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Ultrasound-Assisted Catheter-Directed Thrombolysis vs. Low-Dose Intravenous Tissue-Type Plasminogen Activator Treatments in Acute Intermediate-High Risk Pulmonary Embolism: Insights from a Retrospective Study

ABSTRACT

Background: Comparative data on ultrasound-assisted catheter-directed thrombolysis (USAT) and systemic low-dose tissue-type plasminogen activator (tPA) for intermediate-high-risk (IHR) pulmonary embolism (PE) remain limited. The efficacy and safety outcomes of USAT vs. intravenous (IV) low-dose tPA were evaluated in this population.

Methods: This study enrolled 329 IHR PE patients treated with USAT (n = 205) or IV low-dose tPA (n = 124). Post-treatment changes in clot burden (Qanadli score), right ventricular (RV) strain, and long-term mortality (median follow-up 95.8 months) were assessed. Propensity score analysis with inverse probability weighting (IPW) was employed to adjust for confounders.

Results: Ultrasound-assisted catheter-directed thrombolysis was predominantly bilateral (82.9%), with a mean tPA dose of 38.5 ± 13.6 mg. In the IV tPA cohort, 58.9% required a second infusion to achieve stabilization. While IV tPA was associated with more pronounced early reductions in heart rate and RV/LV (left ventricle) ratio, USAT provided significantly greater thrombus resolution (all $P < .005$). After IPW adjustment, USAT demonstrated clear superiority over IV tPA in reducing residual clot burden ($P < .001$). However, improvements in oxygen saturation, tricuspid annular plane systolic excursion , and pulmonary artery systolic pressure (PASP) were comparable. No significant differences were observed in in-hospital mortality, PE recurrence, or long-term survival between cohorts. Higher PE severity indexes scores independently predicted in-hospital adverse events, whereas older age, male sex, and higher discharge PASP were predictors of shortened long-term survival.

Conclusions: In IHR PE, IV low-dose tPA relates to more pronounced early hemodynamic and RV diameter improvements, whereas USAT achieves superior thrombus resolution. Despite these divergent surrogate responses, both strategies yield comparable early and long-term clinical outcomes, supporting their roles as viable reperfusion options.

Keywords: Pulmonary embolism, ultrasound-assisted thrombolysis and systemic thrombolysis

INTRODUCTION

Acute pulmonary embolism (PE) has been reported as one of the most frequent lethal cardiovascular diseases in the world.[1,2] Acute onset hemodynamic deterioration develops following the thrombotic obstruction in 30%-50% of the pulmonary arteries (PA), resulting in right ventricular (RV) failure, and increased right ventricle to left ventricle (RV/LV) diameter ratio either assessed by echocardiography or computed tomographic pulmonary angiography predicts clinical worsening irrespective of the initial clinical status.[1-5] The aims of reperfusion strategies in acute PE are to achieve quick reversal of obstructive burden and RV pressure strain, restoration of RV to PA coupling, and hemodynamic stabilization. European Society of Cardiology/European Respiratory Society (ESC/ERS) 2019 PE Guidelines have recommended an updated risk-based treatment strategy.[2] Patients at high-risk (HR) status or initially at intermediate- or low-risk (IR or LR) status but

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developing acute hemodynamic instability has been considered for urgent reperfusion therapies.[2]

Although global trends have demonstrated an increasing incidence with a decreasing all-cause or PE-related 30-day mortality, rates of systemic thrombolytic therapies (STT), catheter-directed therapies (CDTs), or surgical reperfusion therapies have remained unsatisfactory.[6-11] This underutilization is likely driven by concerns regarding the increased risk of bleeding despite the proven benefits from STT over anticoagulants against the mortality and/or PE recurrence risks.[12,13]

Therefore, various CDTs have been developed to attain PA reperfusion quickly with minimal thrombolytic dosages or even without the need for thrombolytics in HR and intermediate-high-risk (IHR) patients.[14-36] Currently, 6 CDT systems are approved by the Food and Drug Administration Committee for interventional PE treatments, and according to their mechanisms, they can be classified as catheter-directed thrombolysis (CDL) or mechanical aspiration thrombectomy (MT) systems.[1,2,14-36] Ultrasound-assisted catheter-directed thrombolysis (USAT) represents the most frequently used CDL therapy in patients with PE at HR or IHR status.[14-28,31]

Although STT remains as the recommended therapeutic option in cases of deterioration to the higher risk status, safety concerns for bleeding risk have driven the search for reduced-dose lytic regimens.[1,2,37-40] Current evidence suggests that satisfactory PA reperfusion, improvements in RV function, and hemodynamic status may not require full-dose tissue-type plasminogen activator (tPA) regimens in IHR PE, and reduced-dose protocols may offer an efficacy comparable to those in full-dose regimens with the advantage of a lower risk of major bleeding events.[1,2,37-40]

In this single-center PE study, the IHR patients who underwent USAT or intravenous (IV) low-dose tPA therapies were retrospectively evaluated, and the post-treatment improvements in the PA thrombolysis, and pressure strain and recovery of RV function, as well as clinical efficacy and safety outcomes during the in-hospital stay period and long-term follow-up, were compared.

HIGHLIGHTS

- Ultrasound-assisted thrombolysis provides significantly greater thrombus resolution and reduction in residual clot burden compared to intravenous (IV) low-dose tissue-type plasminogen activator (tPA).
- Intravenous low-dose tPA achieves more pronounced early improvements in heart rate and right ventricular/left ventricular ratio during the initial treatment.
- Both reperfusion strategies yield comparable outcomes regarding in-hospital mortality, pulmonary embolism (PE) recurrence, and long-term survival rates.
- Higher PE severity indexes scores and discharge pulmonary artery systolic pressure serve as independent predictors for adverse events and mortality.

