarction was demonstrated on CT in nearly one-third of acute PE, and patients with infarction were younger, with fewer comorbidities, and more likely to present with pleuritic chest pain and hemoptysis. Overall, there was no difference in length of stay, in-hospital death, bleeding complication, and readmission rate between patients with and without infarction, and patients with infarction were less likely to require oxygen on discharge. The presence of pulmonary infarction did not correlate with poorer outcomes and should not be

considered a supporting factor nor a contraindication for advanced reperfusion therapy for PE.

Author contributions: KUL is the primary author, collected and analyzed the data, and is the guarantor of the article, taking responsibility for the integrity of the work as a whole from inception to the published article. OO and PR are responsible for the study concept and helped write the manuscript. RB, GC, VL, and JP reviewed the imaging studies and treated the patients who underwent catheter-directed thrombolysis. SB and BRL helped write the manuscript.

Conflict of interest: There are no financial or other conflicts of interest to disclose.

Ethics approval: This study was approved by the Institutional Review Board (Protocol #26021) at Temple University Hospital and informed consent was waived due to the retrospective nature of the study.

Patient consent for publication: Not required.

Funding statement: This study received no funding.

Data sharing statement: All data relevant to the study are included in the article or uploaded as supplementary information.

Reference

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Figure 1. Patient selection flow diagram.

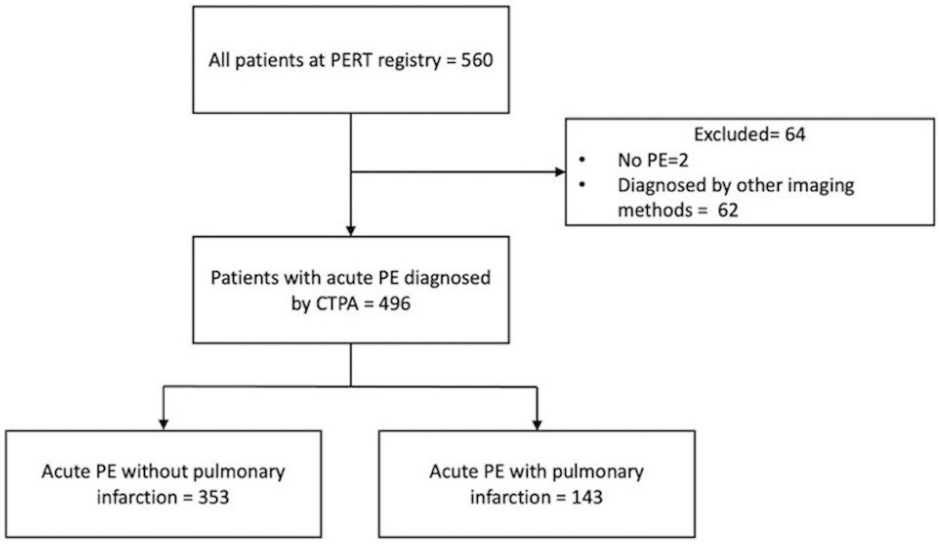

Figure 1. Patient selection flow diagram.

32x19mm (800 x 800 DPI)

Supplemental material, table 1. Treatment and outcomes between patients with and without infarction.

	All (496)	Without infarction (353)	With infarction (143)	P-value
Anticoagulation alone	357 (72%)	259 (73%)	98 (69%)	0.545
CDT	70 (14%)	53 (15%)	17 (12%)	0.365
Thrombolysis				0.212
Half dose	25 (5%)	15 (4%)	10 (7%)	
Full dose	14 (3%)	8 (2%)	6 (4%)	
Mechanical thrombectomy	19 (4%)	10 (3%)	9 (6%)	0.069
Surgical thrombectomy	9 (2%)	6 (2%)	3 (2%)	0.763
ECMO	11 (2%)	6 (2%)	5 (4%)	0.218
Mechanical ventilation	48 (10%)	30 (9%)	18 (13%)	0.163
Antimicrobials	39 (8%)	19 (5%)	22 (15%)	<0.001
In-hospital death	37 (8%)	27 (8%)	10 (7%)	0.801
Disposition				0.759
Home	349 (76%)	245 (75%)	104 (78%)	
ECF	100 (22%)	74 (23%)	26 (20%)	
Hospice	10 (2%)	7 (2%)	3 (2%)	
Length of stay, days	10±13.0	9.5±12.3	10.7±14.7	0.698
Bleeding complication				0.089
Minor bleeding	31 (6%)	25 (7%)	6 (4%)	
Major bleeding	32 (7%)	18 (5%)	14 (10%)	
Need for transfusion	63 (13%)	41 (12%)	22 (16%)	0.253
Readmission within 30 days	76 (16.6%)	52 (16%)	24 (18%)	0.584
New O2 on discharge	75 (16%)	61 (19%)	14 (11%)	0.031
Pulmonary follow-up	199 (42%)	144 (44%)	55 (40%)	0.610

CDT= catheter-directed thrombolysis; ECMO= extracorporeal membrane oxygenation; ECF= extended care facility

Supplemental material, table 2. Outcomes and complication rates in CDT.

