

Pulmonary embolism in patients with interstitial lung disease admitted for acute respiratory worsening

Nimrod Urtreger

`nimrodo@tlvmc.gov.il`

Tel Aviv Ichilov-Sourasky Medical Center: Tel Aviv Sourasky Medical Center <https://orcid.org/0009-0006-8556-4383>

Noa Hallak

Tel Aviv Ichilov-Sourasky Medical Center: Tel Aviv Sourasky Medical Center

Ophir Freund

Tel Aviv Ichilov-Sourasky Medical Center: Tel Aviv Sourasky Medical Center

Ariel Melloul

Tel Aviv Ichilov-Sourasky Medical Center: Tel Aviv Sourasky Medical Center

Eyal Kleinhendler

Tel Aviv Ichilov-Sourasky Medical Center: Tel Aviv Sourasky Medical Center

Aviv Kupershmidt

Tel Aviv Ichilov-Sourasky Medical Center: Tel Aviv Sourasky Medical Center

Doron Cohn-Schwartz

Tel Aviv Ichilov-Sourasky Medical Center: Tel Aviv Sourasky Medical Center

Sharon Enghelberg

Tel Aviv Ichilov-Sourasky Medical Center: Tel Aviv Sourasky Medical Center

Amir Bar-Shai

Tel Aviv Ichilov-Sourasky Medical Center: Tel Aviv Sourasky Medical Center

Avraham Unterman

Tel Aviv Ichilov-Sourasky Medical Center: Tel Aviv Sourasky Medical Center

Research Article

Keywords: Interstitial lung disease, CT angiography, Prognosis, Pulmonary Embolism, Exacerbations

Posted Date: August 18th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-9801756/v1>

Abstract

Introduction: Acute respiratory worsening (ARW) in interstitial lung disease (ILD) is a critical clinical event with a broad differential diagnosis. Pulmonary embolism (PE) is a potential trigger, but its prevalence, predictors, and impact in this setting remain poorly defined.

Objective: To evaluate PE prevalence, clinical predictors, and prognostic significance in patients with ILD presenting with ARW.

Methods: This retrospective cohort study analyzed ILD patients admitted to a tertiary center (2017–2023) for ARW who underwent CT pulmonary angiography (CTA) within 72 hours. Data was retrieved using the MDCclone platform, including demographic, clinical, and laboratory variables. A non-ILD control group was matched based on age, sex, and smoking status.

Results: Of 2,564 ILD admissions, 439 were due to ARW, CTA was performed in 77 (17.5%). PE was diagnosed in 14 of these (18.2%). Conventional predictors (tachycardia, hypoxemia, elevated D-dimer, malignancy, and clinical signs of deep vein thrombosis) did not differ between PE-positive and PE-negative patients. In the setting of ARW in ILD, risk of PE was significantly elevated in never-smokers compared to current or former smokers (30.6% vs. 7.3%; OR 5.43; 95% CI 1.3–21.4) and was numerically higher compared to matched controls (18.2% vs. 11.9%, $p=0.11$). PE was not associated with short- or long-term survival difference.

Conclusion: PE was a frequent finding in ILD patients with ARW, particularly among never-smokers. Since conventional diagnostic markers and clinical prediction rules appear unreliable in this population, clinicians should maintain a low threshold for CTA to identify this potentially reversible contributor to respiratory deterioration.

Introduction

Acute exacerbation in interstitial lung diseases (ILD) is a critical clinical event associated with high morbidity and mortality (1–3). These episodes present a diagnostic challenge for clinicians, as the differential diagnosis is broad and includes infection, disease progression, heart failure, and thromboembolic disease. Despite the life-threatening nature of these deteriorations, management remains largely inconsistent and guided by individual clinician judgment rather than standardized, evidence-based algorithms (4).