METHODS

Study Design and Population

In this study, 329 patients with acute PE at IHR out of the 976 patients diagnosed with acute PE in the tertiary cardiovascular center between October 2012 and April 2025 were retrospectively evaluated. The treatment regimen was USAT and systemic tPA (alteplase) infusion in 205 and 124 patients, respectively. The systematic work-up for the initial diagnosis of acute PE and risk stratification, including multidetector contrast-enhanced computed tomography (CT) angiography, echocardiography assessments, pulmonary embolism severity indexes (PESI), and biomarker evaluation, was based on the criteria recommended by the European Society of Cardiology / European Respiratory Society (ESC/ERS) 2014 and 2019 PE guidelines.[1,2] Patients at LR or ILR, and patients at HR who were treated with different CDT other than USAT, those with symptom onset longer than 14 days, and those with the following contraindications for thrombolytics were excluded: Hemorrhagic stroke or stroke of unknown cause at any time, ischemic stroke within the last 6 months, central nervous system damage or malignancy, gastrointestinal bleeding within the last month, known bleeding diathesis. The study protocol was approved by the Institutional Ethics Committee [no. 2025/06/1093, date: April 22, 2025].

Chest Computed Tomography Pulmonary Angiography and Echocardiography

Computed tomography images were acquired by using 64-slice helical CT angiography (Toshiba Aquilion 64, Toshiba Medical Systems Corp., Tokyo, Japan). A validated CT score for PA occlusion proposed by Qanadli et al [Qanadli score (QS)], RV/LV ratio, RV diameter, right atrial to left atrial diameter ratio (RA/LA ratio), and main, left, and right PA diameters were measured from CT images.[41] Pulmonary infarction is defined as a peripheral wedge-shaped pulmonary consolidation in a hypoperfused segment of the lung. Computed tomography images were evaluated at admission and 72-96 hours after the initiation of treatment.

Transthoracic echocardiogram (TTE) was performed on all patients on the first day of admission and repeated at discharge. Tricuspid annular plane systolic excursion (TAPSE) and tissue Doppler (S') measurements were obtained to assess RV function in TTE, and estimated pulmonary artery systolic pressure (PASP) were calculated from the tricuspid regurgitation jet. All measurements and assessments were made in accordance with the American Society of Echocardiography guidelines.[42]

Right Heart Catheterization, Pulmonary Angiography, and Ultrasound-assisted Thrombolysis Procedure

All procedures were performed via the femoral vein (6-F sheath), and arterial puncture was avoided. A 6F multipurpose catheter was used for initial PA pressure measurements and selective angiograms. The EkoSonic Endovascular Device (EKOS, Bothell, Washington) was employed, which includes the Intelligent Drug Delivery Catheter and the MicroSonic Device equipped with multiple small ultrasound transducers distributed across the treatment zone. Procedural details were given in the previous papers.[24-26] The

preferred treatment approach involved operator-driven selection of tPA dose and treatment duration on an individual basis, tailored to each patient's risk status and comorbidities. Approximately 4 hours after the completion of tPA delivery, the system catheters and sheath were removed under fluoroscopic control. Intravenous heparin was started after termination of the USAT procedure with a targeted activated partial thromboplastin time (aPTT) around 60 seconds. Procedural details are summarized in Supplementary Materials.

Low-Dose Intravenous Tissue-Type Plasminogen Activator Treatment Protocol

The thrombolytic treatment strategy was implemented as part of an institutional protocol informed by expert consensus. Patients fulfilling at least one of the following criteria have been included in the study: systolic blood pressure ≤ 110 mm Hg, heart rate > 100 bpm, pulse oximetric saturation (SpO_2) < 90% on room air, respiratory rate > 20 breaths per minute, or serum lactate > 2 mmol/L. Exclusion criteria were the presence of any contraindication for STT, age <18 years, and duration from symptom onset to PE diagnosis >14 days. According to the institutional protocol, patients who met inclusion criteria and none of the exclusion criteria received initial weight-adjusted unfractionated heparin, followed by a 25 mg intravenous infusion of tPA over 4-6 hours. After this first infusion, a bedside clinical reassessment was performed. If any of the following criteria were still present—heart rate >100 bpm, SpO_2 < 90%, or signs of organ hypoperfusion—a second 25 mg tPA infusion was administered in the same manner. In case of persistent clinical deterioration, repeated infusions were given according to the same dosing strategy.

Primary Measures of Effectiveness

Baseline and post-treatment RV/LV ratio and PA obstruction severity (Qs), along with their changes from baseline, were assessed by CT imaging, and baseline and post-treatment TAPSE and its change were evaluated by TTE as measures of treatment effectiveness.

Safety Measures

For safety endpoints, major and minor bleeding events, as well as in-hospital deaths from all causes, were recorded. Major bleeding was defined as overt hemorrhage associated with a fall in the hemoglobin level ≥2.0 g/dL or with transfusion of 2 units of packed red blood cells or involvement of a critical site bleeding including airway, intra-abdominal, and intracranial and other central nervous system bleeding, pericardial tamponade, hemothorax, and retroperitoneal hematoma.[43] Clinical overt bleeding not fulfilling the criteria of major bleeding was classified as a minor bleeding complication.[43]

Statistical Analysis and Modelling

Continuous variables were presented as mean ± SD or median with interquartile range (IQR), based on normality. Categorical data were expressed as frequencies and percentages. Group comparisons were performed using the independent samples *t*-test, Mann–Whitney *U*-test, Pearson's χ^2 or Fisher's exact tests, as appropriate. Within-group changes from baseline were assessed using paired *t*-tests or Wilcoxon signed-rank tests. Missing data (up to 10% for numerical and 5% for categorical variables) were handled via the missForest imputation algorithm.

