Clinical and imaging outcomes after intermediate- or high-risk pulmonary embolus

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Abstract

Long-term outcomes after acute pulmonary embolism vary from complete resolution to chronic thromboembolic pulmonary hypertension (CTEPH). Guidelines after acute pulmonary embolism are generally limited to anticoagulation duration. We assessed patients with estimated prognosis > 1 year in our pulmonary hypertension clinic 2–4 months after treatment for intermediate- or high-risk acute pulmonary embolism. At follow-up, ventilation-perfusion scan and echocardiogram were offered. The aim of this study was to assess for recurrent symptomatic disease, residual imaging defects or right ventricular dysfunction, and functional disability after acute management of pulmonary embolism. After treatment for acute intermediate- or high-risk pulmonary embolism, 104 patients followed up in pulmonary hypertension clinic. Of those, 55% of patients had self-reported limitation in activity. No patients had symptomatic recurrence of pulmonary embolism. Forty-eight percent of patients had residual perfusion defects on perfusion imaging, while 91% of patients had either normal or only mildly enlarged right ventricles. We identified heart failure preserved ejection fraction, iron deficiency, and obstructive sleep apnea as significant contributors to breathlessness. Treatment of these conditions was associated with improvement. Surprisingly, we diagnosed CTEPH in nine patients; for some, chronic thrombus may have already been present at the time of index evaluation. Our findings suggest that follow-up in a dedicated pulmonary hypertension clinic 2–4 months after acute intermediate- or high-risk pulmonary embolism may add value to patient care. We identified treatable comorbidities that could be contributing to post-pulmonary embolism syndrome as well as CTEPH.

Keywords
pulmonary embolism, pulmonary hypertension, anticoagulants

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In the last decade, pulmonary embolus response teams (PERT) have more frequently managed acute pulmonary embolism (PE). They have variable functions across institutions, but the ultimate goal is to improve short-term outcomes in intermediate- or high-risk PE.1 PERT may shorten time to the initiation of anticoagulation2 and often provides expert input regarding advanced therapies3 (systemic thrombolysis,4 catheter-directed interventions,5,6 ECMO,7 surgical embolectomy3). Despite the use of more aggressive therapies, there has not been a clear decrease in hospital mortality,3 as co-morbidities (i.e. advanced malignancy) are sometimes the reason for short-term mortality. The impact of multidisciplinary management on acute PE in terms of disease recurrence, residual right ventricular...
dysfunction, and post-PE syndrome/quality of life is not known.

Previously reported data evaluating function (post-PE syndrome), residual perfusion defects, and chronic thromboembolic pulmonary hypertension (CTEPH) after any acute PE (not just intermediate or high risk) were acquired when acute treatment consisted primarily of anticoagulation alone and without multidisciplinary input. With more advanced therapies recommended by PERT to treat acute intermediate- or high-risk PE, it is of interest to follow outcomes after hospital discharge. Thus, the aim of this study was to determine the rate of clinical thromboembolic recurrence, functional disability (post-PE syndrome), and residual right ventricular dysfunction 2–4 months after treatment for acute intermediate- or high-risk PE in the era of multidisciplinary management.

**Methods**

This was an initially retrospective and subsequently prospective observational cohort study evaluating imaging and clinical outcomes, including the rate of thromboembolic recurrence, at a follow-up visit 2–4 months after management for an intermediate- or high-risk PE between November 2016 (PERT was initiated at this time) and June 2019. The study protocol was approved by the local Institutional Review Board. Beginning in August 2017, at the time of hospital discharge for an acute intermediate- or high-risk PE, patients with prognosis >1 year (based on the assessment of the discharging physician) were offered follow-up at our Pulmonary Hypertension Association accredited Comprehensive Care Center. We scheduled a ventilation–perfusion (V/Q) scan, echocardiogram, and office visit to assess for PE resolution and clinical indications of treatment failure. Acute diagnosis of PE with an elevated cardiac biomarker (troponin or NT-pro BNP) or signs of right ventricular dysfunction on imaging (CT or echocardiogram) without shock or hypotension was classified as intermediate risk. Acute diagnosis of PE with shock or hypotension in the setting of right ventricular dysfunction or elevated cardiac biomarker was classified as high risk.