Pulmonary embolism (PE) is a leading cause of global mortality, accounting for an estimated 50,000 to 100,000 deaths annually in the United States alone (5). It represents a significant, yet potentially under-recognized, contributor to respiratory failure (6, 7), particularly during acute respiratory deteriorations in ILD. This diagnostic uncertainty is reflected in clinical practice; international surveys indicate that only 34% of pulmonologists routinely perform CT angiography (CTA) to evaluate acute worsening in specific ILDs (4).

Existing literature on PE in ILD (8, 9) is limited by modest sample sizes, inclusion of cohorts restricted to patients who underwent diagnostic imaging for suspected PE, and the absence of appropriate control populations and outcome analyses. Moreover, most prior studies were not specifically designed to examine patients presenting with acute respiratory worsening (ARW), a clinically distinct and high-risk state in which timely identification of reversible causes is critical.

We therefore aimed to assess the prevalence of pulmonary embolism in ILD patients presenting with ARW, identify clinical predictors, and evaluate its prognostic impact.

Methods

Study population and design

This retrospective cohort study was conducted at Tel Aviv Sourasky Medical Center, a tertiary university-affiliated hospital, and was approved by the institutional review board (IRB # TLV-0561-23). Informed consent was waived due to the retrospective design.

We included all adult patients (aged > 18 years) with a known ILD diagnosis who were admitted to the emergency department (ED) between 2017 and 2023 for ARW and underwent chest CTA within 72 hours of presentation. Patients were allowed to be included in the study more than once if the interval between visits was at least one month. The study cohort was compared to a matched control group of non-ILD patients, as described below. Because ILD patients could contribute more than one admission, matching to controls was performed at the patient level, such that each control patient was included only once, thereby preserving independence of observations in the control cohort.

Data source, measurements, and variables

A preliminary list of all ILD patients who underwent CTA was extracted on February 25, 2024, using MDClone, a query platform that provides comprehensive patient-level data across a wide range of variables within a defined timeframe surrounding an index event. The list of ILD diagnoses used for the query is provided in Supplementary Table 1. Subsequently, individual electronic medical files were reviewed to assess appropriateness for study inclusion and to evaluate all study variables. Extracted variables included age, sex, presence of active malignancy (defined as diagnosis or treatment of malignancy within the past five years), history of venous thromboembolism (VTE), smoking history, use of anticoagulant medications, reason for ED presentation, CTA findings, pulmonary function test (PFT) results, vital signs, physical examination findings at presentation, and laboratory values at presentation, including D-dimer, troponin, and B-type natriuretic peptide (BNP) levels.

All CTA studies were reviewed, and the diagnosis of PE was confirmed by a board-certified radiologist, who also assessed its distribution (main, lobar, segmental, or sub-segmental).

Control Cohort

For comparison, a control cohort was generated from non-ILD patients who presented to the ED during the same study period and underwent CTA within 72 hours of admission. Patients with ILD, chronic obstructive pulmonary disease (COPD), or missing smoking history were excluded, as COPD has been associated with a higher prevalence of PE (10) and could confound group comparisons. Because matching was performed at the patient level, 268 control patients were matched to the 67 unique ILD patients who underwent CTA in a 4:1 ratio based on age, sex, and smoking status. These variables were selected because they are established determinants of PE risk (11–13). Matching was performed with researchers blinded to CTA findings.

Study Outcome Measures

The primary outcome measure was a diagnosis of PE on CTA performed within 72 hours of admission to the ED. Secondary outcomes included all-cause mortality and 30-day all-cause mortality. Mortality data were retrieved via MDClone, which sources this information directly from the Israeli national population registry. PE-related treatments and complications, including direct interventions, were also assessed.

Statistical Analysis

Normality was assessed using the Kolmogorov–Smirnov test. Continuous variables with a normal distribution are presented as mean ($\pm$ standard deviation) and were compared using the Student's t-test. Non-normally distributed variables are reported as median (interquartile range) and were compared using the Mann–Whitney–Wilcoxon test. Categorical variables were compared using the Chi-square test; however, when any expected cell count was less than 5, the Fisher's exact test was applied. Survival curves were generated using Kaplan–Meier (KM) analysis and compared using the log-rank test. A p-value < 0.05 was considered statistically significant. Survival analyses were performed at the patient level using unique individuals as some patients contributed more than one admission. All analyses were performed using IBM SPSS Statistics for Windows, version 29.0 (Armonk, NY: IBM Corp).