To mitigate potential selection bias and confounding inherent in the retrospective design, propensity score analysis (PSA) using inverse probability weighting (IPW) was employed. Variables for the PSA, including age, sex, baseline heart rate, oxygen saturation, PESI score, postoperative status, and comorbidities, were selected based on baseline differences and clinical relevance. Covariate balance before and after weighting was assessed using absolute standardized mean differences (Figure 1).

Following IPW adjustment, weighted multiple linear regression models were constructed to evaluate primary effectiveness outcomes (RV/LV, Qs, TAPSE, and their respective changes). Long-term mortality was analyzed using a weighted multivariable Cox regression model, adjusted for age, sex, PESI score, and discharge measurements of TAPSE and PASP. Statistical significance was defined as a 2-tailed $P < .05$. All analyses were performed using Jamovi and R software (version 4.3.2) with packages Hmisc, missForest, ipw, matchit, cobalt, survival, survminer, and rms. During the preparation of this manuscript, artificial intelligence-assisted technologies were utilized solely for grammatical refinement and linguistic clarity.

RESULTS

Baseline Demographic and Clinical Characteristics

The demographic, clinical, and laboratory characteristics of the patients who underwent USAT and those who received low-dose IV tPA are presented in Table 1. Mean and median doses were comparable between the USAT and systemic

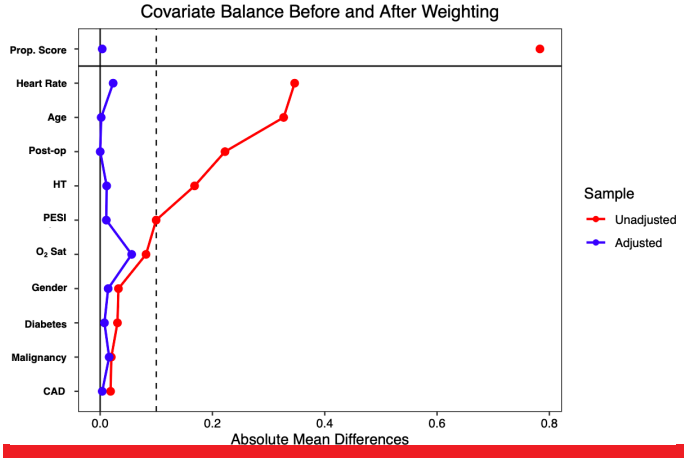

Figure 1. Assessment of covariate balance via propensity score weighting. Absolute standardized mean differences (ASMD) for baseline clinical and demographic variables before (red circles) and after (blue circles) inverse probability weighting. The vertical dashed line represents the threshold for optimal balance (ASMD < 0.1). Post-weighting, all covariates demonstrated significant balance, mitigating potential selection bias between the ultrasound-assisted thrombolysis and intravenous low-dose tissue-type plasminogen activator cohorts.

Table 1. Patients' Demographic, Clinical, and Laboratory Characteristics

	USAT (n = 205)	IV tPA (n = 124)	*P*
Age, years	64 (49.7-73)	55.5 (44-66.6)	<.003
Gender (male), n (%)	91 (44.4)	51 (41.1)	.563
Hypertension, n (%)	94 (45.9)	32 (25.8)	.001
Diabetes, n (%)	35 (17.1)	17 (13.7)	.501
CAD, n (%)	22 (10.7)	9 (7.2)	.387
Heart failure, n (%)	3 (1.5)	3 (2.4)	.669
Hyperlipidemia, n (%)	15 (7.3)	11 (8.8)	.700
COPD, n (%)	18 (8.8)	4 (3.2)	.083
Atrial fibrillation, n (%)	15 (7.3)	2 (1.6)	.104
Stroke, n (%)	5 (2.4)	0 (0)	.329
Past VTE, n (%)	10 (9.8)	15 (12.1)	.505
Acute DVT, n (%)	131 (63.9)	61 (49.2)	.029
Malignancy, n (%)	14 (6.8)	6 (4.8)	.464
Postoperative status, n (%)	77 (37.6)	19 (15.3)	<.001
Orthopedic surgery/fractures, n (%)	15 (7.3)	6 (4.8)	.373
HRT/OCS, n (%)	6 (2.9)	3 (2.4)	.701
Prolonged travelling, n (%)	18 (8.3)	6 (4.8)	.220
Thrombophilia, n (%)	3 (1.5)	1 (0.85)	.293
Syncope, n (%)	54 (26.3)	34 (27.4)	.831
Symptom duration, days	4 (2-7)	3 (2-7)	.14
SBP, mm Hg	120 (109-133)	123 (110-140)	.11
DBP, mm Hg	76 (70-85)	80 (65-90)	.76
Heart rate, /min	108 (95-115)	113 (98.4-125)	<.001
Oxygen saturation, %	89 (87-92)	89 (85-93)	.46
PESI	98 (80.7-117.3)	96.5 (72.8-115.6)	.42
PESI Class	3 (2-4)	3 (2-4)	.50
sPESI	1 (1-2)	1 (1-2)	73
d-Dimer, mg/L	8.1 (4.7-15)	9.8 (5.1-18.9)	.47
Troponin, ng/mL	0.1 (0-0.2)	0.1 (0-0.3)	.39
CRP, mg/L	3.5 (2-8.5)	8.5 (2.2-26)	<.001

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DBP, diastolic blood pressure; DVT, deep vein thrombosis; HRT/OCS, hormone replacement therapy/oral contraceptive drug; IV, intravenous; PESI, Pulmonary Embolism Severity Index; SBP, systolic blood pressure; tPA, tissue-type plasminogen activator; USAT, ultrasound-assisted thrombolysis; VTE, venous thromboembolism.

tPA groups (36.6 ± 13.8 mg - 35 (IQR 30-45) mg, and 47.6 ± 24.8 mg - 50 (IQR 25-50) mg, respectively). Patients in the USAT cohort were significantly older ($P = .003$) and had a higher prevalence of hypertension ($P = .001$) and acute deep vein thrombosis ($P = .029$). No significant baseline differences were observed regarding other comorbidities, symptom duration, or oxygen saturation. Notably, heart rate was lower in the USAT group at admission ($P < .001$). No significant differences were observed regarding PESI scores or sPESI between the groups.

