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Percutaneous Reperfusion Therapies vs. Anticoagulation in Patients With Acute Intermediate-High-Risk Pulmonary Embolism: The PRETHA Randomized Clinical Trial

Taida Ivanauskienė[1,2] | Andrius Berūkštis[1,2] | Greta Burneikaitė[1,2] | Aurelija Daubaraitė[1] | Kastė Ivanauskaitė[3] | Mindaugas Matačiūnas[1,2] | Giedrius Navickas[1,2] | Rasa Kūgienė[1,2] | Marcin Kurzyna[4] | Sigita Glaveckaitė[2]

[1]Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania | [2]Clinic of Cardiovascular Diseases, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania | [3]Department of Psychology, UVA Universiteit van Amsterdam, Amsterdam, Netherlands | [4]Department of Pulmonary Circulation, Thromboembolic Diseases and Cardiology, Centre of Postgraduate Medical Education, European Health Center Otwock, Warsaw, Poland

Correspondence: Taida Ivanauskienė (taida.ivanauskiene@santa.lt)

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ABSTRACT

The optimal treatment strategy for patients with acute intermediate–high-risk pulmonary embolism (PE) remains uncertain. This randomized clinical trial (PRETHA) aimed to evaluate the efficacy and safety of percutaneous reperfusion therapies—trans-catheter thrombectomy and trans-catheter thrombolysis—compared with standard anticoagulation therapy. In this single-center, prospective trial conducted between April 2020 and April 2022, 39 patients with acute intermediate–high-risk PE were randomly assigned (1:1:1) to receive trans-catheter thrombectomy, trans-catheter thrombolysis, or conservative medical therapy with anticoagulation. Echocardiographic, hemodynamic, and biomarker parameters were assessed at baseline, 48 h, and at 1-, 6-, and 12-month follow-up. At 48 h, both interventional groups demonstrated significant improvement in right ventricular (RV) function and pulmonary pressures. The RV/LV ratio decreased by 0.3 (95% CI: 0.13–0.69; $p < 0.0002$) in the thrombectomy group and by 0.4 (95% CI: 0.12–0.96; $p < 0.0002$) in the thrombolysis group. Noninvasively measured systolic pulmonary artery pressure decreased by 29% in the thrombectomy group and by 39% in the thrombolysis group (both $p < 0.001$). Significant reductions in direct systolic and mean pulmonary artery pressures were also observed ($p = 0.0002$). However, at longer (1 to 12 months) follow-up, all three treatment groups represent similar positive changes of echocardiographic parameters and

Abbreviations: ABP, arterial blood pressure; APTT, activated partial thromboblastin time; BNP, B-type natriuretic peptide; CANARY, Catheter-Directed Thrombolysis vs Anticoagulation in Patients with Acute Intermediate-High-Risk Pulmonary Embolism; CDT, catheter-directed thrombolysis; CI, confidence interval; CNS, central nervous system; CRB, C-reactive protein; CT, computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; CTPA, computed tomography pulmonary angiography; DVT, deep vein thrombosis; ESC, European Society of Cardiology; EXTRACT-PE, Evaluating the Safety and Efficacy of the Indigo® Aspiration System in Acute Pulmonary Embolism; FLARE, FlowTriever Pulmonary Embolectomy clinical study; FLASH, FlowTriever All-Comer Registry for Patient Safety and Hemodynamics; HIT, heparin induced thrombocytopenia; HR, heart rate; IASF, informed consent form; ICOPER, International Cooperative Pulmonary Embolism Registry; INR, international normalized ratio; KNOCOUT PE, EkoSonic Registry of the Treatment and Clinical Outcomes of Patients With PE; LV, left ventricle; OR, odds ratio; PA, pulmonary artery; PAP, pulmonary artery pressure; PE, pulmonary embolism; PEITHO, Pulmonary Embolism Thrombolysis study; PESI, pulmonary embolism severity index; PTT, partial thromboplastin time; RA, right atrium; RCT, randomized controlled trial; RR, risk ratio; rt-PA, recombinant tissue plasminogen activator; RV, right ventricle; RVEF, right ventricular ejection fraction; SEATTLE II, Submassive and Massive Pulmonary Embolism Treatment With Ultrasound Accelerated Thrombolysis Therapy; sPAP, systolic pulmonary pressure; TAPSE, tricuspid annular plane systolic excursion; TTE, transthoracic echocardiography; ULTIMA, Ultrasound Accelerated Thrombolysis of Pulmonary Embolism; USCDT, ultrasound-assisted catheter-directed thrombolysis; VRBTEK, Vilnius Regional Committee for Biomedical Research Ethics; VTE, venous thromboembolism; VUH SK, Vilnius University Hospital Santaros Klinikos.

The Guarantor: Vilnius University, Prof. Sigita Glaveckaite, Tel.: +370 68240937.

cardio-specific biomarkers independent of the treatment tactic chosen in the acute period. Functional capacity and quality of life were superior in the interventional groups compared with anticoagulation alone. The incidence of adverse events was highest in the thrombolysis group (38%), whereas thrombectomy and medical therapy demonstrated more favorable safety profiles. Percutaneous reperfusion therapies were associated with earlier improvements in hemodynamic and functional surrogate parameters compared with anticoagulation alone; however, at 1-year follow-up, echocardiographic measures and biomarkers of cardiac function were similar across all treatment groups. These findings should be interpreted as mechanistic and hypothesis-generating.

1 | Introduction

Venous thromboembolism (VTE), which manifests clinically as deep vein thrombosis and pulmonary embolism (PE), is the third most common cardiovascular condition following myocardial infarction and stroke [1]. Epidemiological studies estimate the incidence of pulmonary embolism to be between 39 and 115 cases per 100,000 population per year, while the incidence of DVT ranges from 53 to 162 cases per 100,000 population per year [2]. Analyses of cases in Europe and North America suggest that implementing interventional treatment approaches could reduce deaths associated with this condition [3–8]. Over the past decade, treatment recommendations for PE have evolved significantly, influenced by the introduction of new medications (such as low molecular weight heparins, direct oral anticoagulants, and thrombolytics) and interventional treatments (including trans-catheter thrombectomy and trans-catheter thrombolysis).

Currently, there is no consensus on the optimal treatment strategy for intermediate-high-risk pulmonary embolism [9]. Guidelines suggest starting anticoagulant therapy and considering trans-catheter interventions if the patient experiences haemodynamic deterioration [10]. While there is a consensus that patients with right ventricular (RV) dilatation or dysfunction, elevated cardio-specific biomarker levels (such as brain natriuretic peptide (BNP) and troponin), and an acute DVT diagnosis are at greater risk of haemodynamic deterioration [11], an effective treatment approach that significantly improves the clinical outcomes is still being sought. Non-randomized studies with small-sample sizes have indicated a significant beneficial effect of interventional therapies on prognosis in patients with intermediate-high-risk PE [12–14].

Intermediate-risk PE can progress to high-risk PE following a repeated embolization episode, potentially leading to cardiogenic shock. The occurrence of more adverse clinical events in intermediate-high-risk PE suggests that treatment may need to be more intensive than anticoagulant therapy alone. This raises the question: Should clinicians pursue reperfusion therapy to achieve rapid clinical recovery, or should they continue with anticoagulation alone?