Results

Between 2017 and 2023, 2,564 ED admissions occurred among patients with established ILD. Of these, 439 admissions (17.1%) were attributed to ARW in 264 patients. CTA, within 72 hours of presentation, was performed in 77 cases (17.5%), representing 67 individual patients. Among these 77 admissions, 38 (49.4%) occurred in males, the median age was 75 years (69–79), and 54 (70.1%) had a non-IPF ILD diagnosis (Table 1, Figure 1). PE was identified in 14 admissions (18.2%, 95% CI 9.3–27.0%) in 14 patients. Of these, one event (7.1%) involved the main pulmonary artery, 3 (21.4%) involved a lobar artery, 7 (50.0%) involved segmental arteries, and 3 (21.4%) involved subsegmental arteries. Only one case had evidence for concurrent deep vein thrombosis (DVT). of which 11 cases (78.6%) involved segmental or more proximal emboli.

Associations with the presence of PE

Baseline characteristics of admissions with and without PE are summarized in Table 1. The median age was similar between groups (77 years [IQR 73–82] vs 75 years [IQR 63–79], $p=0.16$). There were no significant differences in ILD type, pulmonary function, history of VTE, active malignancy, and anticoagulant use.

Vital signs at presentation, including heart rate, systolic blood pressure, oxygen saturation, and body temperature, were also comparable between groups.

Median D-dimer levels were elevated in both groups and were numerically higher among admissions with PE (1.77 mg/L, IQR 1.46–3.51 vs 0.94 mg/L, IQR 0.62–1.52), although the difference did not reach statistical significance ($p=0.14$). BNP and troponin levels were also comparable between groups.

A higher proportion of never-smokers was observed among admissions with PE compared with those without PE (78.6% vs 39.6%, $p=0.01$), corresponding to an odds ratio of 5.43 (95% CI 1.3–21.4). When analyzed by smoking status, pulmonary embolism was identified in 11 of 36 never-smokers (30.6%) compared with 3 of 41 current or former smokers (7.3%).

Treatment and patient outcomes

All patients diagnosed with PE received therapeutic anticoagulation. One patient was already receiving anticoagulation at the time of presentation, while the remaining patients initiated treatment a median of 9 hours after presentation to the ED (IQR, 3–31 hours). One patient underwent catheter-directed thrombolysis.

Among the 67 unique patients who underwent CTA for ARW, the median follow-up time was 181 days (IQR, 46–348 days). During follow-up, 37 patients (55.2%) died, including 31 (56.4%) in the PE-negative group and 6 (46.2%) in the PE-positive group. There was no significant difference in overall survival (HR 0.76, 95% CI 0.31–1.8) or 30-day mortality (HR 1.95, 95% CI 0.5–7.6) (Figure 2) between the two groups. When the PE-positive group was compared with the entire cohort of ILD patients admitted with ARW, no significant differences were observed in either overall survival (HR 1.1, 95% CI 0.5–2.4) or 30-day mortality (HR 1.4, 95% CI 0.5–3.8) (Figure 3).

Prevalence of PE in matched controls

To further explore the relevance of PE in ILD patients, the study cohort was compared with a matched control group, as described in the methods. The control cohort included 50.7% females, 43.3% never-smokers, and had a mean age of 72.1 years (± 11.2) (Table 2). PE was diagnosed in 32 control patients (11.9%, 95% CI 8.0-15.8%), a prevalence lower than that observed among ILD patients (18.2%), although this difference did not reach statistical significance ($p = 0.11$).

Table 1, Baseline Characteristics of PE positive vs negative groups.