Baseline Echocardiographic and Tomographic Findings

Baseline echocardiographic and tomographic assessments are summarized in Table 2. Although RV function parameters TAPSE and S' were similar between groups, PASP and thrombus burden quantified by Qs were significantly higher in the USAT group ($P < .001$ for both). Right ventricular diameter and RV/LV ratio at admission were higher in the IV tPA group ($P < .001$ for both), while no significant difference was found in RA/LA ratio, PA diameters, or presence of pulmonary infarction (P = NS).

Procedural Characteristics

As illustrated in Figure 2, most USAT procedures (82.9%) were bilateral, with a mean tPA dose of 38.5 ± 13.6 mg and an average infusion duration of 25.2 ± 6.6 hours. Ultrasound-assisted thrombolysis resulted in significant acute reductions in systolic, diastolic, and mean pulmonary artery pressures (Figure 2). In the low-dose IV tPA group, the mean and median total tPA dose was 47.6 ± 24.8 - 50 mg (IQR: 25-50 mg), with an infusion duration of 6 hours (IQR: 4-10 hours). 58.9% of patients required a second infusion, and 11.3% received up to 4 infusions to achieve clinical stabilization (Figure 2) (Detailed data provided in Supplementary Materials).

Post-Treatment Clinical and Imaging Outcomes

Table 3 demonstrates post-treatment clinical, echocardiographic, and tomographic measurements. While systolic and diastolic blood pressures remained similar between groups at discharge, oxygen saturation was modestly higher in the IV tPA group ($P = .004$). No difference between groups was observed in TAPSE, S', RV/LV ratio, or PA diameters at discharge. However, PASP remained significantly lower in the

Table 2. Echocardiographic and Tomographic Measures

	USAT (n = 205)	IV tPA (n = 124)	*P*
TAPSE, mm	1.8 (1.5-2.1)	1.8 (1.5-2.1)	.75
S′, cm/s	11 (9.5-12.1)	12 (8.9-13)	.56
PASP, mm Hg	55 (50-65)	50 (40-60)	<.001
Qanadli score	24 (20-28.1)	20 (18-23.1)	<.001
RV/LV_1 ratio	1.17 (1.1-1.3)	1.28 (1.1-1.4)	<.001
RV diameter, mm	43.8 (40-47)	47.3 (41.9-50)	<.001
RA/LA_1 ratio	1.32 (1.1-1.5)	1.29 (1.1-1.5)	.47
Main PA diameter, mm	30.5 (28.2-34)	30.4 (27.9-32.1)	.24
Left PA diameter, mm	22.8 (21-25.6)	22.7 (20-24.6)	.22
Right PA diameter, mm	23.8 (21.5-26)	22.9 (20.3-25)	.12
Main PA/Aorta ratio	0.9 (0.8-1.0)	0.9 (0.8-1.0)	.42
Pleural effusion, n (%)	26 (12.7)	20 (16.1)	.524
Pulmonary infarction, n (%)	41 (20)	26 (21)	.881

IV, intravenous; LA, left atrium; LV, left ventricle; PA, pulmonary artery; PASP, systolic pulmonary artery pressure; RA, right atrium; RV, right ventricle; S′, right ventricle tissue Doppler; TAPSE, tricuspid annular plane systolic excursion; tPA, tissue-type plasminogen activator.
$_1$Measurement at admission.

IV tPA group ($P = .014$), whereas the post-treatment RA/LA ratio was higher in the USAT group ($P < .001$). Pleural effusion and pulmonary infarction were more prevalent among USAT-treated patients ($P = .002$ and $P = .031$, respectively). Changes in clinical and imaging parameters from baseline are summarized in Table 4. The reduction in heart rate was greater in the IV tPA group ($P = .023$), whereas improvements in oxygen saturation and TAPSE were comparable between groups. The decrease in thrombus burden (Qs) was significantly higher among USAT-treated patients ($P < .001$). Conversely, the reduction in RV/LV ratio was more pronounced in the IV tPA group ($P < .001$), while PASP improvement did not differ significantly between groups (Figure 3).

Adjusted Treatment Effects

After adjustment for confounders using IPW, USAT demonstrated superiority in thrombus resolution over IV tPA. Systemic low-dose IV tPA was associated with a significantly higher residual thrombus burden (Qs_2) (Estimate = 1.92; 95% CI = 0.77-3.07; $P = .001$) and a markedly lower overall