Acknowledging this gap in the evidence, we initiated the single-center prospective, randomized parallel-group clinical trial titled PRETHA (Percutaneous Reperfusion Therapies vs. Anticoagulation in Patients with Acute Intermediate-High-risk Pulmonary Embolism). This study aims to assess the efficacy and safety of reperfusion therapies (trans-catheter thrombectomy or trans-catheter thrombolysis) in patients with acute intermediate-high-risk PE. We hypothesized that trans-catheter reperfusion therapies would result in earlier improvements in right ventricular load and pulmonary hemodynamics, as assessed by imaging and invasive measurements, compared with anticoagulation alone.

2 | Methods

The study was approved by the Vilnius Regional Biomedical Research Ethics Committee (approval number 2020/3-1208-693). Participants identified as having an intermediate-high risk PE and who met predefined inclusion and exclusion criteria agreed to participate in this clinical trial and signed a consent form, were randomly assigned to one of three treatment groups: Group 1 received trans-catheter thrombectomy, Group 2 underwent trans-catheter thrombolysis, and Group 3 received conservative medical therapy with anticoagulants alone (standard care treatment), Figure 1. The assignment of subjects to each treatment group was based on a randomization list created in advance using statistical software specifically developed for this study. A total of 39 patients were prospectively enrolled, with 13 patients in each arm. Blinding was not possible due to ethical considerations.

[a]Among 92 patients not meeting the eligibility criteria, 3, 39, and 50 patients were categorized as having low, intermediate-low, and high-risk PE, respectively. [b]Among 38 patients who met the exclusion criteria: 12 patients had 1 or more contraindication to fibrinolytic therapy; 2 patients had end-stage kidney disease; 7 patients had a mental illness and no meaningful contact was possible to make with them; 3 patients had thrombus in the right heart; 4 patients were bedridden (and therefore unable to attend follow-up visits); 8 patients have active cancer with poor prognosis (life expectancy less than 6 months); 2 patients were isolated due to COVID-19 disease.

The primary study efficacy endpoints were surrogate endpoints of early haemodynamic improvement: (1) changes in echocardiographic and laboratory biomarkers measured 48 h after the initiation of the treatment, as well at 1, 6, and 12 months follow up; (2) changes in direct systolic and mean pulmonary pressures assessed invasively before and after interventional procedures (data are available only for patients undergoing invasive treatment). Secondary efficacy endpoints included surrogate endpoints of functional and quality of life improvements: (1) changes in functional status measured by the 6-min walk test (6 MWT); (2) changes in quality of life assessed through the Pulmonary Embolism Quality of Life (PEmb-QoL) questionnaire. Additionally, secondary safety endpoints, which consisted of treatment-related adverse events during hospitalization, including deaths, major bleeding, and periprocedural complications, were evaluated. The study was underpowered to assess hard efficacy endpoints such as mortality and recurrences.

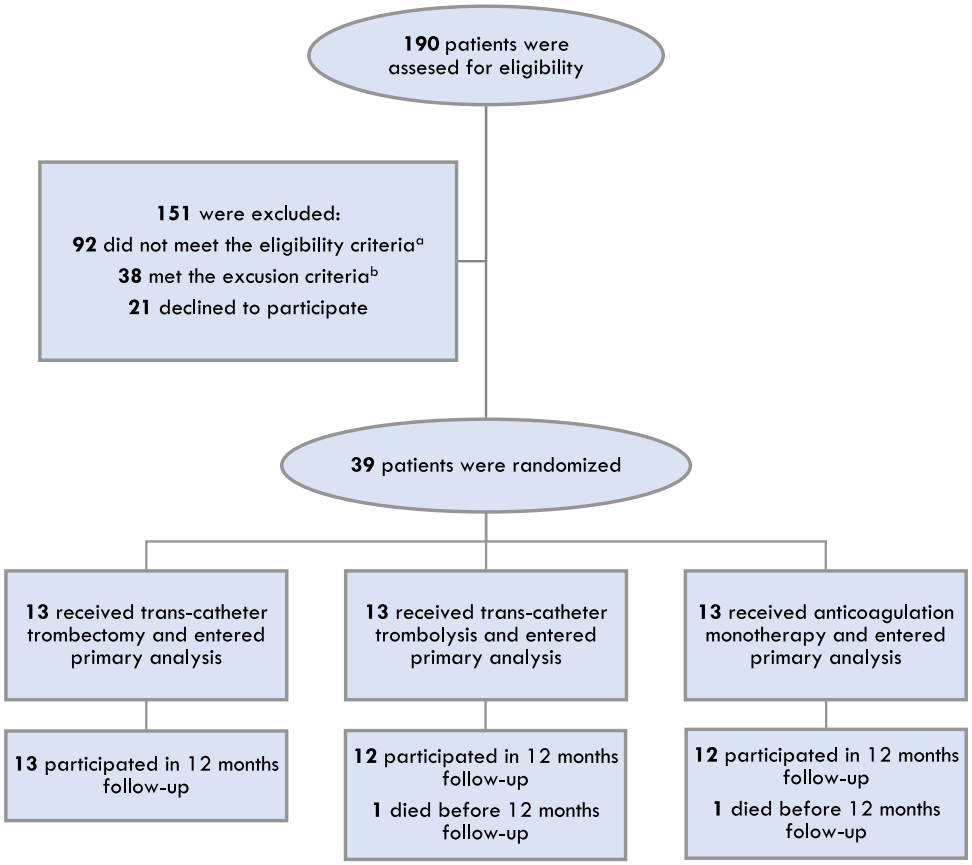

FIGURE 1 | Enrollment and randomization flow chart.

From April 24, 2020 to April 1, 2022, a total of 39 patients diagnosed with intermediate-high risk PE and treated at the tertiary Vilnius University Hospital Santaros klinikos (VUH SK) were randomized in the study. Informed consent was obtained from all subjects involved in the study. All patients who were randomized met the inclusion and exclusion criteria specified in Table 1.

2.1 | RV – Right Ventricle, LV – Left Ventricle, BP – Blood Pressure

Trans-catheter thrombectomy was performed using Penumbra CAT-8 catheter system. Penumbra's Indigo CAT 8 system is a flexible 8F aspiration catheter connected to a continuous vacuum system. The catheter's lumen contains a wire with an olive-shaped distal tip that enhances clot fragmentation and recovery. A thromboaspiration is performed using the Indigo CAT8 catheter connected to the Indigo Pump MAX vacuum system.

2.1.1 | Trans-Catheter Thrombolysis

For trans-catheter thrombolysis, alteplase was administered as 1 mg/hour infusion through a pigtail catheter placed in one or both branches of the pulmonary artery for up to 24 h.

Trans-catheter interventions were performed according to the treatment methodologies approved by the VUH SK, developed in line with the ESC guidelines [15]. Only two experienced interventional cardiologists (TI, AB) carried out these procedures.

The conservative treatment group (Group 3) received intravenous heparin infusion for 3 days, maintaining Partial Thromboplastin Time (PTT) at 70–80 s, after which they were transitioned to oral anticoagulants. All patients were treated with oral anticoagulants during the follow-up period.

Echocardiographic parameters and laboratory biomarkers were collected from each patient at 48 h after the initiation of the treatment, and subsequently at 1, 6, and 12 months follow-up.