Variable		Total (77)	PE negative (63)	PE positive (14)	P value
Male (%)		38 (49.4)	30 (47.6)	8 (57.1)	0.52
Age (median)		75 (69-79)	75 (63-79)	77 (73-82)	0.16
Diagnosis (%)	Unclassifiable	24 (31.2)	20 (31.7)	4 (28.6)	0.79
	IPF	23 (29.9)	17 (27.0)	6 (42.9)	
	CTD-ILD	13 (16.9)	11 (17.5)	2 (14.3)	
	HP	6 (7.8)	5 (7.9)	1 (7.1)	
	Others	11 (14.2)	10 (15.9)	1 (7.1)	
D-dimer (mg/L)		1.0 (0.69-1.77)	0.94 (0.62-1.52)	1.77 (1.46-3.51)	0.14
Troponin-I (ng/L)		10 (6-72.5)	10 (6-47)	17 (5.5-94)	0.46
BNP (pg/ml)		117 (43-239)	88 (42.5-254)	140 (117-193)	0.5
Systolic Blood Pressure (mmHg)		138 ($\pm$ 25)	139 ($\pm$ 25)	134 ($\pm$ 24)	0.47
*SpO2 %		90 (84-95)	90.5 (83-96)	91 (84-94)	0.62
Body temperature (°C)		36.7 (36.5-37.1)	36.7 (36.5-37.1)	36.65 (36.5-36.9)	0.63
Heart rate (BPM)		89 ($\pm$ 16)	88 ($\pm$ 16)	93 ($\pm$ 19)	0.35
Signs of DVT on physical exam (%)		1 (1.3)	0 (0)	1 (7.1)	0.18
DLCO (%)		44.9 ($\pm$ 17.2)	44.6 ($\pm$ 16.4)	46.6 ($\pm$ 24.7)	0.82
FVC (%)		66.4 ($\pm$ 14.6)	66.3 ($\pm$ 14)	67.0 ($\pm$ 17)	0.9
Previous VTE (%)		4 (5.2)	3 (4.8)	1 (7.1)	0.72
Never Smoker (%)		36 (46.7)	25 (39.6)	11 (78.6)	0.01
Active Malignancy (%)		17 (22.0)	14 (22.2)	3 (21.4)	0.95
On Anticoagulation (%)		5 (6.5)	4 (6.3)	1 (7.1)	0.9

* Measured in room air. Abbreviations: BPM, beats per minute; BNP, Brain natriuretic peptide; CTD, Connective tissue disease; DLCO, diffusing capacity of the lungs for carbon monoxide; DVT, Deep vein

thrombosis; FVC, Forced vital capacity; HP, hypersensitivity pneumonitis; ILD, Interstitial lung disease; IPF, idiopathic pulmonary fibrosis; PE, pulmonary embolism.

Table 2, Comparison of baseline characteristics between control cohort and study population.

Variable	Study population (n=67)	Matched control (n=268)	P value
Age	71.9 (±11.3)	72.1 (±11.2)	0.92
Female	50.7 (n=34)	50.7 (n=136)	1
Never smokers	43.3 (n=29)	43.3 (n=116)	0.8

Discussion

Acute respiratory worsening in ILD represents a high-risk clinical scenario in which identifying reversible triggers is critical. In this study, we evaluated the prevalence and risk factors of PE in patients with ILD presenting with ARW. Among 77 ED admissions in which CTA was performed, the prevalence of PE was 18.2%. Although this figure was not statistically higher than that observed in matched non-ILD controls, it remains substantially higher than reported rates in the general population (14, 15), underscoring PE as a clinically relevant and potentially under-recognized contributor to acute deterioration in ILD.

Previous studies evaluating PE in ILD have been limited by small cohorts, cohorts restricted to patients who underwent diagnostic imaging for suspected PE, and lack of control groups or outcome analyses (8, 9). Our study extends this literature by focusing specifically on ILD patients with ARW, incorporating a matched control cohort, and examining survival outcomes.