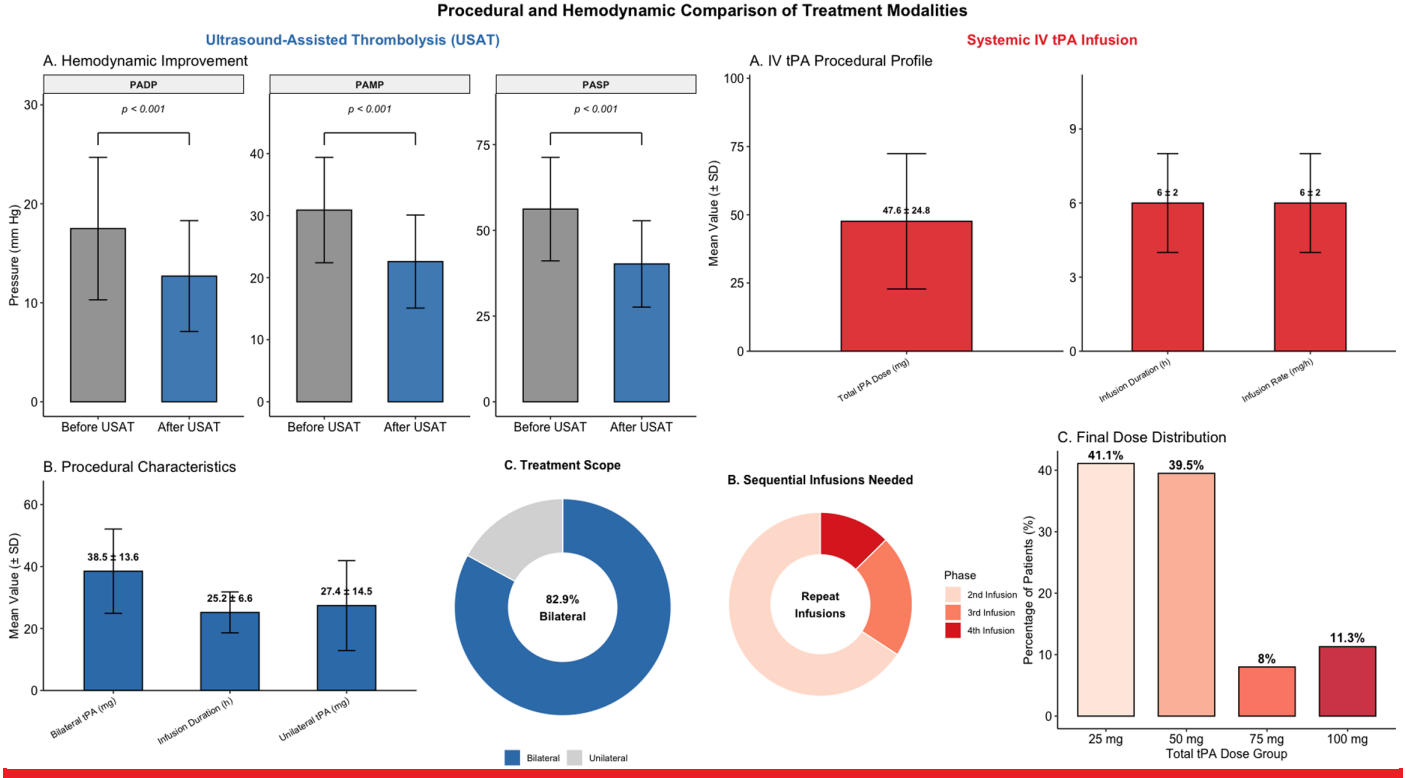

Figure 2. Procedural and hemodynamic profiles of treatment modalities. A head-to-head comparison of procedural characteristics and acute responses.

Table 3. Post-treatment Clinical, Echocardiographic, and Tomographic Measurements

	USAT (n = 205)	IV tPA (n = 124)	*P*
SBP, mm Hg	124 ± 17.2	123 ± 14.9	.848
DBP, mm Hg	75.5 ± 10.5	76 ± 10.5	.776
Heart rate, /min	81.7 ± 12.7	82.2 ± 11.3	.706
Oxygen saturation, %	95 (93-97)	96 (94-97.3)	.004
TAPSE, cm	2.29 ± 0.4	23 ± 0.3	.872
S′, cm/s	14.2 ± 2.4	14.1 ± 2.5	.648
PASP, mm Hg	35 (30-40)	30 (29.5-35.8)	.014
Qanadli score	8 (5-13)	9 (6.75-13)	.169
RV/LV_2 ratio	0.91 ± 0.11	0.90 ± 0.13	.275
RA/LA_2 ratio	1.14 ± 0.22	1.02 ± 0.18	<.001
Main PA diameter, mm	28 ± 4.6	27.8 ± 4	.718
Left PA diameter, mm	21.3 ± 3.3	20.8 ± 2.9	.243
Right PA diameter, mm	21.8 ± 3.5	21.6 ± 3.45	.623
Main PA/Aorta ratio	0.82 ± 0.13	0.86 ± 0.12	.053
Pleural effusion, n (%)	90 (43.9)	26 (20.9)	.002
Pulmonary infarction, n (%)	71 (34.6)	25 (20.1)	.031
Major bleeding, n (%)	12 (5.9)	6 (4.8)	.695
Minor bleeding, n (%)	19 (9.4)	4 (3.2)	.027
In-hospital mortality, n (%)	10 (4.9)	6 (4.8)	.987

IV, intravenous; LA, left atrium; LV, left ventricle; PA, pulmonary artery; PASP, pulmonary artery systolic pressure; RA, right atrium; RV, right ventricle; S′, right ventricle tissue Doppler; TAPSE, tricuspid annular plane systolic excursion; tPA, tissue-type plasminogen activator.
$_2$Measurement after treatment.

reduction in clot load (ΔQs, Estimate = −3.31; 95% CI = −4.63 to −1.99; $P < .001$) (Figure 4). No significant associations were observed between treatment modality and post-treatment RV/LV ratio or TAPSE changes. The results of the weighted models assessing the treatment effect are summarized in Table 5 and Supplementary Tables.

In-Hospital Outcomes and Long-Term Mortality

Weighted logistic regression analysis revealed no significant difference between groups regarding in-hospital mortality or PE recurrence ($P = .694$) (Table 6). Among covariates, higher PESI scores were independently associated with increased risk of in-hospital death or PE recurrence ($P = .003$).