	All (70)	Without infarction (53)	With infarction (17)	P-value
In-hospital death	4 (6%)	3 (6%)	1 (6%)	0.973
Disposition Home ECF	 57 (86%) 9 (14%)	 42 (84%) 8 (16%)	 15 (94%) 1 (7%)	0.436
Length of Stay	9±14.2	7±8.4	15±24.4	0.044
Readmission within 30 days	4 (6%)	1 (2%)	3 (18%)	0.047
New O2 on discharge	10 (16%)	8 (17%)	2 (12%)	0.609
Pulmonary follow-up	47 (72%)	38 (76%)	9 (56%)	0.166
Complications				
Bleeding Minor Major	 10 (14%) 5 (7%)	 8 (15%) 3 (6%)	 2 (12%) 2 (12%)	0.676
RBC transfusion	10 (14%)	7 (13%)	3 (18%)	0.649
Access site hematoma	3 (5%)	1 (2%)	2 (13%)	0.134

ECF= extended care facility; RBC= red blood cell

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	(a) Page 2, line 3-4 (b) Page 4	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1.1: Page 2, line 3-4 1.2: Page 2, line 3-4
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 6, line 5-35		
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6, line 36-40		
Methods					
Study Design	4	Present key elements of study design early in the paper	Page 6		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 6, line 47- page 7, line 10		

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	Page 6, line 47- page 7, line 10	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	6.1: Page 6, line 47- page 7, line 10 6.2: not applicable 6.3: figure 1
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Page 7	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Page 7
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 7		

Bias	9	Describe any efforts to address potential sources of bias	Page 8, line 3-4		
Study size	10	Explain how the study size was arrived at	Page 9, line 5-10		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Page 7, line 17-54		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	Page 8, line 33-51		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	Page 6, line 47-page 7, line 10

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Not applicable
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	Page 9, line 5-10	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Page 9, line 5-10
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	Page 9, line 5-35; Page 10, line 29-44 Table 1 and 2		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure	Page 12, line 54 to Page 13 line 13 Table 4		

		category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 12, line 54 to Page 13 line 13 Table 4		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Page 12, line 54 to Page 13 line 13 Table 4		
Discussion					
Key results	18	Summarise key results with reference to study objectives	Page 14 line 36-55		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 17 line 5-36	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Page 17 line 5-36
Interpretation	20	Give a cautious overall interpretation of results considering objectives,	Page 17 line 38-53		

		limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 17 line 5-36		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 18 line 24		
Accessibility of protocol, raw data, and programming code		..	Page 18 line 26-27	RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Page 18 line 26-27

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

BMJ Open

Clinical Outcomes and Factors Associated with Pulmonary Infarction Following Acute Pulmonary Embolism: A Retrospective Observational Study at a US Academic Center

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-067579.R2
Article Type:	Original research
Date Submitted by the Author:	28-Nov-2022
Complete List of Authors:	Lio, Ka U; Lewis Katz School of Medicine at Temple University, Department of Medicine O'Corragain, Oisin; Lewis Katz School of Medicine at Temple University, Department of Thoracic Medicine and Surgery Bashir, Riyaz ; Lewis Katz School of Medicine at Temple University, Cardiology Brosnahan, Shari; NYU Langone Health, Pulmonary, Critical Care and Sleep Medicine Cohen, Gary; Lewis Katz School of Medicine at Temple University, Radiology Lakhter, Vladimir; Lewis Katz School of Medicine at Temple University, Cardiology Panaro, Joseph; Lewis Katz School of Medicine at Temple University, Radiology Rivera-Lebron, B; University of Pittsburgh School of Medicine, Pulmonary and Critical Care Medicine Rali, Parth; Lewis Katz School of Medicine at Temple University, Thoracic Medicine and Surgery
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Cardiovascular medicine, General practice / Family practice, Intensive care, Radiology and imaging
Keywords:	Thromboembolism < CARDIOLOGY, RESPIRATORY MEDICINE (see Thoracic Medicine), Thoracic medicine < INTERNAL MEDICINE

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Clinical Outcomes and Factors Associated with Pulmonary Infarction Following Acute Pulmonary Embolism: A Retrospective Observational Study at a US Academic Center

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Word count: 2643 words

Keywords: pulmonary embolism, pulmonary infarction, venous thromboembolism, shortness of breath, pleuritic chest pain

Abbreviations: BNP= B-type natriuretic peptide; CDT= catheter-directed thrombolysis; CKD= chronic kidney disease; CT= computed tomography; CTPA= computed tomography pulmonary angiography; PA= pulmonary artery; PE= Pulmonary embolism; RV= Right ventricular; sPESI= simplified pulmonary embolism severity index

Abstract

Objective: Pulmonary infarction is a common clinical and radiographic finding in acute pulmonary embolism (PE), yet the clinical relevance and prognostic significance of pulmonary infarction remain unclear. The study aims to investigate the clinical features, radiographic characteristics, impact of reperfusion therapy, and outcomes of patients with pulmonary infarction.

Design, **setting and participants**: A retrospective cohort study of 496 adult patients (≥ 18 years of age) diagnosed with PE who were evaluated by the pulmonary embolism response team (PERT) at a tertiary academic referral center in the US. We collected baseline characteristics, laboratory, radiographic, and outcome data. Statistical analysis was performed by Student t-test, Mann-Whitney U test, Fischer's exact or X^2 test where appropriate. Multivariate logistic regression was used to evaluate potential risk factors for pulmonary infarction.