PE location on initial CT angiogram was classified as the most proximal clot was identified. V/Q scans were performed using 30 mCi of aerosolized Tc-99 m-DTPA followed by intravenous administration of 2–4 mCi Tc-99 m-MAA. Residual clot was defined as mismatched or partly mismatched segmental V/Q defects. Thirty random V/Q scans were blindly evaluated to evaluate inter-reader reliability. Board certified cardiologists interpreted echocardiograms, and we abstracted data from the reports focusing on the right ventricular size and function. Right ventricular size was estimated based on the size relative to the left ventricle (RV/LV): normal RV/LV ratio <0.5, mildly enlarged RV/LV ratio 0.5–0.75, moderately enlarged RV/LV ratio 0.75–1, and severely enlarged RV/LV ratio >1. Right ventricular function was estimated based on TAPSE (>2 cm normal) in combination with visual estimate of both circumferential and longitudinal RV contraction. The short axis was evaluated for evidence of pressure overload. With the limitations associated with echocardiogram and inter-reader variability both right ventricular size and function were categorized as either normal/mild or moderate/severe. For histopathology, thromboemboli were formalin fixed and processed for light microscopy in the hospital histopathology laboratory. Four micron-thick sections were stained with hematoxylin and eosin, Masson trichrome, and Verhoeff elastic tissue stains; they were also immunostained with anti-CD31 to identify endothelial cells using an automated stainer according to the manufacturer’s protocol (DAKO Omnis with Flex Detection, DAKO Corp. Cupertino, CA). Slides were independently evaluated for time-dependent microscopic changes by two pathologists. The PH physicians made clinical and functional assessments. In patients who were still symptomatic with self-limited activity, fatigue, dyspnea, or edema, we evaluated for sleep apnea, heart failure with preserved ejection fraction (HFrEF), and iron deficiency (defined by FAIR-HF and CONFIRM-HF) as part of our standard of care assessment. Using a standardized clinical approach once patients were optimized in regards to apparent volume status, we referred those in whom we expected pre-capillary pulmonary hypertension (PH) for right heart catheterization (RHC) to assess for CTEPH after at least three months of anticoagulation. Patients were classified as having CTEPH based on the hemodynamic definition of PH at the 5th World Symposium. Patients were classified as having “likely CTEPH” if the clinical assessment suggested CTEPH but patients declined catheterization for sensible reasons like advanced neurologic disease.

**Statistical analysis**

Categorical variables are expressed as median and interquartile range, while discrete variables are expressed as counts with proportion. Linear and logistic regression analyses were performed using SAS 9.4.

**Results**

Of 362 patients evaluated by PERT during the observation period (Fig. 1), 104 patients followed up in our PH clinic 2–4 months after management of acute intermediate- or high-risk PE with the demographics and presentation shown in Tables 1 and 2. Proximal thrombotic disease (saddle or main pulmonary artery) on CT angiography was treated with anticoagulation alone in 44 patients, while 25 patients underwent more advanced therapies. Similarly, 17 patients with severe right ventricular enlargement were treated with anticoagulation alone and the other 15 patients underwent advanced therapies. All of the embolectomy specimens had a histologically estimated age of at least three days based on
Table 1. Baseline characteristics of patients with intermediate- or high-risk PE.