Table 4. Changes in Clinical and Imaging Measurements of Patients

	Mean Change from Baseline (Standard Error)		
	USAT	IV tPA	*P*
Heart rate, /min	24.5 (1.4)	29.6 (1.7)	.023
Oxygen saturation, %	5.1 (0.6)	5.4 (0.8)	.788
TAPSE, cm	0.46 (0.03)	0.46 (0.04)	.995
Qs	14.5 (0.4)	10.1 (0.6)	<.001
RV/LV ratio	0.28 (0.01)	0.37 (0.02)	<.001
PASP, mm Hg	19.1 (0.9)	17.6 (1.4)	.394

IV, intravenous; LV, left ventricle; PASP, pulmonary artery systolic pressure; Qs, Qanadli score; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; tPA, tissue-type plasminogen activator.

The median follow-up period was 95.8 months (IQR: 76.6-104.3). One-year survival rates were comparable between the USAT and IV tPA groups (89.1% vs. 89.5%, respectively) (Figure 5). Weighted Cox regression confirmed no significant difference in long-term mortality between the 2 treatment arms (Table 7). Older age and higher PASP at discharge emerged as independent predictors of mortality, while female sex was associated with lower risk. Notably, neither PESI scores nor discharge TAPSE values were significantly associated with long-term survival.

DISCUSSION

This single-center study retrospectively evaluated the USAT vs. IV low-dose tPA in acute PE patients at IHR status. The reductions in heart rate and in RV/LV ratio were more pronounced with IV tPA, whereas the lysis of thrombi was significantly higher with USAT. However, improvements in the oxygen saturation, TAPSE, and PASP were comparable. After adjustment for confounders, the superiority of USAT over IV tPA in terms of clot resolution was significant, while in-hospital mortality, PE recurrence and long-term mortality were similar between the 2 arms. A higher PESI score independently associated with the risk of in-hospital death or PE recurrence, whereas an older age, male sex and a higher PASP at discharge were independent predictors for shortened long-term survival.

The decisions for urgent reperfusion strategies in acute PE seem to require innovative risk algorithms that consider the changes in cardiorespiratory, metabolic, renal, and cerebrovascular parameters under initial therapies as the

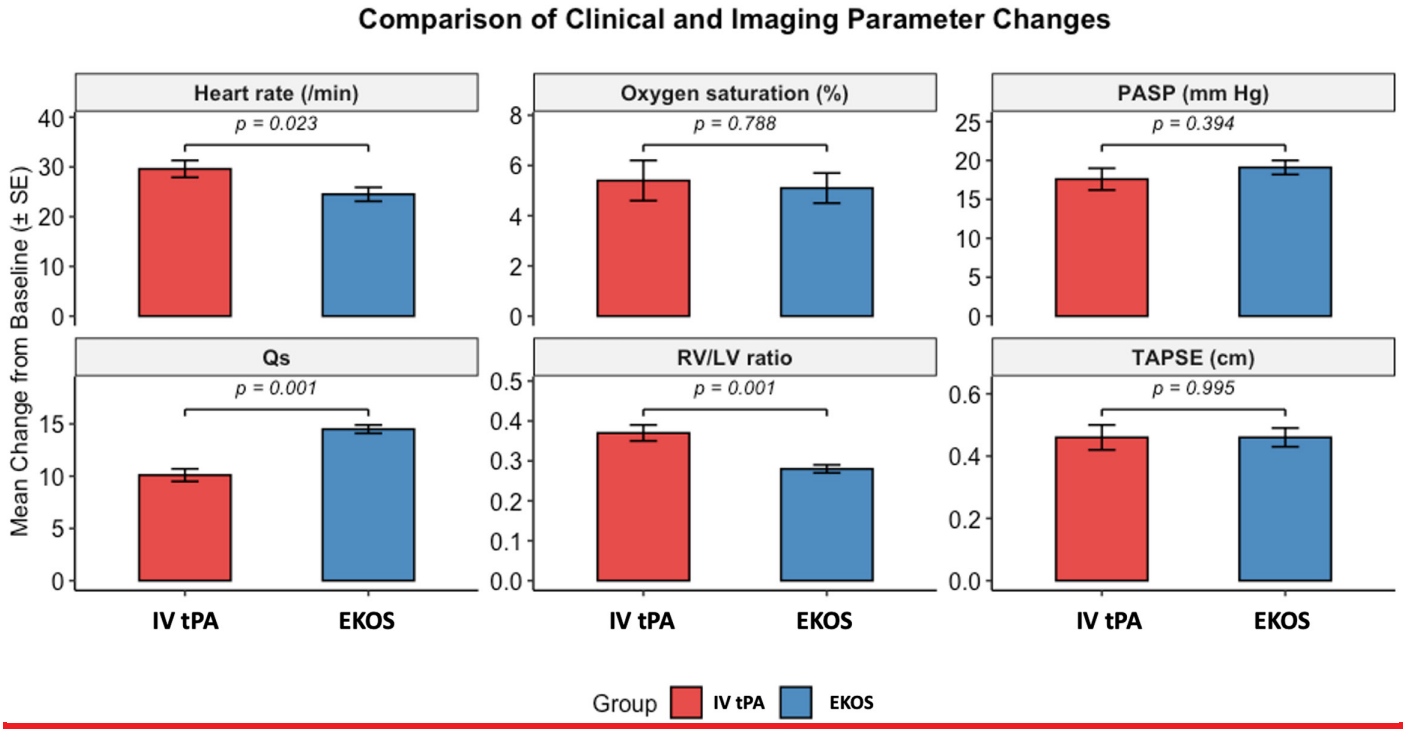

Figure 3. Comparison of acute clinical and imaging response metrics. Bar plots representing the absolute changes from baseline to discharge in key parameters. While ultrasound-assisted thrombolysis (blue) demonstrated significantly greater reductions in thrombus burden (Qanadli score), intravenous low-dose tissue-type plasminogen activator (red) was associated with more pronounced early improvements in heart rate and right ventricle (RV)/left ventricle ratio. Improvements in oxygen saturation and RV functional markers were comparable between the 2 reperfusion strategies.