2.1.2 | Echocardiography

Transthoracic echocardiographic studies were performed with a commercially available ultrasound machine (System Vivid 9, GE Healthcare, Horten, Norway) with a 1.5 – 4.6 MHz transducer. The echocardiographic parameters were collected (Appendix Table 1): RV diameter in parasternal long-axis view, basal right ventricular/left ventricular (RV/LV) ratio, right ventricular ejection fraction, tricuspid annular plane systolic excursion (TAPSE), systolic pulmonary artery pressure (sPAP). The above-mentioned echocardiographic indices were measured according to recommendations issued by the American Society of Echocardiography [15] and the European Society of Cardiology [11] and were conducted by two experienced cardiologists (TI, GB).

2.1.3 | Invasive Parameters

The direct systolic pulmonary artery pressure (sPAP) and mean pulmonary artery pressure (mPAP) were measured during the interventional procedure (before and after) for both interventional treatment groups. In the conservative therapy group, right heart catheterization was not performed due to ethical considerations and the associated risks of the procedure.

TABLE 1 | Inclusion and exclusion criteria of the study.

Inclusion criteria	Exclusion criteria
• Men and women, aged over 18 years • Acute PE, occurring within 14 days from the onset of symptoms • PE confirmed by computed tomography pulmonary angiography (CTPA)[a] • PE meeting the criteria for intermediate-high risk: ◦ Right ventricular dysfunction detected on transthoracic echocardiography (TTE) or CTPA (Appendix Table 1) [11]: RV/LV ratio >1.0, in the absence of persistent hypotension <90 mmHg or a decrease in systolic BP of at least 40 mmHg for at least 15 min with signs of peripheral organ hypoperfusion (cold extremities, urine output <30 mL/h, or altered consciousness), and without the need for vasopressors to maintain a systolic BP of ≥90 mmHg or cardiopulmonary resuscitation. ◦ Elevated troponin >3 times the upper normal values or BNP > 100 ng/L, ◦ Pulmonary embolism severity index (PESI) II-IV (scores 86–125) or simplified PESI ≥ 1 (Appendix Table 2) [11].	• Refusal to provide informed consent • Systolic BP < 90 mmHg for at least 15 min, or requiring inotropes to maintain systolic BP ≥ 90 mmHg • Pulmonary hypertension with direct peak pulmonary artery pressure >70 mmHg • History of severe or chronic pulmonary hypertension • Hematocrit < 28% • Platelet count < 100,000 μL • Serum creatinine > 159 μmol/L • International Normalized Ratio (INR) > 3 • Partial Thromboplastin Time >50 s (in the absence of anticoagulant treatment) • History of heparin-induced thrombocytopenia • Contraindications to anticoagulants • Major trauma within the last 14 days • Cardiovascular surgery in the past 7 days • Active oncological disease • Proven allergy to iodine contrast agents • Life expectancy < 90 days • Presence of cardiac thrombi • High bleeding risk, HAS-BLED > 3 (HAS-BLED bleeding risk assessment (Appendix Table 3) [11]. • Contraindications for PA catheterization: tricuspid or pulmonary artery valve prosthesis or vegetations, acute myocardial infarction, chronic kidney disease • Contraindications to thrombolysis (Appendix Table 4) [11].

[a]Acute thrombosis of the left, right, or both branches of the pulmonary artery, lobar thrombosis.

2.1.4 | *Computed Tomography*

Percentage of residual chronic thromboembolic pulmonary hypertension, pulmonary artery diameter, RV/LV ratio were evaluated by pulmonary computed tomography angiography (CTPA). CTPA was repeated, provided there were no contraindications, at an average follow-up period of 6.8 months. CTPA images from baseline and follow-up were assessed using methods approved by the recommendation of the respective Societies of Radiology [16–18] and evaluated by a single experienced radiologist (MM).

2.1.5 | *Biomarkers*

TnI and BNP levels were measured using routine hospital assays.

2.1.6 | *6 MWT*

Functional capacity was measured by using 6-min' walk test (6 MWT). The 6-min walk test measures the distance walked over a 6-min period and serves as an indicator of submaximal aerobic capacity [19].

2.1.7 | *Quality of Life*

Health-related Quality of life was assessed with the PEmb-QoL questionnaire [20], Appendix Table 5. The questionnaire contains six dimensions based on the items' contents: frequency of complaints, activities of daily living (ADL) limitations, work-related issues, social limitations, intensity of complaints, and emotional complaints. The total score for the PEmb-QoL ranges from 6 to 27, with higher scores indicating worse quality of life. A score of 1 point for all dimensions signifies no complaints.

2.1.8 | *Bleeding*

Major bleeding was assessed by using predefined World Health Organization (WHO) definitions presented in Appendix Table 6.

We based our sample size calculation on available literature for the medium-high-risk PE group (randomization applies). After 48 h after treatment, the mean reduction in RV/LV ratio was found to be 0.03 for standard treatment, 0.3 for percutaneous thrombolysis, and 0.38 for percutaneous thrombectomy. With an alpha level set at 0.05 and a power of 95%, we determined the means (0.03, 0.30, and 0.38) and a standard deviation (SD) of

0.20. The estimated effect size (f) was calculated to be 0.749, leading to a required sample size (n) of 33 participants (11 in each group). To account for a possible high dropout rate of 20%, either from premature withdrawal or deaths during the follow-up period, we planned to enroll 13 subjects in each group, and a total of 39 participants for the entire study.

Baseline patients' characteristics were descriptively summarized: continuous variables were expressed as mean value ± standard deviation (SD), non-normally distributed data were expressed as median and quartile difference (Q1–Q3), whereas categorical variables were expressed as absolute number (percentage).

Comparisons between different groups were conducted using either the Student's t-test (for normally distributed data) or the Wilcoxon–Mann–Whitney test (for non-normally distributed data). Additionally, data were evaluated using a one-way analysis of variance with Bonferroni adjustment. Categorical variables were compared using the χ^2 test or Fisher's exact test.

Changes in quantitative parameters were assessed before and after treatment at 1, 6, and 12 months between groups. For normally distributed data, Pearson correlation coefficients were employed, while Spearman correlation coefficients were used for non-normally distributed data to determine the impact of the periprocedural variables on applied treatment performance. For categorical data, odds ratios were calculated. p values < 0.05 (two-sided) were considered statistically significant. Statistical analyses were performed with SPSS 20.0 (SPSS).

3 | Results

A total of 39 patients (mean age 60.9 [26–82] years, 62% male) were randomly assigned (1:1:1) to three groups, consisting of 13 patients each. Baseline characteristics of the study groups are presented in Table 2. The mean body mass index was 31.4 [22.17–39.0]) and did not differ significantly between the groups. The majority of patients presented with DVT (84.6%), arterial hypertension (74.4%), and dyslipidaemia (79.5%). The most common risk factors were obesity (48.7%) and immobility (41%). Only 6 (15.3%) patients were current smokers, and 5 (12.8%) had a previous history of VTE. Most patients were classified as being in PESI III class, with 61.5% in the trans-catheter thrombectomy group, 46.2% in the transcatheter thrombolysis group, and 46.2% in the usual care group. The length of hospital stay was similar between the trans-catheter thrombectomy and the conservative treatment groups (7.8 ± 1.5 days vs. 7.6 ± 2 days), while patients in the trans-catheter thrombolysis group had a longer hospital stay (9 ± 5.2 days).