The elevated prevalence of PE among ILD patients may be explained by several mechanisms. Systemic inflammation, which is characteristic of certain ILDs such as CTD-ILD (16) or sarcoidosis (17), may contribute to a prothrombotic state. Additionally, elevated levels of procoagulant factors, including factor VIII, and increased platelet activation described in IPF (18), may further predispose these patients to thromboembolic events. Reduced mobility and deconditioning among ILD patients (19, 20) may also play a role in increasing PE risk.

Interestingly, traditional clinical and laboratory predictors of PE, such as signs of DVT, tachycardia, hypoxemia, elevated D-dimer levels, prior VTE, or a history of malignancy (21–23) did not discriminate between PE-positive and PE-negative ILD patients in our cohort. This lack of diagnostic discrimination is likely multifactorial. Many ILD patients already exhibit baseline hypoxemia, and elevated D-dimer levels due to chronic inflammation or tissue injury, thereby limiting the specificity of these findings for PE. In our cohort, median D-dimer levels were elevated even among PE-negative patients, consistent with previous studies showing increased D-dimer concentrations in patients with interstitial lung abnormalities (24). This may reflect systemic inflammation (25) or heightened activation of coagulation

and fibrinolytic pathways, as described in IPF (18). These findings suggest that commonly used clinical prediction rules [e.g., Wells score (26), PERC (27)] may be unreliable in ILD, supporting a lower threshold for imaging in this population.

Another possible explanation for the low prevalence of DVT signs and the absence of traditional clinical predictors of PE in our cohort is that these cases may represent in situ pulmonary thrombosis rather than classic embolic disease originating from peripheral deep veins. This mechanism has previously been proposed in other forms of acute pulmonary injury and respiratory deterioration, including COPD exacerbations (28, 29) and chest trauma (29, 30), in which pulmonary vascular inflammation, endothelial injury, local hypoxia, and activation of coagulation pathways may promote thrombosis directly within the pulmonary circulation (29). Such a process could explain the very low prevalence of concomitant DVT in our cohort, the lack of association with traditional thromboembolic risk factors, and the absence of a clear mortality signal. In this context, pulmonary thrombosis may represent a marker of acute inflammatory or vascular injury accompanying respiratory worsening, rather than the primary driver of clinical deterioration.

Our analysis revealed a novel and somewhat unexpected finding: never-smokers with ILD who experienced ARW had a significantly higher prevalence of PE compared to current or former smokers (30.6% vs. 7.3%, respectively). This association corresponded to a more than fivefold increase in the odds of PE (OR 5.43; 95% CI 1.3–21.4). This contrasts with studies in the general population, where smoking is typically identified as a risk factor for PE (31, 32). A possible explanation for this discrepancy is that acute respiratory symptoms in smokers may often be attributed to other conditions, such as COPD, pneumonia (33) or heart failure (34), given the higher prevalence of these comorbidities in smokers. Given our data, PE should be suspected in never-smokers with ILD presenting with ARW.

Contrary to other clinical contexts such as cancer, COPD, or ischemic stroke (35–39), PE was not associated with increased short- or long-term mortality in our cohort. This likely reflects the already poor prognosis associated with acute exacerbations of certain ILDs, particularly IPF, where in-hospital mortality can exceed 50% (40). Consistent with this, the all-cause mortality rate in our study was 55.2% over a median follow-up of 181 days (IQR, 46–348). Nevertheless, the absence of a survival signal should not diminish the clinical importance of PE detection, as anticoagulation may improve outcome, and prevent recurrent thromboembolic events and long-term complications such as post-PE syndrome and chronic thromboembolic pulmonary hypertension (41, 42).