Results: We identified 143 (29%) cases of pulmonary infarction in 496 patients with PE. Patients with infarction were significantly younger (52 ± 15.9 vs. 61 ± 16.6 years, $p<0.001$) and with fewer comorbidities. Most infarctions occurred in the lower lobes (60%) and involved a single lobe (64%). The presence of right ventricular (RV) strain on computed tomography (CT) imaging was significantly more common in patients with infarction (21% vs 14%, $p=0.031$). There was no significant difference in advanced reperfusion therapy, in-hospital mortality, length of stay, and readmissions between groups. In multivariate analysis, age, and evidence of RV strain on CT and hemoptysis increased the risk of infarction.

Conclusions: Radiographic evidence of pulmonary infarction was demonstrated in nearly one-third of patients with acute PE. There was no difference in the rate of reperfusion therapies and the presence of infarction did not correlate with poorer outcomes.

Strengths and limitations of this study:

- This study represents the largest cohort describing the clinical characteristics and outcomes of patients with pulmonary infarction.
- This study highlights the potential role of pulmonary infarction in the risk stratification of acute PE.
- Cases of pulmonary infarction were identified based on CT findings and there was no histological correlation to differentiate between true necrosis (infarction) versus alveolar hemorrhage.
- Not all patients underwent CT imaging post-discharge and thus we are unable to comment on the precise timing of the resolution of infarction and its long-term significance.

Introduction

Acute pulmonary embolism (PE) is the third leading cause of cardiovascular death following myocardial infarction and stroke, with approximately 100,000 annual deaths in the United States (1, 2). Pulmonary infarction is a common complication of acute PE with a reported radiographic prevalence of up to 36% (3). The dual blood supply of lungs has been thought to be protective against ischemic insults, with the bronchial circulation and other collateral vessels undergoing hypertrophy or remodeling to maintain blood flow to ischemic lung tissues through anastomoses at the level of alveoli and respiratory bronchioles (4, 5). Nevertheless, obstruction of the pulmonary artery by acute PE can cause infarction. In the past, the presence of infarction has been regarded as a sign of poor outcomes due to its association with compromised cardiac function, which leads to increased pulmonary venous pressure and impairment of forwarding flow through the bronchial circulation (6, 7). Contrarily, recent studies have suggested that younger, healthier patients are at the highest risk for infarction, because of their less robust collateral blood supply (8, 9). The clinical relevance and prognostic significance of pulmonary infarction remain unclear. The aim of this study is to investigate the clinical features, radiographic characteristics, impact of reperfusion therapy, and outcomes of patients with pulmonary infarction.

Methods

Study population

We conducted a single-center retrospective review of all patients between January 2017 and June 2020 at Temple University Hospital who underwent evaluation by the pulmonary embolism response team (PERT) and included all cases of acute PE diagnosed by computed tomography pulmonary angiography (CTPA). Cases of acute PE diagnosed by other imaging modalities were

excluded from the study. Cases of pulmonary infarction were identified by review of the final CT reports by board-certified thoracic radiologists. Our study met approval by the Institutional Review Board (Protocol #26021) and informed consent was waived due to the retrospective nature of the study. Figure 1 demonstrates patient selection.

Patient and public involvement

Patients or the public were not involved in the design, recruitment, conduct, reporting, or dissemination of our research.

Data Collection

Clinical data

Patient demographic, clinical features, laboratory data, echocardiographic data, radiographic characteristics, and patient outcomes were extracted from electronic medical records. Demographics included age, gender, race, and body mass index (BMI). Clinical features included symptoms at presentation, comorbid conditions, calculated simplified pulmonary embolism severity index (sPESI), and PE severity per the European Society of Cardiology (ESC) guideline at the time of diagnosis (i.e., low, intermediate-low, intermediate-high, and high risk).(10) Laboratory data included B-type natriuretic peptide (BNP; positive if ≥100pg/ml) and troponin I (positive if ≥ 0.1ng/ml). Data regarding treatment modalities, length of stay, in-hospital mortality, readmission within 30 days, new oxygen requirement on discharge, complications including major and minor bleeding using the International Society on Thrombosis and Haemostasis (ISTH) criteria(11), need for transfusion, access site hematoma, and pulmonary follow-up were recorded.

Radiographic data

All CTPAs performed at the time of acute PE diagnosis were retrieved. The diagnosis of infarction was based on generally accepted criteria with the presence of a peripheral wedge-shaped consolidation within the region of an obstructed vessel, with or without the presence of the other suggestive findings including: (i) central lucency; (ii) vessel signs; (iii) and air bronchogram (12). In case of discrepancies, a final decision was reached by consensus. A central PE was defined as the presence of thrombus in the main trunk of the pulmonary artery (PA) or the left or the right main PA. A peripheral PE was defined as thrombus in the lobar, segmental, or subsegmental PA. Signs of right ventricular (RV) strain were defined as the presence of one, or a combination of the following signs: 1) right-to-left ventricular ratio >0.9; 2) pulmonary artery enlargement; 3) abnormal interventricular septum (flattening of septum or leftward septal bowing); and 4) inferior vena caval contrast reflux. Parameters including PE distribution (central vs distal), infarct location and burden, signs of RV strain, and other parenchymal abnormalities were collected. All available follow-up CT chest imaging up to 1-year post-discharge were reviewed by board-certified thoracic radiologists to determine the resolution of infarctions or residual abnormalities on available scans. All echocardiograms were reviewed, and data regarding left ventricular ejection fraction (LVEF), RV dilation, and RV dysfunction were collected.