3.1 | Haemodynamic Improvement Across Treatment Groups

In the trans-catheter thrombectomy and trans-catheter thrombolysis groups, significant improvements in echocardiographic parameters (including RV diameter, RV/LV ratio, sPAP, RV ejection fraction and TAPSE) were observed after 48 h post interventional treatment (Table 3). Systolic pulmonary artery pressure (sPAP) as measured noninvasively by echocardiography, decreased by 29% in the thrombectomy group and by 39% in the thrombolysis group (both $p < 0.001$) as compared with a conservative treatment group, where change by 7.2% was nonsignificant ($p = 0.207$). A significant decrease in TnI and BNP was noted only in the trans-catheter thrombolysis group. In contrast, no positive changes in echocardiographic or laboratory biomarkers were observed in the conservative treatment group at 48 h follow-up. At 1-month follow-up, statistically significant improvements in echocardiographic indices and biomarkers were observed in all three groups and remained relatively stable at 6 and 12 months of follow-up.

After 48 h, both interventional groups showed a significant reduction in RV/LV ratio (Figure 2). In the trans-catheter thrombectomy group, the mean decrease was 25.4% (0.3, 95% CI 0.13-0.69, $p < 0.0002$), and in the trans-catheter thrombolysis group – 29.2% (0.4, 95% CI 0.12–0.96, $p < 0.0002$). In contrast, in the conservative treatment group a nonsignificant decrease in RV/LV ratio of 6.8% ($p = 0.19$) was observed.

In both interventional treatment groups, there was a significant reduction in direct systolic pulmonary artery pressure (sPAP) and mPAP after the interventional procedure, as measured invasively ($p = 0.0002$), see Table 4. In the trans-catheter thrombectomy group, sPAP was reduced by 16.2% and mPA by 20.3%. In the trans-catheter thrombolysis group, sPAP was reduced by 23.9% and mPA by 30.2% (Table 4).

3.2 | Functional and Quality of Life Improvement of Study Subgroups

The results of the 6-min walking test (6MWT) reveal significant disparities in functional capacity among treatment groups. At the end of hospitalization, and during follow-up at 1, 6 and 12 months, the conservative treatment group consistently demonstrated the lowest performance, with distances of only 284.4 ± 63.8 m at discharge, increasing modestly to 324.6 ± 59.3 m at 1 month, 335 ± 80.5 m at 6 months, and peaking at 316.7 ± 69.8 m at 12 months ($p < 0.01$). In stark contrast, patients in the trans-catheter thrombectomy group achieved remarkable improvements, walking an average of 413.1 ± 128.8 m at discharge, with a consistent upward trajectory of 432.9 ± 98.9 m at 1 month, 449 ± 123 at 6 months, 440 ± 113.5 at 12 months ($p < 0.01$). The trans-catheter thrombolysis group also showed substantial gains, recording distances 353.1 ± 161.7, 418.1 ± 87.1, 435 ± 77.92, and 470 ± 94.51 meters ($p < 0.01$) respectively.

To further assess quality of life, the PEmb-QoL questionnaire was administered to 38 participants 12 months following the index event. Notably, the medical treatment group achieved the highest scores across all six categories, indicating a poorer quality of life. In contrast, the percutaneous treatment groups exhibited significantly lower scores ($p < 0.01$) compared to the standard medical treatment group (Table 5).

Pulmonary CT angiography was conducted to assess the residual chronic thromboembolic pulmonary hypertension after a mean follow-up of 6.8 months (6–10) in 36 patients. The findings revealed that chronic thrombosis of low-to-moderate extend was diagnosed in 6 out of 12 patients (50%) in the trans-catheter thrombolysis group, 4 out of 13 patients (31%) in the trans-catheter thrombectomy group, and 5 out of 12 (42%) in

TABLE 2 | Baseline characteristics of study patients.

	Trans-cath thrombectomy $N = 13$	Trans-cath thrombolysis $N = 13$	Conservative treatment $N = 13$
Age (years, mean)	60.9	53.7	68.0
Gender (% male)	84.6	61.5	38.4
PESI index (class - %)	III - 61.5% IV – 23.1% V – 7.7%	I –15.4% II – 23.1% III – 46.2% IV – 15.4%	II – 23.1% III – 46.2% IV – 30.8%
BMI (kg/m^2)	32	29.5	32
DVT (*n*)	10	10	13
History of PE (*n*)	1	3	0
Recurrent PE after current episode (*n*)	3	0	2
PE risk factors			
Current smoker (*n*)	2	1	3
Limb fracture/ immobilization (*n*)	1	1	3
Long hospitalization (*n*)	0	0	1
Autoimmune disease (*n*)	0	0	2
Oral contraceptives (*n*)	0	1	0
Congestive heart failure (*n*)	0	0	1
Acute infection (*n*)	1	2	1
Inflammatory bowel disease (*n*)	1	0	0
History of cancer (*n*)	1	2	1
Immobility (*n*)	5	5	6
Obesity (*n*)	8	5	6
Varicose veins (*n*)	1	2	0
Medical history			
Diabetes (*n*)	0	1	1
Arterial hypertension (*n*)	10	8	11
Dyslipidaemia (*n*)	11	10	10
Chronic kidney disease (*n*)	2	1	1
Chronic coronary disease (*n*)	2	0	3
De novo cancer diagnosis (after this PE) (*n*)	2	1	1
De novo thrombophilia (after this PE) (*n*)	0	2	0

Abbreviations: BMI, body mass index; DVT, deep vein thrombosis; PE, pulmonary embolism; PESI, pulmonary embolism severity index.

the conservative treatment group. PCTA showed signs of pulmonary hypertension in three patients of the conservative treatment group, two in the trans-catheter thrombectomy group, and one in the trans-catheter thrombolysis group. The clinical development of pulmonary hypertension requires a longer period, which requires longer follow-up of patients.

Remarkably, the assessment by CTPA demonstrated a substantial reduction in pulmonary artery diameter across all three treatment groups as compared to baseline. In the trans-catheter thrombectomy group, the diameter decreased by 21% from 36 to 28 mm ($p < 0.001$), in the trans-catheter thrombolysis group by 12% from 32 to 28 mm ($p = 0.07$), and by 15% in the medical therapy group from 34 to 29 mm ($p = 0.009$).

3.3 | Safety Across All Treatment Arms

During the acute phase, most complications were observed in the trans-catheter thrombolysis group, and all were related to the treatment. In this group, 3 of 13 (23%) patients experienced hematomas at the groin puncture site. Of these, two patients did not require special treatment (WHO grade 2 bleeding), while one patient was treated with a blood transfusion (WHO grade 3

TABLE 3 | Dynamic changes in echocardiographic and laboratory parameters at baseline, at 48 h, and at 1-, 6- and 12-month follow-up.