| Demographics                  | Total (n = 104) | Intermediate low risk (n = 5) | Intermediate high risk (n = 87) | High risk (n = 12) |
|-------------------------------|----------------|-----------------------------|--------------------------------|-------------------|
| Age (yrs)                     | 60 (47, 72)    | 73 (56, 80)                 | 60 (47, 71)                     | 61 (50, 70)       |
| Male                          | 57 (55%)       | 3 (60%)                     | 53 (61%)                       | 1 (8%)            |
| Caucasian                     | 82 (79%)       | 5 (100%)                    | 68 (78%)                       | 9 (75%)           |
| BMI (kg/m²)                   | 34 (28, 41)    | 31 (28, 42)                 | 34 (28, 42)                    | 33 (28, 37)       |
| BMI >40 kg/m²                 | 29 (%)         | 1 (20%)                     | 27 (31%)                       | 1 (8%)            |
| Underlying disease            |                |                             |                                |                   |
| Active smoking                | 12 (%)         | 1 (20%)                     | 9 (10%)                        | 2 (17%)           |
| CAD                           | 9 (8%)         | 0 (9%)                      | 8 (9%)                         | 1 (8%)            |
| CKD >II                       | 4 (4%)         | 1 (20%)                     | 3 (3%)                         | 0                 |
| Atrial fibrillation           | 9 (9%)         | 1 (20%)                     | 7 (8%)                         | 1 (8%)            |
| Diabetes                      | 24 (23%)       | 2 (40%)                     | 20 (%)                         | 2 (17%)           |
| Hypertension                  | 60 (58%)       | 5 (100%)                    | 51 (59%)                       | 4 (33%)           |
| Risk factors                  |                |                             |                                |                   |
| Splenectomy                   | 6 (6%)         | 0                           | 4 (5%)                         | 2 (17%)           |
| Hypothyroidism                | 15 (14%)       | 2 (40%)                     | 13 (15%)                       | 0                 |
| Obstructive sleep apnea*      | 41 (39%)       | 2 (40%)                     | 37 (43%)                       | 2 (17%)           |
| Provoked                      | 34 (33%)       | 1 (20%)                     | 29 (33%)                       | 4 (33%)           |
| Post-operative                | 22 (21%)       | 1 (20%)                     | 17 (20%)                       | 4 (33%)           |
| Active malignancy             | 7 (7%)         | 1 (20%)                     | 6 (7%)                         | 0                 |
| Prior VTE                     | 23 (22%)       | 1 (20%)                     | 19 (22%)                       | 3 (25%)           |
| Confirmed thrombophilia labs* | 4 (4%)         | 0                           | 4 (5%)                         | 0                 |

BMI: body mass index; CAD: coronary artery disease; CKD: chronic kidney disease; PE: pulmonary embolism; VTE: venous thromboembolism.

*Diagnosis made prior to presentation or after.
microscopic changes of neutrophil nuclei; 9/16 had evidence of early organization, i.e., endothelial ingrowth and/or focal collagenization, and 4/16 had recanalization present. These findings were observed prior to treatment with anticoagulation. At discharge, 65% of the entire cohort were prescribed a direct oral anticoagulant (DOAC; Table 2).

**Functional assessment at follow-up**

Fifty-seven (55%) patients reported self-limited activity because of fatigue or breathlessness post PE (Table 3). Twenty-three patients (40%) had underwent an advanced therapy. Twenty-six patients (46%) had a normal perfusion

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**Table 2. Clinical information at admission.**