Statistical analysis

All continuous variables were tested for normality and presented as mean with a standard deviation (SD), or median with an interquartile range (IQR) if distribution was skewed. Categorical variables were presented as absolute number (percentage). Comparisons between patients with and without infarction were performed using Student t-test or Mann-Whitney U for continuous variables, or Fischer's exact or X^2 test for categorical variables, as appropriate.

Univariable and multivariable logistic regression models were used to evaluate risk factors associated with pulmonary infarction. The software SPSS Statistics for Mac, version 26.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. P-values of <0.05 (two-sided) were considered statistically significant.

Results

Patient characteristics

Out of 560 patients in the PERT registry, 62 cases were excluded due to diagnosis by other imaging modalities, and 2 cases were excluded after diagnosis of PE was ruled out. Hence, 496 patients were included in the study with a mean age of 58 years and 48% were female. Twenty-nine percent (143 of 496) of patients had evidence of pulmonary infarction on CTPA. Patients with pulmonary infarction were younger (52 ± 15.9 vs. 61 ± 16.6 years, p<0.001) and with a significantly lower prevalence of comorbidities including cardiac disease (30% vs 42%, p=0.014), chronic kidney disease (CKD) (5% vs 42%, p=0.018), diabetes mellitus (17% vs 26%, p=0.032), hypothyroidism (4% vs 9%, p=0.039) and malignancy (16% vs 25%, p= 0.032). Although results did not reach statistical significance, chronic obstructive pulmonary disease (COPD) was less prevalent in the infarction group. Patients with infarction were more likely to present with pleuritic chest pain (32% vs 20%, p=0.004) and hemoptysis (8% vs 3%, p= 0.04), while patients without infarction were more likely to present with syncope (6% vs 11%, p=0.05). The baseline characteristics and symptoms of presentation of the study population are reported in Table 1.

Table 1. Baseline characteristics and symptoms of presentation.

	All (496)	Without infarction (353)	With infarction (143)	P-value
Gender (female)	238 (48%)	168 (48%)	70 (49%)	0.784
Age, mean (±SD)	58 ±16.9	61 ± 16.6	52 ± 15.9	<0.001

Race, n (%)				0.017
Black	249 (50%)	168 (48%)	81 (57%)	
White	98 (20%)	81 (23%)	17 (12%)	
Other	149 (30%)	104 (30%)	45 (32%)	
BMI, mean (±SD)	31.8 ± 9.3	31.8 ± 9.5	32.0 ± 8.7	0.421
Symptoms at presentation, n (%)				
Dyspnea	297 (60%)	207 (59%)	90 (63%)	0.376
Hypoxia	237 (49%)	173 (50%)	64 (46%)	0.371
Pleuritic chest pain	114 (23%)	69 (20%)	45 (32%)	0.004
DVT symptoms	50 (10%)	40 (11%)	10 (7%)	0.146
Syncope	48 (10%)	40 (11%)	8 (6%)	0.05
Hemoptysis	21 (4%)	9 (3%)	12 (8%)	0.04
Altered mental status	38 (8%)	28 (8%)	10 (7%)	0.722
Cardiac arrest	22 (4%)	15 (4%)	7 (5%)	0.752
Comorbidities, n (%)				
Cardiac diseases	191 (39%)	148 (42%)	43 (30%)	0.014
COPD/asthma	71 (14%)	54 (15%)	17 (12%)	0.326
CKD	49 (10%)	42 (12%)	7 (5%)	0.018
Diabetes mellitus	115 (23%)	91 (26%)	24 (17%)	0.032
Hypothyroidism	36 (7%)	31 (9%)	5 (4%)	0.039
Malignancy	111 (22%)	88 (25%)	23 (16%)	0.032
Recent surgery	68 (14%)	52 (15%)	16 (11%)	0.299
Current anticoagulation	59 (12%)	41 (12%)	18 (13%)	0.762

COPD= chronic obstructive pulmonary disease; CKD= chronic kidney disease; BMI= body mass index; DVT= deep vein thrombosis; SD= standard deviation.

Risk stratification of PE

Troponin elevation (>0.1ng/ml) was less frequently observed in patients with infarction (39% vs 49%, p= 0.031). The presence of RV strain on CT was significantly higher in patients with infarction (58% vs 45%, p=0.009), although no differences in signs of RV dilation or dysfunction on echocardiogram between infarction and non-infarction group were noted. There was no significant difference in sPESI risk group, BNP elevation, PE severity, or evidence of RV dysfunction on electrocardiography and echocardiogram between groups. Table 2 describes factors associated with PE severity.

Table 2. PE severity indices.