pa TTE parameter rameter	Baseline $N = 39$	48-h $N = 39$	p	1 month $N = 38$	p	6 months $N = 37$	p	12 months $N = 37$	p
Trans-catheter thrombectomy group									
RV/LV ratio	1.2 (0.19)	0.89 (0.13)	<0.01	0.75 (0.06)	<0.01	0.76 (0.046)	<0.01	0.78 (0.028)	<0.01
RV diameter, cm	3.62 (0.48)	2.96 (0.4)	0.0002	2.85 (0.4)	0.0024	3.0 (0.23)	<0.01	2.93 (0.47)	<0.01
TAPSE, cm	1.53 (0.33)	2 (0.4)	0.0002	2.17 (0.22)	0.0002	2.32 (0.29)	<0.01	2.19 (0.25)	<0.01
RV EF, %	25.86 (11.25)	35.84 (9.53)	0.0417	42.54 (7.27)	0.0034	38.5 (7.57)	<0.01	41.2 (5.16)	<0.01
sPAP, mmHg	47.77 (5.21)	34 (9.54)	0.0005	28.69 (10.93)	0.0002	23.16 (12.9)	<0.01	24.25 (13.2)	<0.01
Tn, ng/L	377.9 (317.1)	198.4 (256.25)	0.05	3.07 (2.59)	0.0002	N/A		N/A	
BNP, ng/L	189.4 ± 303	179.8 ± 172.4	1.00	56.6 (72)	0.05	51.69 (34.4)	0.02	34.36 (42.7)	0.03
Trans-catheter thrombolysis group									
RV/LV ratio	1.27 (0.21)	0.88 (1.15)	<0.01	0.8 (0.09)	<0.01	0.7 (0.059)	<0.01	0.78 (0.073)	<0.01
RV diameter, cm	3.64 (0.91)	2.90 (0.39)	0.0002	2.65 (0.29)	0.0005	2.8 (0.2)	<0.01	2.8 (0.4)	<0.01
TAPSE, cm	1.55 (0.33)	2.13 (0.34)	0.0002	2.25 (0.3)	0.0005	2.33 (0.61)	<0.01	2.33 (0.29)	<0.01
RV EF, %	24.58 (12.96)	32.38 (9.02)	0.0266	40.4 (13.08)	0.0137	39.1 (8.3)	<0.01	41.7 (6.3)	<0.01
sPAP, mmHg	49.92 (11.593)	30.6 (14.25)	0.0005	19.66 (12.09)	0.0005	27.12 (5.69)	<0.01	21.6 (13.3)	<0.01
Tn, ng/L	208.9 (290)	51 (57)	0.0002	4 (5.0)	0.0005	N/A		N/A	
BNP, ng/L	583.4 (506)	133.37 (224.1)	0.0005	43.1 (31.9)	0.0015	38.4 (24.8)	0.01	42.8 (60.9)	0.01
Conservative treatment group									
RV/LV ratio	1.23 (0.2)	1.12 (0.14)	0.07	0.82 (0.88)	<0.01	0.75 (0.06)	<0.01	0.73 (0.12)	<0.01
RV diameter, cm	3.57 (0.524)	3.47 (0.43)	0.2622	2.95 (0.429)	0.002	2.7 (0.14)	<0.01	2.68 (0.24)	<0.01
TAPSE, cm	1.69 (0.63)	1.62 (0.25)	0.969	2.15 (0.23)	0.0103	2.08 (0.23)	<0.01	2.2 (0.09)	<0.01
RV EF, %	24.51 (12.4)	29.19 (9.91)	0.0942	36.54 (10.3)	0.0161	42.8 (6.6)	<0.01	45.4 (16.4)	<0.01
sPAP, mmHg	47.25 (8.4)	43.85 (6.92)	0.207	27.33 (19.65)	0.0029	26.6 (7.5)	<0.01	23.1 (17.0)	<0.01
Tn, ng/L	363 (510)	158 (141)	0.12	4.9 (4.54)	0.0005	N/A		N/A	
BNP, ng/L	625.5 (547)	404 (289)	0.21	67.8 (95.3)	0.009	60.39 (105.1)	0.02	73.69 (97.4)	0.03

Abbreviations: BNP, brain natriuretic peptide, EF, ejection fraction, LV, left ventricle; RV, right ventricle; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; Tn, troponin; TTE, transthoracic echocardiogram.

bleeding). Unfortunately, one patient died during hospitalization due to brain hemorrhage (WHO grade 4).

In the thrombectomy group, 1 of 13 (8%) patients experienced non-significant haemoptysis (WHO grade 2) 5 days after the procedure. Additionally, 1 (8%) patient in the conservative treatment group and 1 (8%) patient in the trans-catheter thrombolysis group developed uneventful pneumonia.

4 | Discussion

A single center prospective, randomized parallel group PRETHA clinical trial demonstrated that percutaneous reperfusion therapies, either thrombectomy or thrombolysis, are associated with faster early (at 48 h) reversal of right ventricular dysfunction and pulmonary hypertension, as reflected by echocardiographic, invasive hemodynamic, and biomarker-based surrogate endpoints in patients with acute intermediate-high risk PE. Importantly, these early physiological differences did not translate into divergent longer-term cardiac remodeling at up to 12 months. Measures of functional capacity and patient-reported quality of life favored the interventional groups; however, the study was not powered to determine the clinical significance or durability of these differences. Percutaneous reperfusion therapies are generally safe in patients with acute intermediate-high risk PE.

Patients with PE from different risk groups should not be treated equally. To date, there is no consensus on the optimal algorithm for the treatment of intermediate-high-risk pulmonary artery thromboembolism [21]. Treatment guidelines recommend starting anticoagulant therapy and trans-catheter intervention as soon as haemodynamic deterioration occurs [22]. Although there is a consensus that patients with RV dilatation, elevated markers of heart failure and ischemia (BNP, Tn), and a diagnosis of acute DVT are at increased risk of haemodynamic deterioration [11], there is still a need for an effective treatment modality that significantly improves the clinical outcome. Intermediate-risk PE progresses to high-risk PE after a repeated episode of embolization, with clinical development of cardiogenic shock. The fact that more adverse clinical events occur in intermediate-high-risk PE suggests that treatment should be more aggressive than anticoagulant therapy alone.

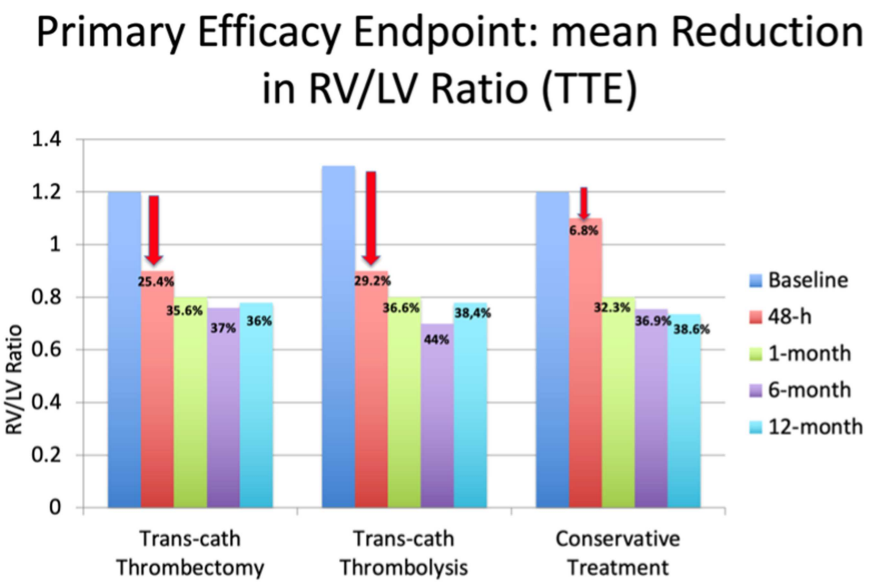

FIGURE 2 | Primary efficacy endpoint: mean RV/LV ratio reduction as assessed by transthoracic echocardiography at baseline and follow-up.