benefit, failure or deterioration, and tendency for major bleedings.[1,2,14-16,44] Moreover, treatment goals of CDTs and STT are also different between HR and IHR statuses.[1,2,14-16,44] Therefore definitions of treatment success or failure need to be tailored, and comorbidities should also be taken into the account.[1,2,14-16,44] In the clinical consensus statement of the ESC for percutaneous treatments for acute PE, CDT is proposed for HR and IHR patients in the absence of stabilization in vital parameters under initial unfractionated or low-molecular-weight heparin therapies and the presence

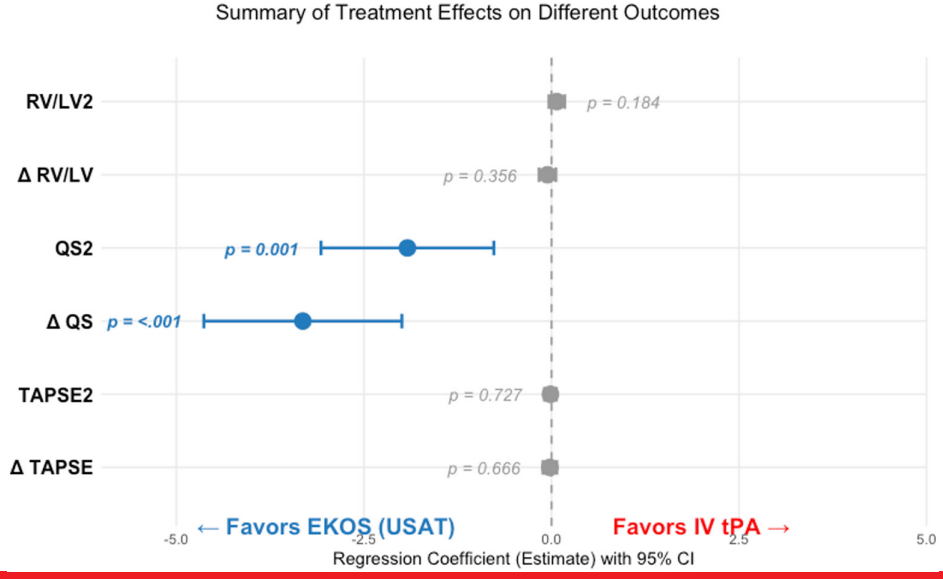

Figure 4. Forest plot of adjusted treatment effects (intravenous (IV) tissue-type plasminogen activator (tPA) vs. ultrasound-assisted thrombolysis (USAT)). Weighted linear regression analysis following inverse probability weighting adjustment. Estimates represent the independent association of IV low-dose tPA with clinical outcomes relative to USAT (Reference).

Table 5. Summary of IV tPA Effects on Different Clinical Outcomes (Weighted Linear Regression)

Outcomes	Estimate (IV tPA)	95% CI Lower	95% CI Upper	*P*
RV/LV_2	0.071	−0.033	0.175	.184
Δ RV/LV	−0.053	−0.164	0.058	.356
QS_2	1.920	0.768	3.072	.001
Δ QS	−3.314	−4.634	−1.994	<.001
$TAPSE_2$	−0.014	−0.094	0.066	.727
Δ TAPSE	−0.021	−0.113	0.071	.666

USAT (EKOS) is the reference group. Positive estimates indicate higher values in the IV tPA group; negative estimates indicate lower values in the IV tPA group compared to USAT. $_2$Measurement after treatment. IV, intravenous; LV, left ventricle; Qs, Qanadli score; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; tPA, tissue-type plasminogen activator; USAT, ultrasound-assisted thrombolysis.

Table 6. Weighted Logistic Regression for in-Hospital Death and Re-embolism

Variables	Estimate (log-odds)	Standard Error	*z*	*P*
IV tPA	−0.226	0.575	−0.393	.694
PESI	0.038	0.013	2.991	.003
Age (per year)	−0.015	0.021	−0.717	.474
Gender (female)	0.469	0.583	0.805	.421

IV, intravenous; PESI, pulmonary embolism severity indexes; tPA, tissue-type plasminogen activator.

of contraindications for STT.[15] In the further decision-making for the selection of optimal CDT devices in PE, location, extension, and age of clot, and risk of bleeding are regarded as major determinants.[14-16,44] A more distal and acute thrombus is considered to favor USAT or other CDL systems, whereas MT seems to be the first treatment of choice in cases of more proximal and subacute thrombus, and there is a need to avoid bleeding. [45,46]

The USAT system produces high frequency and low power pulses of varying waveforms facilitating the penetrance of tPA to deeper layers of clot without disruption of fibrin crosslinks.[17] The efficacy and safety of USAT with adjunctive reduced-dose t-PA regimens have been confirmed by 2 RCTs, retrospective and prospective studies, and meta-analyses.[17-31] In the previously reported series, USAT therapy was associated with significant improvements in the measures of PA thrombotic obstruction, RV/LV and RA/LA ratios, TAPSE, PA diameters, and PA pressures in patients with PE at HR or IHR.[17-31] Thirty-day mortality rate was related to HR status whereas long-term mortality was predicted by aging over 65 years.[46] The OPTALYSE-PE RCT provided the first evidence for low-dose/short-duration t-PA regimen in USAT, and long-term follow-up over a 1-year period revealed sustained benefit in terms of RV function, functional status, and quality of life.[19-21] Thereafter, KNOCOUT-PE multicenter registry also provided the robust evidence for the efficacy and safety of USAT with low-dose/short-duration tPA regimen in real-life settings.[22] Most recently, the HI-PEITHO trial demonstrated that USAT plus anticoagulation significantly reduced the composite risk of PE-related death, cardiorespiratory decompensation, or recurrence within 7 days compared