	All (496)	Without infarction (353)	With infarction (143)	P-value

sPESI score				0.108
Low risk (0 points)	89 (21%)	57 (19%)	32 (26%)	
High risk (≥1 points)	327 (79%)	238 (81%)	89 (74%)	
Elevated BNP	242 (54%)	169 (53%)	73 (55%)	0.629
Elevated troponin	228 (46%)	173 (49%)	55 (39%)	0.031
Evidence of RV strain on EKG	77 (16%)	48 (14%)	29 (21%)	0.137
PE severity				
Low risk	132 (27%)	93 (26%)	39 (27%)	0.994
Intermediate low risk	173 (35%)	124 (35%)	49 (34%)	
Intermediate high risk	144 (29%)	103 (29%)	41 (29%)	
High risk	47 (10%)	33 (9%)	14 (10%)	
EKG evidence of RV strain	77 (16%)	48 (14%)	29 (21%)	0.137
CT evidence of RV strain	242 (49%)	159 (45%)	83 (58%)	0.009
Echocardiogram				
RV dilation	251 (54%)	173 (52%)	78 (57%)	0.302
RV dysfunction	235 (50%)	162 (49%)	73 (54%)	0.338
LVEF	38 (8%)	23 (7%)	15 (11%)	0.306
LE DVT	227 (50%)	161 (51%)	66 (50%)	0.928
UE DVT	39 (22%)	27 (22%)	12 (21%)	0.916

BNP= B-type natriuretic peptide; CT= computed tomography; DVT= deep vein thrombosis; EKG= electrocardiography; LE= lower extremity; LVEF= left ventricular ejection function; sPESI= simplified pulmonary embolism severity index; RV= right ventricular; LVEF= left ventricular ejection fraction; PE= pulmonary embolism; UE= upper extremity

Radiographic characteristics

There was no difference in PE distribution and clot burden between groups and 50% of patients with infarction had thrombus located at the main PAs including those who had saddle PE. Most infarctions occurred in the lower lobe (60%) and involved a single lobe (64%). Patients with infarction were more likely to have parenchymal abnormalities including consolidation (21% vs 12%, p= 0.007), pulmonary edema (13% vs 7%, p= 0.036), pleural effusion (33% vs 24%, p=0.038) and ground glass opacity (20% vs 13%, p= 0.042). Table 3a demonstrates the radiographic characteristics of patients with acute PE. Table 3b demonstrates the radiographic characteristics of pulmonary infarction. Fifty-eight (41%) patients had follow-up CT-chest imaging for a variety of reasons performed up to 1-year post-discharge. Resolution of pulmonary infarction was observed in 53% (17 out of 32), 85% (12 out of 14), and 92% (11 out of 12) of patients who had imaging at 3-month, 6-month, and 1-year intervals.

Table 3a. Radiographic characteristics of patients with acute pulmonary embolism.

	All (496)	Without infarction (353)	With infarction (143)	P-value
RV strain on CT	242 (49%)	159 (45%)	83 (58%)	0.009
RV to LV ratio ≥1	155 (31%)	106 (30%)	49 (34%)	0.640
Dilated PA	99 (20%)	59 (17%)	40 (28%)	0.011
Septal position				0.030
Rightward bowing	131 (27%)	102 (29%)	29 (20%)	
Flattened	112 (23%)	66 (19%)	46 (32%)	
Leftward bowing	50 (10%)	32 (9%)	18 (13%)	
PE distribution				0.052
Central PE	216 (44%)	144 (41%)	72 (50%)	
Distal PE	280 (57%)	209 (59%)	71 (50%)	
Clot burden				0.200
Main, saddle or proximal	215 (43%)	143 (41%)	72 (50%)	
Interlobar to lobar	124 (25%)	94 (27%)	30 (21%)	
Segmental	150 (30%)	110 (31%)	40 (28%)	
Subsegmental	7 (1%)	6 (2%)	1 (1%)	
Parenchymal abnormalities				
Pulmonary edema	42 (9%)	24 (7%)	18 (13%)	0.036
Consolidation	71 (14%)	41 (12%)	30 (21%)	0.007
Emphysema	65 (13%)	48 (14%)	16 (11%)	0.469
Fibrosis	42 (9%)	30 (9%)	12 (8%)	0.969
Pleural effusion	128 (26%)	84 (24%)	47 (33%)	0.038
Atelectasis	161 (33%)	113 (32%)	48 (34%)	0.738
Ground glass opacity	72 (15%)	44 (13%)	28 (20%)	0.042

CT= computed tomography; LV= left ventricular; RV= right ventricular; PA= pulmonary artery; PE= pulmonary embolism

Table 3b. Radiographic characteristics of pulmonary infarction.

	Infarcts, number (%)
Infarct location	
Upper lobe	31 (22%)
Middle lobe	8 (6%)
Lower lobe	86 (60%)
Multiple	18 (12%)
Infarct burden	
Single lobe	91 (64%)
Multiple lobes	52 (36%)

Treatment and outcomes

There was no significant difference in the number of patients receiving advanced reperfusion therapy between groups. Most patients with pulmonary infarction received anticoagulation alone (69%), followed by catheter-directed thrombolysis (12%), and systemic thrombolysis (11%). There were more patients with infarction who received antimicrobial therapy compared to those without infarction (15% vs 5%, p<0.001). Among the 47 patients who had concomitant infarction and pleural effusion, six patients (13%) underwent diagnostic and/or therapeutic thoracocentesis and five had an exudative pleural effusion. Patients with infarction were less likely to require oxygen on discharge (11% vs 19%, p= 0.031), and those who required oxygen on discharge were more likely to have multiple lobe infarctions than single lobe infarction (19% vs 7%, p= 0.032). There was no significant difference between patients with infarction and without infarction regarding length of stay (10.7±14.7 vs 9.5±12.3, p=0.698), in-hospital death (7% vs 8%, p= 0.801), disposition (home: 78% vs 75%, p=0.759), bleeding complications (24% vs 12%, p=0.089) and readmission within 30 days (18% vs 16%, p=0.584) (Supplemental material online, table 1).