TABLE 4 | Reduction of direct systolic and mean pulmonary artery pressures after the index procedures.

Direct PA pressure (mmHg)	*N*	Before treatment (mmHg)	After treatment (mmHg)	*p*	Percentage pressure drop (%)
Trans-cath Thrombectomy group					
sPAP	13	54.3 ± 9	45.4 ± 10	0.0002	16.2
mPAP	13	32.9 ± 6.7	26.2 ± 5	0.0002	20.3
Trans-cath Thrombolysis group					
sPAP	13	57.2 ± 14.7	43.5 ± 13.9	0.0002	23.9
mPAP	13	35.4 ± 9.4	24.7 ± 9.4	0.0002	30.2

Abbreviations: mPAP, mean pulmonary artery pressure; PA, pulmonary artery; sPAP, systolic pulmonary artery pressure.

4.1 | Percutaneous Thrombolysis Versus Anticoagulation Alone

Systemic thrombolysis is the main treatment for high-risk pulmonary embolism (PE). While patients with high-risk PE and systemic thrombolysis have a lower mortality rate, the benefit in patients with intermediate risk PE is uncertain [23, 24]. According to current guidelines, routine use of primary systemic thrombolysis for intermediate risk PE is not recommended (Class III, Level of Evidence B). However, rescue thrombolysis is recommended if haemodynamic deterioration occurs during anticoagulation treatment (Class I, Level of Evidence B) [25].

The largest randomized controlled trial examining the impact of systemic thrombolysis in normotensive patients with intermediate risk pulmonary embolism was The Pulmonary Embolism Thrombolysis (PEITHO) study. This study showed a benefit in the study's composite primary outcome of death or hemodynamic decompensation within 7 days (odds ratio 0.44, 0.23 to 0.87; $p = 0.02$) but at a significant cost of major bleeding (major extracranial bleeding: odds ratio 5.55, 2.3 to 13.39; $p < 0.001$). No difference in overall death was seen between the two groups [26]. Three-year follow-up in PEITHO study showed no effect of thrombolysis therapy on residual dyspnea, RV dysfunction, or overall mortality [27].

Relying on the results of PEITHO study, systemic thrombolysis is only recommended as life-saving reperfusion therapy. Because of these findings, we did not include systemic thrombolysis as a treatment option in our study. In patients with stable haemodynamic, the search for effective (and thus safe) therapies continues. These could include trans-catheter thrombectomy (mechanical aspiration of thrombus through a catheter) and trans-catheter thrombolysis with low-dose thrombolytics (slow dissolution of the thrombus by administering a thrombolytic directly into the thrombus via a catheter).

In conventional catheter-directed thrombolysis, a pharmacological agent is delivered by catheters directly into the pulmonary arteries, thereby reducing the total dose of the thrombolytic agent and possibly reducing bleeding complications. Kroupa et al. [28] compared the use of catheter-directed thrombolysis (CDT) using the Cragg–McNamara catheter with anticoagulation alone in a single-center randomized clinical trial of 23 patients with intermediate risk PE. A reduction of ≥25% in the RV/LV ratio was more frequently observed in the CDT group (7 out of 12 patients) than in the anticoagulation group (2 out of 11 patients; $p = 0.03$), as was a decrease in systolic PAP by ≥30% (11 out of 12 patients in the CDT group vs. 2 out of 11 patients in the anticoagulation group; $p = 0.001$). Safety endpoints were similar in both groups, with no

TABLE 5 | Results of the PEmb-QoL scores, which are presented as median with interquartile range.

	FO: Frequency of complaints (max 6)	ADL: activities of daily living limitations (max 3)	WR: Work-related problems (max 2)	SL: Social limitations (max 5)	IO: Intensity of complaints (max 6)	EC: Emotional complaints (max 6)
Medical treatment group ($n = 13$)						
Median PEmb-QoL scores	3.04 [1,3–5]	2,15 [1–3]	1,77 [1,2]	3,15 [1–5]	2,69 [1–4]	2.92 [1–4]
Trans-catheter thrombectomy group ($n = 13$)						
Median PEmb-QoL scores	1,91 [1,2,95]	1,14 [1–1.8]	1,27 [1,2]	1,38 [1–3]	1,54 [1–3]	1,43 [1,2]
Trans-catheter thrombolysis group ($n = 12$)						
Median PEmb-QoL scores	1,53 [1,2,66]	1,08 [1,3]	1,25 [1,2]	1,33 [1,2]	1,33 [1,2]	1,52 [1–3]

Abbreviations: ADL, activities of daily living limitations (max score 3); EC, emotional complaints (max score 6); FO, frequency of complaints (max score 6); IO, intensity of complaints (max score 6); PEmb-QoL, Pulmonary Embolism Quality of Life; SL, social limitations (max score 5); WR, work related problems (max score 2).

intracranial or life-threatening bleeding reported. However, it is important to consider the small sample size and short observation period.

Another open-label, randomized study comparing the effectiveness of CDT with anticoagulation alone in patients with intermediate-high risk PE was the CANARY trial (sample size 94 patients). At 3 months, the primary efficacy end point (the proportion of patients with an RV/LV ratio >0.9 at 3-month follow-up) did not significantly differ between the groups. However, the median RV/LV ratio at 3-month follow-up was significantly lower in the CDT group compared with the anticoagulation group (0.7 [0.6–0.7] vs. 0.8 [0.7–0.9]; $p = 0.01$). Moreover, RV recovery was seen more frequently at 3 months after CDT as compared with a conservative treatment group (43 out of 46 patients vs. 28 out of 39 patients, respectively; $p = 0.009$). Eight bleeding events were reported in the CDT group compared with none in the anticoagulation group [29]. The CANARY trial is the largest RCT to date comparing conventional CDT and anticoagulation, but the trial was underpowered and stopped prematurely.

In our clinical trial, we used transcatheter thrombolysis with a similar technique as in the above-mentioned studies; however, we compared the efficacy of this treatment not only with the medical group but also with the transcatheter thrombectomy group. After 48 h in both interventional groups, a significant reduction in RV/LV ratio was observed (Figure 2): mean decrease by 29.2% (0.4) (95% CI (0.12–0.96; $p < 0.0002$) in the transcatheter thrombolysis group. Meanwhile, the respective decrease by 6.8% in the conservative treatment group was nonsignificant. From a clinical point of view, the changes in the RV/LV ratio are an important feature to assess the efficacy of treatment and prognosis of the disease [30, 31]. Unlike the above studies, in our clinical trial, after just a 1-month follow-up, statistically significant positive dynamics of echocardiographic indices and laboratory biomarkers were observed in all three groups and remained almost stable at 6 and 12 months of follow-up.