|                  | Total (n = 104) | Intermediate low risk (n = 5) | Intermediate high risk (n = 87) | High risk (n = 12) |
|------------------|-----------------|------------------------------|--------------------------------|--------------------|
| **Treatment**    |                 |                              |                                |                    |
| Anticoagulation alone | 74 (71%)       | 5 (100%)                     | 69 (79%)                       | 0                  |
| Systemic thrombolysis | 8 (8%)          | 0                            | 4 (5%)                         | 4 (33%)            |
| Catheter-directed lysis | 6 (6%)          | 0                            | 4 (5%)                         | 2 (17%)            |
| Surgical embolectomy    | 16 (15%)        | 0                            | 10 (11%)                       | 6 (50%)            |
| Peak HR (BPM)         | 112 (96, 123)   | 107 (82, 124)                | 110 (95, 121)                  | 120 (113, 137)     |
| **Signs/Symptoms**    |                 |                              |                                |                    |
| Symptoms duration (days) | 2 (1.7)         | 2 (1.4)                      | 3 (1.10)                       | 1 (1.3)            |
| Cardiac arrest        | 3 (3%)          | 0                            | 0                              | 3 (25%)            |
| Chest pain            | 44 (43%)        | 3 (60%)                      | 36 (41%)                       | 5 (42%)            |
| Syncope               | 21 (20%)        | 0                            | 17 (20%)                       | 4 (33%)            |
| Presyncope            | 28 (27%)        | 1 (20%)                      | 22 (25%)                       | 5 (42%)            |
| Dyspnea               | 91 (88%)        | 5 (100%)                     | 77 (89%)                       | 9 (75%)            |
| Hypoxia               | 65 (63%)        | 5 (100%)                     | 52 (60%)                       | 8 (66%)            |
| **Laboratory**        |                 |                              |                                |                    |
| NT-pro BNP (pg/mL)    | 1161 (380, 3385) | 873 (339, 1130)              | 1141 (293, 3530)               | 2090 (1222, 9083)  |
| Troponin (ng/mL)      | 0.05 (0.01, 0.15) | 0.01 (2)                     | 0.08 (0.01, 0.145)             | 0.03 (0.01, 0.19)  |
| Troponin high sensitivity (ng/L) | 56 (30, 131) | 17 (14, 17) | 52 (30, 107) | 210 (68, 382) |
| **CT imaging**        |                 |                              |                                |                    |
| Saddle               | 38 (38%)        | 1 (20%)                      | 29 (35%)                       | 8 (73%)            |
| Main                 | 31 (31%)        | 2 (40%)                      | 29 (35%)                       | 0                  |
| Lobar                | 28 (28%)        | 2 (40%)                      | 23 (26%)                       | 3 (27%)            |
| Segmental            | 2 (2%)          | 0                            | 2 (4%)                         | 0                  |
| Right heart enlargement | 83 (83%)       | 0                            | 74 (89%)                       | 9 (82%)            |
| **Echocardiogram**    |                 |                              |                                |                    |
| Right ventricular enlargement Moderate/Severe | 67 (66%) | 0 | 56 (65%) | 11 (100%) |
| Mild/None            | 35 (34%)        | 4 (100%)                     | 31 (35%)                       | 0                  |
| Right ventricular dysfunction Moderate/Severe | 64 (63%) | 0 | 53 (61%) | 11 (100%) |
| Mild/None            | 38 (37%)        | 4 (100%)                     | 34 (39%)                       | 0                  |
| Echo estimated RVSP (mmHg) | 49 (38, 57) | 36 (33, 42) | 49 (40, 57) | 51 (36, 61) |
| Left ventricular ejection fraction (%) | 65 (62, 72) | 64 (61, 76) | 65 (62, 71) | 65 (64, 75) |
| Confirmed DVT on ultrasound | 59 (61%) | 4 (80%) | 48 (59%) | 7 (70%) |
| Hospitalization duration (days) | 4 (3.8) | 6 (3.7) | 4 (3.8) | 13 (5.19) |
| DOAC prescribed on discharge | 68 (65%) | 2 (40%) | 58 (67%) | 8 (66%) |

BPM: beats per minute; DOAC: direct oral anticoagulant; DVT: deep vein thrombosis; HR: heart rate; NT-pro BNP: N-terminal pro-B-type natriuretic peptide; RVSP: right ventricular systolic pressure.

1Twenty-four patients had troponin T checked.
2Forty-nine patients had high sensitivity troponin checked.
3Fifty-four patients had estimated RVSP measured.
4Ninety-six patients had lower extremity ultrasound performed.
imaging, and 13 patients (23%) had both normal perfusion imaging and echocardiogram. Of the 13 patients with self-limited activity and normal follow-up imaging we identified iron deficiency in five patients, decompensated heart failure in six patients, and suspicion for obstructive sleep apnea (OSA) in five patients. Ultimately, we had four patients we could not identify any pathologic reason for breathlessness and the etiology was felt to be due to deconditioning in combination with obesity. Thirty-one patients (54%) had breathlessness with abnormal perfusion imaging. After excluding patients with CTEPH, we identified iron deficiency in eight patients, decompensated heart failure in 16 patients, and clinical concern for OSA in 17 patients.

Interestingly, we also found four patients with abnormal perfusion imaging without other etiologies contributing to breathlessness we classified as chronic thromboembolic disease. Unadjusted logistic regression analysis showed patients treated with surgical embolectomy (OR = 4.14, 95% CI 1.10–15.57, p = 0.03), hospital duration (OR = 1.11, 95% CI 1.011–1.23, p = 0.02), obese patients (OR = 3.05, 95% CI 1.34–6.92, p = 0.008), patients with deep vein thrombosis (DVT) at the time of diagnosis (OR = 3.26, 95% CI 1.38–7.70, p = 0.007), and decompensated heart failure at follow-up (OR = .25, 95% CI 1.73–30.38, p = 0.0067) were associated with patients reporting self-limitations in activity at follow-up. A multivariate logistic regression analysis showed obese patients (OR = 4.13, 95% CI 1.20–16.72, p = 0.04) and decompensated heart failure at follow-up (OR = 6.36, 95% CI 1.41–28.73, p = 0.01) were associated with patients reporting self-limitation in activity at follow-up. We did not find increased clot burden at presentation, residual perfusion defects on follow-up V/Q imaging, or echocardiogram findings at follow-up were associated with self-reported limitations.