Patients with infarction who underwent CDT had a longer length of stay (15± 24.4 vs 7±8.4, p=0.044) and a higher rate of readmission within 30 days (18% vs 2%, p= 0.047), compared to those without infarction. Readmission diagnoses of patients with infarction who underwent CDT were as follows: one patient developed vaginal bleeding from anticoagulant use, one patient developed acute hypoxic respiratory failure due to multifocal pneumonia, and one patient was admitted for chest pain. There was no significant difference in in-hospital mortality (6% vs 6%, p= 0.973) and complications including minor and major bleeding (24% vs 21%, p=0.676), access site hematoma (13% vs 2%, p= 0.134) and need for transfusion (18% vs 13%, p=0.649) between those with and without infarction (Supplemental material online, table 2).

In univariable regression analyses, we identified several factors independently associated with pulmonary infarction. These included age, history of cardiac diseases, malignancy, hypothyroidism, diabetes mellitus, CKD, elevated troponin, pleuritic chest pain, hemoptysis, and RV strain on CT. A multivariable regression analysis was subsequently performed, and four factors remained significant: Both hemoptysis (OR, 3.034; 95% CI, 1.162-7.924) and presence of RV strain on CT (OR, 2.142; 95% CI 1.365-3.360) significantly increased the risk of infarction, while age (OR, 0.973, 95% CI, 0.959-0.987) and presence of elevated troponin (OR, 0.629; 95% CI 0.398-0.993) decreased risk (Table 4).

Table 4. Univariate and multivariate analysis of potential risk factors.

Variables			Univariate analysis			Multivariate analysis		
	Without infarction (353)	With infarction (143)	Odds ratio	P-value	95% CI	Odds ratio	P-value	95% CI
Age, years	61 ± 16.6	52 ± 15.9	0.968	<0.001	0.956-0.980	0.973	<0.001	0.959-0.987
Cardiac diseases	148 (42%)	43 (30%)	0.596	0.014	0.393-0.902			
CKD	42 (12%)	7 (5%)	0.381	0.022	0.167-0.870			
DM	91 (26%)	24 (17%)	0.581	0.033	0.352-0.957			
Malignancy	88 (25%)	23 (16%)	0.577	0.034	0.348-0.958			
Hypothyroidism	31 (9%)	5 (4%)	0.375	0.047	0.143-0.985			
Elevated troponin	173 (49%)	55 (39%)	0.647	0.032	0.435-0.962	0.629	0.047	0.398-0.993
Pleuritic CP	69 (20%)	45 (32%)	1.890	0.005	1.217-2.935			
Hemoptysis	9 (3%)	12 (8%)	3.491	0.006	1.437-8.479	3.034	0.023	1.162-7.924
RV strain on CT	159 (45%)	83 (58%)	1.688	0.009	1.140-2.500	2.142	<0.001	1.365-3.360

CP= chest pain; CKD= chronic kidney disease; CT= computed tomography DM= diabetes mellites; RV= right ventricular

Discussion

In this study, the estimated prevalence of pulmonary infarction was 29%. Patients with infarction were more likely to present with pleuritic chest pain and hemoptysis. Additionally, those with pulmonary infarction were younger and had a lower prevalence of comorbidities. While the presence of RV strain on CT imaging was more common in patients with pulmonary infarction, the rate of reperfusion therapies, complications, and outcomes was similar in both groups. The presence of hemoptysis and RV strain on CT significantly increased the risk of infarction, whereas age and elevated troponin decreased the risk. Pulmonary infarction resolved in the

majority of patients for whom follow-up imaging was available, which is in concordance with newer studies (8, 9, 13).

The prevalence of pulmonary infarction in our cohort is in keeping with previously reported rates ranging from 9% to 36% (3, 13). Regarding clinical presentation, the higher presence of pleuritic chest pain and hemoptysis in patients with infarction likely represents a result of alveolar hemorrhage, leading to pleural inflammation, irritation, and necrosis. In addition, the presence of pleural effusion was more prevalent in patients with infarction due to pleural inflammation following infarction, however, most of these effusions were not intervened upon and had resolved on follow-up imaging. Although patients with infarction were more likely to present with pleuritic chest pain and hemoptysis, these symptoms were only present in 32% and 8% of patients with infarction respectively. Thus, the majority did not have these symptoms may not be useful in identifying pulmonary infarction. Interestingly, patients with pulmonary infarction were more likely to be treated with antimicrobial therapy than those without. One possible explanation is that other lung processes, such as pneumonia, pulmonary edema, or atelectasis can produce consolidative changes similar to infarction on CT imaging (14), and as a result, pneumonia cannot be excluded especially when combined with a clinically compatible presentation.

In our study, patients with infarction were significantly younger and with fewer comorbid conditions, specifically a lower prevalence of cardiac disease and malignancy that have traditionally been regarded as major risk factors for infarction. This discrepancy may be due to a lack of efficient collateral circulation to lung tissues, which presumably develops in the setting of longstanding local tissue hypoxia (8, 15), and is unlikely to happen in otherwise healthy, young individuals in the absence of cardiopulmonary diseases.