This study has several limitations. The retrospective single-center design limits generalizability, and only a subset of patients underwent CTA, potentially introducing selection bias. The relatively small number of PE events limited statistical power to detect differences in outcomes. Additionally, heterogeneity among ILD subtypes may have obscured disease-specific risk patterns. Finally, follow-up duration varied, which may have influenced long-term outcome assessment. Future prospective, multicenter studies with larger sample sizes are needed to confirm these results and clarify the prognostic implications of PE in ILD.

In conclusion, pulmonary embolism is a frequent and clinically relevant finding among patients with ILD presenting with ARW. Because traditional clinical predictors appear unreliable in this population, clinicians need to have a low threshold for performing CTA when evaluating ARW in ILD. These findings highlight the need for ILD-specific diagnostic algorithms and prospective studies to optimize management of acute respiratory deterioration in this vulnerable population.

Declarations

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest

Dr. Avraham Unterman reports receiving research funding from Boehringer Ingelheim and Abbvie, and personal consulting fees from Boehringer Ingelheim, Kamada, GSK, Splisense, and Metasight within the last 36 months, all outside the submitted work.

Dr. Amir Bar-Shai reports receiving personal consulting fees and lecture fees from Sanofi-Regeneron, Astrazeneca, GSK, Kamada, Boehringer Ingelheim and Roche within the last 36 months, all outside the submitted work.

The remaining authors declare that they have no conflict of interest.

Ethics Approval

This study was approved by the Institutional Review Board of the Tel Aviv Sourasky Medical Center (IRB # TLV-0561-23).

Consent to Participate

Informed consent was waived by the Institutional Review Board due to the retrospective nature of the study design.

Availability of Data and Materials

The data analyzed in this study were retrieved using the MDClone platform at Tel Aviv Sourasky Medical Center. Due to institutional regulations and patient privacy restrictions, the dataset is not publicly available but may be made available from the corresponding author upon reasonable request.

Author Contributions

N.U., N.H., and A.U.: Conceived and designed the study.

N.U., N.H., A.M., O.F., E.K., A.K., D.C.S., and S.E. Collected the data.

N.U., N.H., O.F., and A.U.: Performed data analysis and interpretation.

A.U. and A.B.S.: Provided guidance throughout the experimental design and data interpretation.

A.U.: Critically revised the manuscript for important intellectual content.

All authors: Reviewed and approved the final version of the manuscript for submission.

Prior presentation:

This work was previously presented in a poster format at the 2024 European Respiratory Society Congress.