### Table 3. Clinical information at PH clinic follow-up.

|                    | Total (n = 104) | Intermediate low risk (n = 5) | Intermediate high risk (n = 87) | High risk (n = 12) |
|--------------------|----------------|------------------------------|-------------------------------|-------------------|
| Oxygen saturation at rest (%) | 97 (96, 98) | 96 (95, 97) | 97 (96, 98) | 97 (95, 98) |
| Supplemental oxygen | 6 (6%) | 2 (40%) | 4 (5%) | 0 |
| Self-limiting activity | 57 (55%) | 3 (46%) | 46 (53%) | 8 (75%) |
| 6-Minute walk distance (m) | 395 (305, 468) | 298 (220, 316)* | 399 (329, 482) | 376 (168, 404)* |
| HfPEFa | 55 (53%) | 3 (60%) | 48 (55%) | 4 (33%) |
| Decompensated heart failurea | 38 (67%) | 2 (67%) | 32 (67%) | 4 (100%) |
| Iron deficiencyb | 30 (29%) | 2 (40%) | 22 (25%) | 6 (50%) |
| New OSA diagnosis at follow-up | 21 (20%) | 0 | 19 (25%) | 2 (%) |
| Sleep study recommended but not completed | 23 (22%) | 1 (20%) | 17 (20%) | 5 (42%) |
| NT-Pro BNP follow-upd | 118 (50, 349) | 648* | 110 (50, 191) | 141 (70, 312) |
| Echocardiogram | N = 103 | N = 5 | N = 86 | N = 12 |
| RV enlargement | None/Mild | 94 (91%) | 5 (100%) | 77 (90%) | 12 (100%) |
| Moderate/Severe | 9 (9%) | 0 | 9 (10%) | 0 |
| RV dysfunction | None/Mild | 99 (96%) | 5 (100%) | 82 (95%) | 12 (100%) |
| Moderate/Severe | 4 (4%) | 0 | 4 (5%) | 0 |
| Normal RV size and function on echo | 57 (62%) | 5 (100%) | 43 (50%) | 7 (58%) |
| Perfusion defect on V/Qc | 48 (48%) | 1 (20%) | 39 (47%) | 8 (67%) |
| Normal V/Q and echo | 30 (29%) | 4 (80%) | 22 (27%) | 4 (33%) |
| RHC | 12 (12%) | 1 (20%) | 11 (13%) | 0 |
| Confirmed CTEPHe | 9 (9%) | 0 | 8 (9%) | 0 |
| Likely CTEPH | 11 (11%) | 0 | 6 (7%) | 5 (42%) |
| Total CTEPHf | 20 (19%) | 0 | 14 (16%) | 5 (42%) |

CTEPH: chronic thromboembolic pulmonary hypertension; HfPEF: heart failure with preserved ejection fraction; NT-Pro BNP: N-terminal pro-B-type natriuretic peptide; OSA: obstructive sleep apnea; PH: pulmonary hypertension; RHC: right heart catheterization; RV: right ventricle; V/Q: ventilation-perfusion.

*Clinical diagnosis.

bCriteria from FAIR-HF and CONFIRM-HF.

cOne hundred patients underwent V/Q testing (3 patients in the heparin group and 1 embolectomy patient did not have testing).

dFifty-three patients underwent NT-pro BNP testing.

eOne intermediate high-risk patient was directly referred to a CTEPH center and diagnosed and treated for CTEPH.
Chronic thromboembolic pulmonary hypertension