Our cohort also found that patients with infarction did have higher rates of RV strain, dilated PA, and flattened or leftward bowing of the interventricular septum, although signs of RV strain were not reproducible on echocardiography. A potential explanation for this finding is that patients with infarction were younger with less comorbid diseases, thus without pre-existing RV hypertrophy allowing for tolerance of acute RV afterload elevation. This may also explain our finding that troponin elevation was less likely to be observed in patients with infarction. While troponin elevation is indicative of RV strain, RV myocardium might not necessarily be its only source (16). A mismatch between oxygen demand and supply (demand ischemia) and a decrease in renal clearance could contribute to the higher rates of troponin elevation observed in patients without infarction, as evidenced by their higher prevalence of comorbidities.

Regarding the discrepancy between CT and echocardiographic findings, unlike CTPA which is often the first diagnostic and confirmatory modality for PE, most echocardiography is performed after the initial diagnosis and potentially after reperfusion therapy. In our study, the mean and median time lapse between the availability of CT results to echocardiogram results was 29 hours 40 minutes and 20 hours 11 minutes respectively. Thus, it is possible that the initial signs of RV strain shown on CTPA could have improved or resolved through several potential mechanisms; administration of supplemental oxygen leading to a reversal of hypoxic vasoconstriction, clot burden reduction using reperfusion therapy, or intrinsic thrombolytic activity with anticoagulation support alone.

Importantly, we demonstrated no differences in complication rates and in-hospital mortality in patients who underwent CDT with pulmonary infarction compared to those without, although patients with infarction had a longer length of stay and a higher rate of 30-day readmission for non-PE or CDT-related diagnoses. There remains a theoretical risk of increased bleeding

complications in the area of pulmonary infarction during catheter manipulation and local installation of thrombolytics, however, this was not demonstrated in our cohort.

Study Limitations

To the best of our knowledge, this study represented the largest cohort of patients with acute PE complicated by pulmonary infarction, however, there are several limitations in our study. Cases of pulmonary infarction were identified based on CT findings and there was no histological correlation to differentiate between true necrosis versus alveolar hemorrhage. Patients with conditions that led to pulmonary hypertension could have pre-existing parenchymal changes that resemble acute RV strain caused by PE. In those scenarios, it would be technically difficult to differentiate whether these CT features are related to pre-existing pulmonary hypertension itself, or the combination. Owing to the retrospective nature of this study, not all patients underwent CT imaging post-discharge, thus we were unable to comment on the precise timing of the resolution of pulmonary infarction. We acknowledge the fact that not all patients in our cohort had echocardiography, in particular, patients with low-risk PE when echocardiography was not deemed necessary to change management or patients with high-risk PE who expired prior to the completion of echocardiography. Other limitations included the retrospective, single-center nature of the data, which may be prone to selection bias.

In conclusion, pulmonary infarction was demonstrated on CT in nearly one-third of acute PE, and patients with infarction were younger, with fewer comorbidities, and more likely to present with pleuritic chest pain and hemoptysis. Overall, there was no difference in length of stay, in-hospital death, bleeding complication, and readmission rate between patients with and without infarction, and patients with infarction were less likely to require oxygen on discharge. The presence of pulmonary infarction did not correlate with poorer outcomes and should not be

considered a supporting factor nor a contraindication for advanced reperfusion therapy for PE.

Author contributions: KUL is the primary author, collected and analyzed the data, and is the guarantor of the article, taking responsibility for the integrity of the work as a whole from inception to the published article. OO and PR are responsible for the study concept and helped write the manuscript. RB, GC, VL, and JP reviewed the imaging studies and treated the patients who underwent catheter-directed thrombolysis. SB and BRL helped write the manuscript.

Conflict of interest: There are no financial or other conflicts of interest to disclose.

Ethics approval: This study was approved by the Institutional Review Board (Protocol #26021) at Temple University Hospital and informed consent was waived due to the retrospective nature of the study.

Patient consent for publication: Not required.

Funding statement: This study received no funding.

Data sharing statement: All data relevant to the study are included in the article or uploaded as supplementary information.

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Figure 1. Patient selection flow diagram.

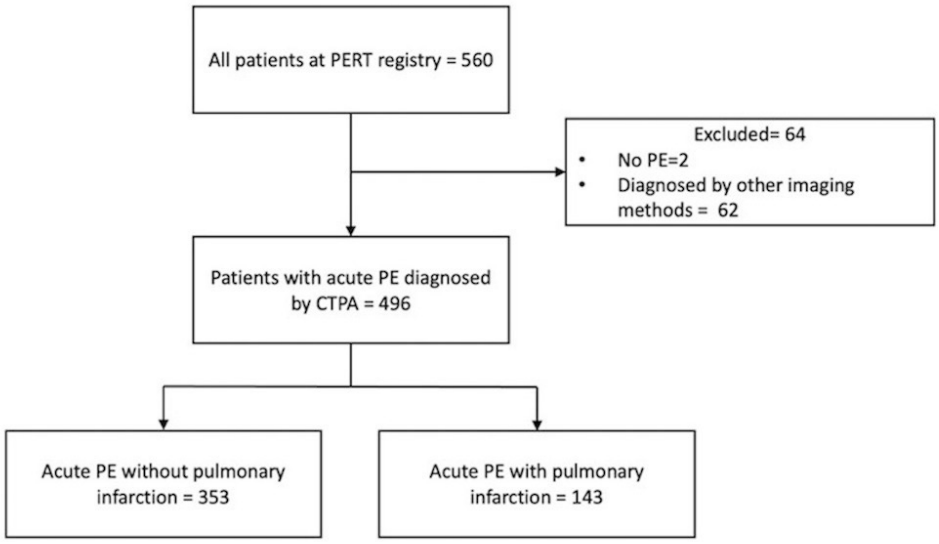

Figure 1. Patient selection flow diagram.