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Figures

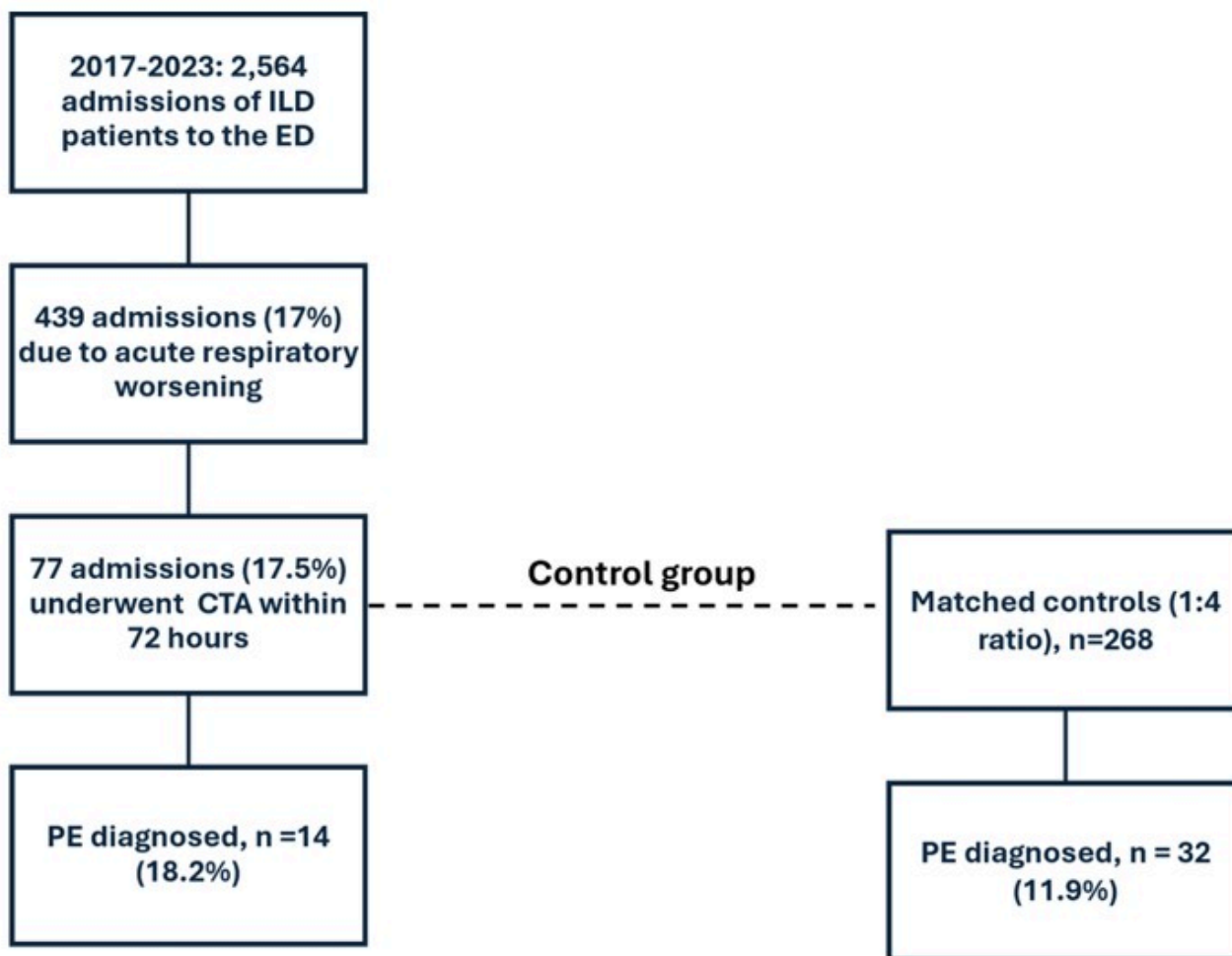


Figure 1

flowchart of the study design. Abbreviations: CTA, CT angiography; ED, emergency department; ILD, interstitial lung disease; PE, pulmonary embolism.