At follow-up, 10 patients had symptoms and imaging (echocardiogram and V/Q) concerning for CTEPH, prompting RHC with angiography after three months of anticoagulation. Of those, eight studies confirmed CTEPH (Table 4). We directly referred an additional patient with concerning imaging and symptoms for pulmonary thromboendarterectomy shortly after hospital discharge, yielding a total of nine patients with CTEPH. Two patients with normal perfusion scans underwent RHC with concern for Group 1 pulmonary arterial hypertension and both had normal resting hemodynamics. We also recommended RHC and angiography in six patients who have thus far declined testing and five patients who have permanently declined testing because of severe cognitive impairment. If we consider eight of those patients as likely having CTEPH based on our confirmation rate, we estimate a prevalence of \( \sim 16{\%} \) (17–20 patients) with presumed CTEPH after intermediate- or high-risk PE (Table 3). Unadjusted logistic regression showed echocardiogram estimated right ventricular systolic pressure on admission (OR \( = 1.100, 95\% \text{ CI } 1.036–1.167, p = 0.0017 \)) and duration of symptoms (OR \( = 1.15, 95\% \text{ CI } 1.072–1.239, p = 0.0001 \)) were associated with RHC confirmed CTEPH. Multivariate logistic regression showed duration of symptoms (OR \( = 1.093, 95\% \text{ CI } 1.005–1.19, p = 0.039 \)) and echocardiogram estimated right ventricular systolic pressure on admission (OR \( = 1.072, 95\% \text{ CI } 1.003–1.145, p = 0.04 \)) were associated with RHC confirmed CTEPH. Because of the histology findings at embolectomy and the lack of clinical response to thrombolytics in two cases, we suspect some of these patients already had chronic disease at the time of initial presentation.

Residual V/Q defects

One hundred patients underwent V/Q testing at follow-up, and we identified 48 patients (48%) with residual perfusion defects (19 of these 48, 40%, with likely CTEPH; Table 3). The use of advanced therapies, clot burden on admission chest imaging, or type of anticoagulation prescribed at discharge were not associated with normal V/Q imaging at follow-up. In 30 images that were blindly reviewed by a nuclear medicine radiologist (VC), we found four scans that were initially read as normal perfusion to have evidence of mild patchy perfusion defects. No patients who were identified as having residual disease before adjudication were determined to be normal.

Residual right ventricular dysfunction

At follow-up 102 patients underwent an echocardiogram. Nine patients (9%) had residual moderate or severe right ventricular enlargement. Four (4%) had residual moderate or severe right ventricular dysfunction. The remainder of patients had significant recovery of right ventricular size and function (Table 3).

Discussion

To the best of our knowledge, this report in a real world cohort of treated intermediate- or high-risk PE patients showing (1) potentially treatable conditions (e.g., HFpEF, OSA, or iron deficiency) which likely contributed to residual functional limitation (‘post-PE syndrome’) and (2) an oddly high rate of CTEPH at follow-up suggesting that the acute presentation already had an element of chronicity. The evaluation was planned in a standardized manner with V/Q and echocardiogram testing performed on 100 patients regardless of symptoms. The cohort may be especially relevant as we specifically excluded patients with high short-term morbidity and mortality not related to the acute PE.

There is limited functional and long-term data on follow-up after intermediate- or high-risk PE in the era of PERT and advanced therapies. Despite most patients in our cohort achieving right ventricular recovery at follow-up, they still experienced dyspnea that limited activity (Table 3). This persistent dyspnea has been classified as ‘post-PE syndrome’,22 and can occur without chronic thromboembolic disease.23 About one-third of all acute PE patients will develop exercise intolerance or chronic dyspnea resulting

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### Table 4. Characteristics of patients diagnosed with CTEPH.

| Sex | Age | NYHA FC | RA (mmHg) | mPAP (mmHg) | PVR (WU) | CI (L/min/m²) | NT-pro BNP | RV size | RV function |
|-----|-----|---------|-----------|-------------|---------|----------------|------------|--------|-------------|
| 1   | F   | 30      | 2         | 13          | 28      | 3              | 2          | 50     | Mild        |
| 2   | M   | 28      | 2         | 8           | 34      | 4              | 2.4        | .      | Moderate    |
| 3   | M   | 46      | 3         | 9           | 44      | 5              | 2.3        | 1017   | Moderate    |
| 4   | M   | 51      | 3         | 4           | 32      | 5              | 2.4        | 50     | Severe      |
| 5   | F   | 40      | 2         | 12          | 27      | 3              | 2.2        | 129    | Normal      |
| 6   | F   | 73      | 2         | 6           | 38      | 8              | 2.6        | 2640   | Mild        |
| 7   | M   | 77      | 2         | 10          | 33      | 3              | 2.4        | 88     | Moderate    |
| 8   | M   | 63      | 2         | 12          | 25      | 3              | 2.1        | 63     | Moderate    |