New trans-catheter thrombolysis (like Ultrasound-assisted catheter-directed thrombolysis (USCDT)) and trans-catheter thrombectomy (the FlowTriever) devices promise good results. USCDT uses high-frequency ultrasound energy with pharmacological thrombolysis to increase the thrombus's surface area and enhance the dose-effect relationship of the thrombolytic agents. The authors of the open-label ULTIMA randomized clinical trial (RCT) assigned 59 patients with intermediate-high risk PE and an RV/LV ratio of ≥1.0 to receive USCDT with unfractionated heparin or heparin alone. The mean difference in RV/LV ratio from baseline to 24 h was 0.30 ± 0.20 versus 0.03 ± 0.16 ($p < 0.001$), respectively. Three minor bleeding events occurred in USCDT group and one in the control group ($p = 0.61$) [32]. The prospective, single group, multicentre SEATTLE II study investigated the safety and efficacy of ultrasound assisted thrombolysis in 31 high-risk and 119 intermediate-high-risk PE. Systolic PAP was reduced by 14.4 mmHg ($p < 0.001$) and the RV/LV ratio was reduced by 0.42 ($p < 0.001$) within 48 h of the procedure. A total of 15 major bleeding events were documented within 30 days of the procedure.

The results of a meta-analysis of 11 observational studies and 1 RCT (ULTIMA trial), including 9789 patients, showed that catheter-directed thrombolysis was associated with significantly lower in-hospital mortality (RR 0.41, 95% CI 0.30 to 0.56,

$p < 0.00001$), as well as lower 30-day and 90-day mortality, compared with anticoagulation alone. The risk of major bleeding did not significantly differ between the strategies (RR 1.31, 95% CI 0.57 to 3.01, $p = 0.53$) [33]. According to another meta-analysis of 8 observational studies, which compared CDT with systemic thrombolysis, CDT was associated with significantly lower in-hospital mortality (risk ratio 0.52, 95% CI 0.40 to 0.68, $p < 0.001$). However, the risk of bleeding was similar between the groups (8.2% of the patients in the CDT group and 7.9% in the systemic thrombolysis group) [34]. Another recent meta-analysis, including data from 44 studies and 20,006 patients, concluded that trans-catheter thrombolysis was associated with a lower risk of death and major bleeding complications than systemic thrombolysis, as well as a lower risk of death and a similar risk of intracerebral hemorrhage, as compared with anticoagulation. Nevertheless, these findings were mostly based on observational studies [35]. Results from the recently published prospective observational KNOCOUT PE study showed a low rate of all-cause mortality at 30 days (1.0%, 5 out of 489 patients) and a low major bleeding rate within 72 h (1.6%, 8 out of 489 patients) in patients with intermediate-high and high-risk PE undergoing USCDT [36].

Treatment with trans-catheter thrombolysis effectively reduces RV failure, but the incidence of bleeding remains high. The risk of intracerebral hemorrhage is lower than with systemic thrombolysis, but is as high as 1.5%, with major bleeding rates of up to 9.3% [37]. The risk of bleeding persists even with low-dose thrombolytic therapy [38]. The incidence of major bleeding in the FLARE trial was 0.9%, and it is important to note that there were no intracerebral hemorrhages at all. The significant reduction in bleeding risk in the FLARE study confirms the safety of trans-catheter thrombectomy treatment, and no vascular complications were observed in the study. Haemodynamic deterioration during treatment was observed in 4 (3.8%) patients, with the same incidence in trans-catheter thrombolysis trials [39]. The presumed causes of deterioration were re-embolization, progression of RV dysfunction, or respiratory failure. A similar patient population was involved in the PEITHO trial, in which the incidence of haemodynamic deterioration was 5% [9]. In our clinical trial, most complications were observed in the trans-catheter thrombolysis group, and all were related to nonfatal bleeding complications in 23% of patients, with 1 death (8%) during hospitalization due to hemorrhage in the brain.

In summary, treatment of patients with intermediate-high-risk PE by using percutaneous thrombolysis is effective in terms of significant and rapid improvement in RV function, RV diameter, and pulmonary hypertension. However, even low doses of thrombolytic agents can cause bleeding and are contraindicated in certain patients at high risk of bleeding.

4.2 | Percutaneous Thrombectomy Versus Anticoagulation Alone

A single-arm, prospective multicentre EXTRACT-PE study enrolled 119 patients with intermediate risk acute PE (systolic blood pressure ≥ 90 mmHg and RV/LV ratio > 0.9) who underwent aspiration thrombectomy with the 8-F Indigo aspiration system (the same as we used in our study). The authors found a statistically significant reduction in RV/LV ratio from baseline to 48 h (0.43; 95% CI: 0.38 to 0.47; $p < 0.0001$), corresponding to a $27 \pm 13\%$ reduction in RV/LV ratio (1.47 ± 0.30 before vs. 1.04 ± 0.16 after). To add, an average reduction in systolic PAP of 7.9% and a low major bleeding event rate (1.7%) was observed [40]. The short follow-up period of only 48 h is a limitation of this study. Although in our study we included patients with intermediate-high risk PE, percutaneous thrombectomy was similarly associated with a significant reduction in RV/LV ratio by 25.4% (0.3) (95% CI 0.13–0.69; $p < 0.0002$) (Figure 2) 48 h after index procedure, as well as decrease in sPAP by 29%.

The authors of the single-arm FLARE study prospectively evaluated the safety and effectiveness of the FlowTriever percutaneous thrombectomy device in 104 patients with intermediate to high-risk PE with right ventricular dysfunction. At 48 h after the procedure, the average reduction in RV/LV ratio was 0.38 (25.1%; $p < 0.0001$). Four patients (3.8%) experienced a total of six major adverse events, including one patient (1.0%) who suffered major bleeding [40]. These findings were further supported by the recently published data from the FLASH registry, which provides real-world evidence on the outcomes of patients treated with similar approaches. The ongoing, multicentre, prospective FLASH registry is designed to investigate the safety and effectiveness of the second-generation FlowTriever device, and the results from the first 800 patients included in the USA have been reported. Of these, approximately 8% had high-risk PE and 92% had intermediate-risk PE (of which 83% were intermediate-high-risk PE). Approximately one-third of the included patients had thrombolytic contraindications. On-table mean PAP decreased from 32.6 ± 9.0 mmHg to 24.9 ± 8.9 mmHg ($p < 0.0001$), and RV/LV ratio decreased from 1.23 ± 0.36 to 0.98 ± 0.31 ($p < 0.0001$) as assessed by echocardiography at 48 h after the procedure. After 30 days, six deaths were reported, none of which were deemed to be related to the device or the procedure; however, two deaths were due to PE or recurrent PE. Major adverse event rate was 1.8% at 48 h [41].

The FLARE trial is the largest study to date to assess the efficacy and safety of mechanical thrombectomy treatment in PE in a patient sample. There are more clinical trials, with smaller sample sizes, evaluating the benefits of trans-catheter thrombectomy devices in the treatment of PE. One of these is the AngioJet rheolytic thrombectomy device. Its efficacy and safety have been evaluated in the treatment of moderate- to high-risk PE [42–44].

Experience with the large-caliber AngioVac thrombectomy system for PE is limited, possibly due to the complexity of the procedure (technically challenging to introduce a relatively rigid and large-diameter device into the pulmonary artery) [45–48].

The observational findings suggest that catheter-directed mechanical thrombectomy using the 8F Indigo (Penumbra) system may improve hemodynamics with an acceptable safety profile in patients with intermediate-high risk and high-risk PE [49]. Aspiration thrombectomy with the Lightning 12 system characterizes an acceptable safety profile, substantial improvements in hemodynamic outcomes, and low mortality for patients with intermediate-high and high-risk PE [50].