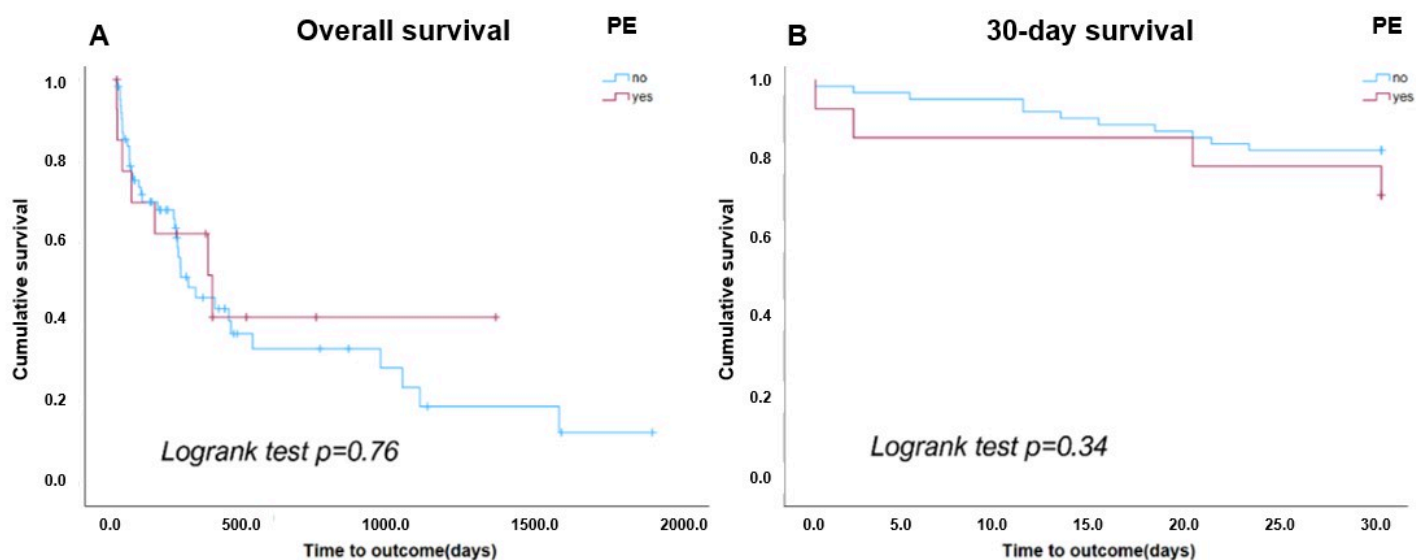


Figure 2

Kaplan-Meier curves for (A) overall survival and (B) 30-day survival comparing interstitial lung disease patients who underwent CT angiography within 72 hours of admission, with (N=14) and without (N=53) pulmonary embolism (PE).

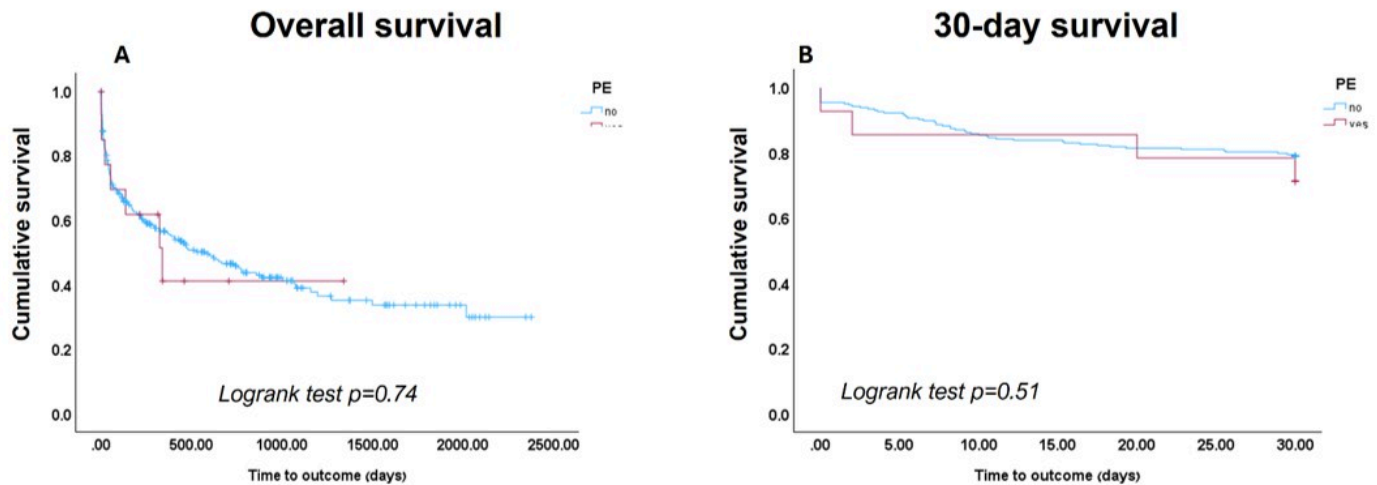


Figure 3

Kaplan-Meier curves for (A) overall survival and (B) 30-day survival among patients with interstitial lung disease presenting with acute respiratory worsening, comparing patients diagnosed with pulmonary embolism (PE) within 72 hours of admission (N=14) with all remaining patients without PE (N=250), including those who did not undergo CT angiography.

Supplementary Files

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