CI: cardiac index; CTEPH: chronic thromboembolic pulmonary hypertension; mPAP: mean pulmonary arterial pressure; NT-pro BNP: N-terminal pro-B-type natriuretic peptide; NYHA FC: New York Heart Association Functional Classification; PVR: pulmonary vascular resistance; RA: right atrium; RV: right ventricle.
in disability despite appropriate anticoagulation use.\textsuperscript{22,24} Recent data suggest that deconditioning is a large contributor to breathlessness after intermediate- or high-risk PE.\textsuperscript{25} Patients are less active and understandably anxious about the safety of exercise or any heavier activity. After identifying and treating decompensated heart failure, iron deficiency, and OSA, we identified only four patients with chronic thromboembolic disease (CTED) and four patients with obesity or deconditioning as the etiology for breathlessness. We and others speculate that a large percentage of post-PE syndrome is really diaphragm weakness,\textsuperscript{26} deconditioning,\textsuperscript{25,27} and multiple untreated comorbidities (HFpEF, OSA, obesity, and iron deficiency with or without anemia). Sensibly treating these comorbidities may address some of the symptoms and disability attributed to 'post-PE syndrome'. Our data suggest advanced interventions do not decrease the rate of dyspnea at follow-up in our cohort; we caution providers in speculating that invasive therapies decrease the symptoms and disability attributed to 'post-PE syndrome'. Our data suggest advanced interventions do not decrease the rate of dyspnea at follow-up in our cohort; we caution providers in speculating that invasive therapies improve longer-term outcomes when no such controlled data exist.

Patients with acute pulmonary embolus are classified as being intermediate risk if they have an elevated pulmonary embolus severity index\textsuperscript{28} and either an elevated cardiac biomarker (troponin or NT-pro BNP) or imaging abnormalities suggestive of right ventricular dysfunction.\textsuperscript{1} Using this definition, we observed that obesity and HFpEF were comorbidities in a large proportion of our acute intermediate-risk PE patients (Tables 1 and 3). At baseline, many patients may have already had either elevated biomarkers or right ventricular dysfunction which made them intermediate-risk with any magnitude PE. We speculate that recognizing this is important as treating heart failure may reduce breathlessness and decrease the risk for further complications from decompensated heart failure. Obesity also increases the risk for recurrent VTE which puts this group at higher risk for long-term complications.\textsuperscript{29}

Thrombus specimens from survivors after acute PE are not routinely available and there are no guidelines for evaluating acute clot specimens. Even at autopsy, clots are rarely evaluated. Much more could be learned about acute PE treatment response and outcomes based on clot morphology at time of diagnosis. The histology from our surgical embolectomy specimens at the time of diagnosis showed older age of thrombus with signs of chronicity, including 25\% with recanalization, even when patients presented with <24 h of symptoms. This pathology data suggests that (1) some intermediate- or high-risk patients may have chronic disease on presentation and are thus unlikely to respond to thrombolytic approaches (two patients had catheter-directed lysis for >24 h without change in imaging\textsuperscript{30} or hemodynamics); (2) having a structured short-term follow-up system for these higher risk patients is critical to ultimately identify CTEPH; and (3) in more severely symptomatic patients, CTEPH might be considered sooner than three months after initiation of anticoagulation. Our findings are supported by another recent surgical embolectomy cohort that showed 8/11 patients (72\%) had intraoperative findings of chronic thromboembolic pulmonary disease after failure to achieve right ventricular recovery following acute massive PE.\textsuperscript{31} In our cohort, none of the patients were considered to have any form of chronic thrombus prior to their initial PE evaluation.