It is of note that compared to trans-catheter thrombolysis, the treatment of PE with trans-catheter thrombectomy is techni-

cally more complex, requiring more effort, skill, experience, and dedicated specialists. This is a reason why the latter treatment approach is not widely adopted. Thus, in summary, the trans-catheter thrombectomy (e.g., with a FlowTriever catheter) without the use of a thrombolytic is a safe and effective treatment option for intermediate—high-risk PE, and should be considered as a relevant treatment option in this setting.

4.3 | Percutaneous Thrombolysis versus Percutaneous Thrombectomy versus Anticoagulation

No randomized trials comparing the efficacy of both reperfusion percutaneous treatments with conservative medical therapy in patients with intermediate-high risk PE have been published to date. There are also no studies comparing trans-catheter thrombolysis with transcatheter thrombectomy, or different devices used for thrombectomy with each other. Our study showed that the time taken to perform a trans-catheter thrombectomy is longer than the time taken to insert a trans-catheter thrombolysis catheter into the pulmonary artery branches (mean 107 [45-180] min vs. 31 [25–40] min). It is clear that there is also a difference in X-ray exposure, with the mean exposure for trans-catheter thrombectomy being 380 [100–730] mGy, whereas for transcatheter thrombolysis it was 26 [14–87] mGy. Moreover, transcatheter thrombectomy requires a skilled operator.

Thus, our study is the first of this kind demonstrating that percutaneous catheter-based therapies may be safe and feasible alternative to conservative treatment, but there is currently limited high-quality evidence to support their efficacy and safety. Data on long-term mortality couldn't be drawn from our study due to the small sample size. Whilst earlier studies have chiefly concentrated on short-term outcomes, there is presently a paucity of information regarding the long-term, functional capacity and quality of life of patients following acute PE. However, certain observational studies and randomized cohorts have reported a high long-term mortality. For instance, in a retrospective study encompassing over 1000 subjects with PE, Ng et al. observed an all-cause mortality rate of approximately 35% following a 4-year follow-up [51]. A recent meta-analysis of publications on the long-term consequences of PE revealed that patients should anticipate an elevated risk of death (11%) and disease recurrence (6%) after primary therapy [52]. Eighteen per cent exhibited persistent RV dysfunction and 11% suffered from respiratory distress, which severely impairs performance in everyday life [52]. The quality of life of patients with acute PE was significantly reduced compared with the general population [52], and a more frequent onset of mental disorders such as depression, anxiety disorder, and post-traumatic stress disorder was described as well [53]. It is unknown so far whether any particular treatment strategy can reduce these long-term outcomes and disease burden among patients with acute PE.

Awaiting the results of the prospective Lungenembolie Augsburg Studie (LEA study) [54], which may answer the questions raised. This prospective, observational cohort study was designed to investigate the long-term course of patients treated for acute PE.

4.4 | Quality of Life, Physical Performance, and Residual Chronic Thromboembolic Pulmonary Hypertension

Quality of life 12 months after the index event, along with longer walking distance, as compared with the conservative treatment group. The findings of older and more recent cohort studies suggest that muscle deconditioning, particularly in the presence of excess body weight and cardiopulmonary comorbidity, is largely responsible for the frequently reported dyspnea and signs of exercise limitation after acute PE. This means that, at least in the majority of cases, poor physical performance after PE does not appear to be attributable to "large" residual thrombi, or persisting/progressive PH and RV dysfunction. Ongoing prospective studies in large numbers of patients may help to better identify predictors of functional and/or haemodynamic impairment after acute PE, and their possible implications for shaping follow-up programmes [55].

The majority of patients who have survived a pulmonary embolism (PE) experience restoration of patency in the pulmonary arterial bed within the first few months following the acute episode [56], as was also observed in our CT findings after 6 months. However, in other patients, thrombi become persistent and organized, which in rare cases may result in chronic thromboembolic pulmonary hypertension (CTEPH). The rarity of this condition is in contrast to the relatively large number of patients who report persisting dyspnea or poor physical performance over several months after acute PE. The prevalence of CTEPH has been documented to range from 0.1% to 9.1% within the initial 2 years following a symptomatic pulmonary embolism (PE) occurrence. This substantial margin of error can be attributed to factors such as referral bias, the absence of early symptoms, and the challenge in distinguishing acute PE from symptoms of pre-existing CTEPH [57, 58].

4.5 | Limitations

Single-center design and small sample size are limitations of the present study. The minimum number of participants required to assess the LV/RV ratio was included. Patients' enrollment was complicated by hospital restrictions imposed due to the COVID-19 pandemic, and permission to conduct the clinical trial was obtained just before the pandemic was declared. Although the sample size was calculated to assess the change in the LV/RV ratio, but the study revealed other important data (such as the difference in functional capacity between groups at baseline), which require a larger sample size in the groups and a longer follow-up period for comparison. A longer at least 5 years follow-up period is needed to monitor the development of CTEPH. Additionally, the study does not compare different thrombectomy devices with each other and for the trans-catheter thrombolysis using a pigtail catheter instead of newer, potentially superior ultrasound-based catheters (EKOS trans-catheter thrombolysis) is a limitation of the present study. Despite this limitation and considering that transcatheter thrombectomies requires well-trained specialists and newer catheters are costly, our study represents a usual practice in smaller centers with restricted finances and personnel. Additionally, due to the relatively small sample

size (39), we did not attempt to assess hard endpoints such as cardiovascular and all-cause mortality; however, the study design remains valid for mechanistic and feasibility evaluation.

5 | Conclusions

In patients with acute intermediate-high-risk pulmonary embolism, percutaneous reperfusion therapies were associated with more rapid early improvements in right ventricular and pulmonary hemodynamic parameters. At mid-term follow-up, cardiac function and biomarker profiles converged across treatment strategies. Given the limited sample size and reliance on surrogate endpoints, these findings should be viewed as mechanistic and exploratory, underscoring the need for adequately powered multicentre trials to define clinical benefit.

Author Contributions

Taida Ivanauskienė: conceptualization. **Taida Ivanauskienė**, **Andrius Berūkštis**, and **Greta Burneikaitė:** methodology. **Kastė Ivanauskaitė:** statistical analysis. **Taida Ivanauskienė** and **Sigita Glaveckaitė:** formal analysis. **Taida Ivanauskienė:** investigation. **Taida Ivanauskienė:** resources. **Taida Ivanauskienė:** data curation. **Taida Ivanauskienė** and **Andrius Berūkštis:** writing – original draft preparation. **Sigita Glaveckaitė**, **Greta Burneikaitė**, **Andrius Berūkštis**, **Rasa Kūgienė**, **Giedrius Navickas**, **Mindaugas Matačiūnas**, and **Kastė Ivanauskaitė:** writing – review and editing. **Taida Ivanauskienė** and **Kastė Ivanauskaitė:** visualization. **Sigita Glaveckaitė:** supervision.

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Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Vilnius Regional Ethics Bioethical Committee, Approval number 2020/3-1208-693.

Consent

Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data are available in Vilnius University Hospital Santaros clinic's database.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.
Table 1: Criteria for assessing right ventricular impairment. **Table 2:** Pulmonary embolism severity index. **Table 3:** Bleeding risk assessment: the HAS-BLED bleeding risk calculator. **Table 4:** Contraindications to thrombolysis. **Table 5:** The PEmb-Qol Questionnaire after having a pulmonary embolism. **Table 6:** WHO Bleeding Grade.