32x19mm (800 x 800 DPI)

Supplemental material, table 1. Treatment and outcomes between patients with and without infarction.

	All (496)	Without infarction (353)	With infarction (143)	P-value
Anticoagulation alone	357 (72%)	259 (73%)	98 (69%)	0.545
CDT	70 (14%)	53 (15%)	17 (12%)	0.365
Thrombolysis				0.212
Half dose	25 (5%)	15 (4%)	10 (7%)	
Full dose	14 (3%)	8 (2%)	6 (4%)	
Mechanical thrombectomy	19 (4%)	10 (3%)	9 (6%)	0.069
Surgical thrombectomy	9 (2%)	6 (2%)	3 (2%)	0.763
ECMO	11 (2%)	6 (2%)	5 (4%)	0.218
Mechanical ventilation	48 (10%)	30 (9%)	18 (13%)	0.163
Antimicrobials	39 (8%)	19 (5%)	22 (15%)	<0.001
In-hospital death	37 (8%)	27 (8%)	10 (7%)	0.801
Disposition				0.759
Home	349 (76%)	245 (75%)	104 (78%)	
ECF	100 (22%)	74 (23%)	26 (20%)	
Hospice	10 (2%)	7 (2%)	3 (2%)	
Length of stay, days	10±13.0	9.5±12.3	10.7±14.7	0.698
Bleeding complication				0.089
Minor bleeding	31 (6%)	25 (7%)	6 (4%)	
Major bleeding	32 (7%)	18 (5%)	14 (10%)	
Need for transfusion	63 (13%)	41 (12%)	22 (16%)	0.253
Readmission within 30 days	76 (16.6%)	52 (16%)	24 (18%)	0.584
New O2 on discharge	75 (16%)	61 (19%)	14 (11%)	0.031
Pulmonary follow-up	199 (42%)	144 (44%)	55 (40%)	0.610

CDT= catheter-directed thrombolysis; ECMO= extracorporeal membrane oxygenation; ECF= extended care facility

Supplemental material, table 2. Outcomes and complication rates in CDT.

	All (70)	Without infarction (53)	With infarction (17)	P-value
In-hospital death	4 (6%)	3 (6%)	1 (6%)	0.973
Disposition Home ECF	 57 (86%) 9 (14%)	 42 (84%) 8 (16%)	 15 (94%) 1 (7%)	0.436
Length of Stay	9±14.2	7±8.4	15±24.4	0.044
Readmission within 30 days	4 (6%)	1 (2%)	3 (18%)	0.047
New O2 on discharge	10 (16%)	8 (17%)	2 (12%)	0.609
Pulmonary follow-up	47 (72%)	38 (76%)	9 (56%)	0.166
Complications				
Bleeding Minor Major	 10 (14%) 5 (7%)	 8 (15%) 3 (6%)	 2 (12%) 2 (12%)	0.676
RBC transfusion	10 (14%)	7 (13%)	3 (18%)	0.649
Access site hematoma	3 (5%)	1 (2%)	2 (13%)	0.134

ECF= extended care facility; RBC= red blood cell

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	(a) Page 2, line 3-4 (b) Page 4	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1.1: Page 2, line 3-4 1.2: Page 2, line 3-4
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 6, line 5-35		
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 6, line 36-40		
Methods					
Study Design	4	Present key elements of study design early in the paper	Page 6		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 6, line 47- page 7, line 10		

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	Page 6, line 47- page 7, line 10	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	6.1: Page 6, line 47- page 7, line 10 6.2: not applicable 6.3: figure 1
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Page 7	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Page 7
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 7		

Bias	9	Describe any efforts to address potential sources of bias	Page 8, line 3-4		
Study size	10	Explain how the study size was arrived at	Page 9, line 5-10		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Page 7, line 17-54		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	Page 8, line 33-51		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	Page 6, line 47-page 7, line 10

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Not applicable
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	Page 9, line 5-10	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Page 9, line 5-10
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	Page 9, line 5-35; Page 10, line 29-44 Table 1 and 2		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure	Page 12, line 54 to Page 13 line 13 Table 4		

		category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 12, line 54 to Page 13 line 13 Table 4		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Page 12, line 54 to Page 13 line 13 Table 4		
Discussion					
Key results	18	Summarise key results with reference to study objectives	Page 14 line 36-55		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 17 line 5-36	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Page 17 line 5-36
Interpretation	20	Give a cautious overall interpretation of results considering objectives,	Page 17 line 38-53		

		limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 17 line 5-36		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 18 line 24		
Accessibility of protocol, raw data, and programming code		..	Page 18 line 26-27	RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Page 18 line 26-27

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.