CTEPH is the most severe complication after acute PE with historical rates varying from 0.57\% to 9.1\%.\textsuperscript{23} pulmonary embolism thrombolysis trial (PEITHO-2), the most rigorous long-term follow-up comparing systemic thrombolysis with tenecteplase to heparin anticoagulation, had an overall low rate of CTEPH at 1.4\% and failed to show long-term benefit of systemic thrombolysis compared to heparin anticoagulation alone.\textsuperscript{32} In our short-term follow-up, we had RHC confirmed CTEPH in nine patients (and likely CTEPH in 17–20 patients) which is a surprisingly high rate. We observed no change in imaging for two patients given catheter-directed thrombolytics, an experience already documented in the literature\textsuperscript{30}; similarly, our histologic data from embolectomy specimens suggest some degree of chronicity. Based on our observations and those already published, we speculate that some patients with intermediate- or high-risk presentations could already have chronic thrombus.\textsuperscript{12,30,33} This has important treatment implications: thrombolytics risks outweigh potential benefit if there is already chronic thrombus. Clinicians considering advanced therapies should be cognizant of the possibility that chronic disease may already be present in these apparently acute presentations. Moreover, PEITHO-2 showed no longer term benefit for thrombolytic vs. conservative treatment; our observational data similarly suggest that a conservative strategy is not inferior.

Developing a screening algorithm for CTEPH and decompensated heart failure detection after intermediate- or high-risk acute PE might improve outcomes and potentially decrease healthcare utilization. Two prospective studies have found CTEPH to occur at a rate of 4.8\% and 0.79\%\textsuperscript{17} when following all types of acute PE out to two years. Neither study focused on an intermediate- or high-risk group, and thus both studies were dominated by low-risk subjects. The acute management in these older studies did not generally utilize a multidisciplinary PERT evaluation. The Swiss national cohort study found that a telephone-based symptom evaluation after acute PE was sufficient to screen for CTEPH.\textsuperscript{34} This novel approach worked in a predominantly low-risk group; in our cohort, we did not find clinically important right ventricular dysfunction in asymptomatic patients. Thus, a symptom-driven approach seems to be a reasonable approach for testing and follow-up even in an intermediate- or high-risk cohort to screen for CTEPH or heart failure.

Perfusion imaging is the test of choice when evaluating for CTEPH.\textsuperscript{35} Historical rates of residual thrombus in follow-up after acute PE varies from 16\% to 73\%.\textsuperscript{36} One study suggested that systemic thrombolysis does not alter the rate of residual thrombus on perfusion imaging.\textsuperscript{37}
further supports our hypothesis that some disease is at least sub-acute on presentation. Our data did not find that advanced interventions altered the rate of residual perfusion defects. We also thought it interesting that the rate of residual thrombotic defects on perfusion scanning did not seem to be related to the degree of central thrombus burden at presentation. Our data do underscore the importance of having a knowledgeable radiologist evaluate perfusion scans with a high degree of suspicion for CTEPH as these were sometimes under-read by radiologists at our own institution. Because duration of anticoagulation is not influenced by residual thrombotic disease in the absence of CTEPH we would not recommend perfusion testing in asymptomatic patients.

There are limitations to this study. This was a single center observational study and in-hospital therapies were not randomized; it is possible that advanced interventions influenced outcomes in ways we did not measure. We relied on the written reports for CT imaging, perfusion lung scanning, and echocardiography and, in particular, we did not have dedicated readers to compare the echocardiograms directly in random order. There is patient recall bias for symptom assessment and we did not have a standardized scoring system used to assess functional status. We do not know anything about the discharge attending’s verbal instructions regarding activity. Standardized instructions and formal measurements of activity would be helpful for future follow-up studies.

Conclusion

In summary, we found a low rate of symptomatic recurrence but a high rate of functional limitations in follow-up after acute intermediate- or high-risk PE. Although this was not a randomized study, we did not find any signal showing advanced therapies as compared to timely anticoagulation improved symptoms at an early follow-up evaluation. Histological specimens and clinical treatment response suggested a degree of chronic thrombus at presentation for some patients, and this might make patients refractory to advanced therapies like thrombolysis. We believe our data strengthen the case for conservative, timely anticoagulation and that more aggressive therapies should be reserved for those believed to be at highest risk for inpatient mortality. Our findings also support expert, early follow-up for those discharged after intermediate- or high-risk PE management, a strategy which was also recently recommended in the 2019 European Society of Cardiology PE guidelines.38

Authors’ contributions

All authors were involved with study data and data collection/analysis. All authors approved the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Ethical approval

The University of Rochester RSRB approved this protocol before the research was completed.

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