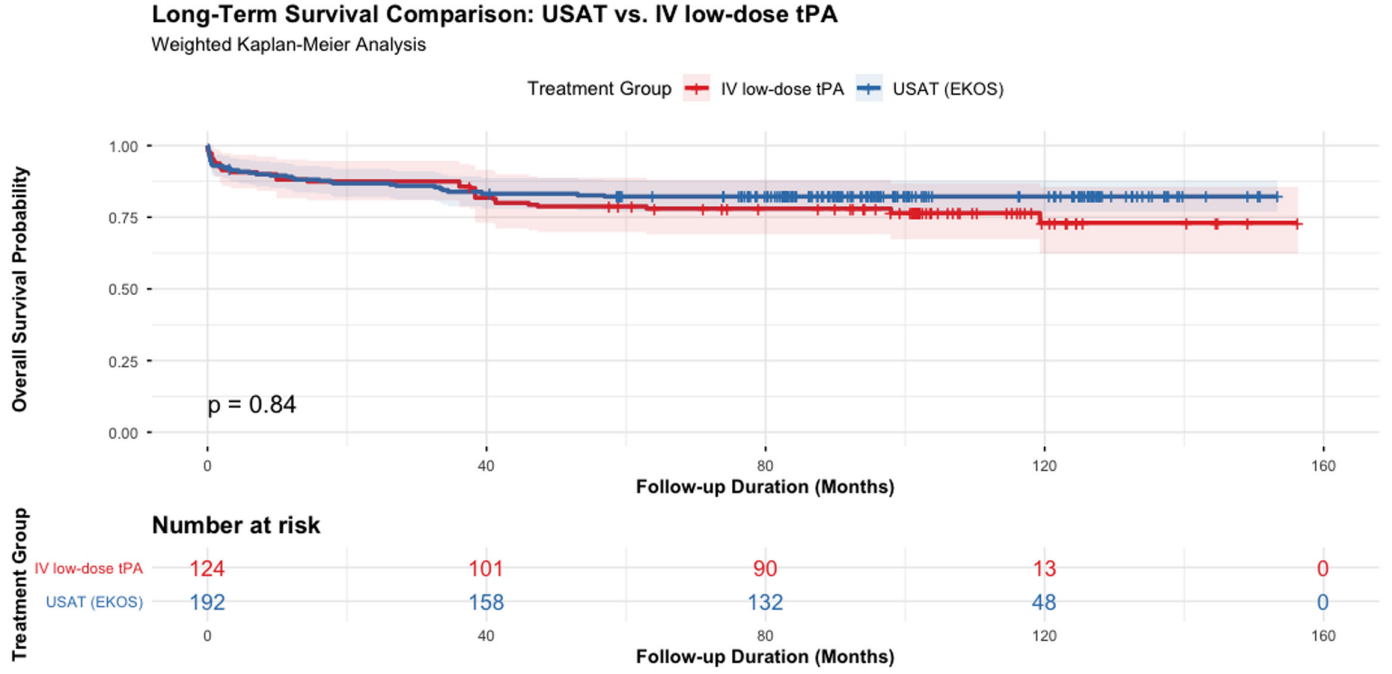

Figure 5. Long-term overall survival: ultrasound-assisted thrombolysis (USAT) vs. intravenous low-dose tissue-type plasminogen activator (tPA). Inverse probability weighted Kaplan–Meier survival curves demonstrating long-term prognosis. The USAT (blue line) and IV low-dose tPA (red line) cohorts exhibited comparable survival probabilities (*P* = NS). The risk table (bottom) displays the number of patients at risk at specific time points throughout the follow-up period.

Table 7. Weighted Cox Regression Results for Long-term Mortality

Variables	HR	95% CI Lower	95% CI Upper	*P*
Age (per year)	1.04	1.01	1.07	.004
Gender (female)	0.51	0.30	0.86	.012
IV tPA	1.42	0.83	2.41	.200
PESI	1.01	1.00	1.02	.133
$TAPSE_2$ (cm)	1.30	0.67	2.53	.444
$PASP_2$ (mm Hg)	1.03	1.00	1.05	.017

HR, hazard ratio; IV, intravenous; PASP, pulmonary artery systolic pressure; PESI, pulmonary embolism severity indexes; TAPSE, tricuspid annular plane systolic excursion; tPA, tissue-type plasminogen activator. $_2$Measurement after treatment.

to anticoagulation alone (4.0% vs. 10.3%, *P* = .005), without increasing major bleeding.[47]

A systematic review and meta-analysis comparing the safety and efficacy of USAT vs. standard CDL with low-dose lytics showed no statistically significant difference between the 2 treatments for odds of in-hospital mortality, intracranial hemorrhage, major bleeding, and for means of hospital or intensive care unit length of stay, or reduction in PA pressures.[48]

On the other hand, dosing of the IV tPA in IHR PE represents another challenging issue.[1,2,37-40] Although STT remains as the recommended therapeutic option in cases of deterioration to the higher risk status, current evidence suggests that satisfactory resolution of PA thrombotic obstruction, improvements in RV pressure strain and hemodynamic status may not require full-dose tPA regimens in IHR PE, and reduced doses may also offer similar efficacy as compared to those in full-dose regimens with the lower risks of bleeding events.[1,2,37-40] In the previously published study, reduced-dose tPA therapies were found to be associated with significant improvements in PASP, RV/LV and RA/LA ratios, and TAPSE in PE patients at IHR.[40] Moreover, the present study demonstrated that the mean and median tPA dose was 47.6 ± 24.8 mg and 50 mg (IQR: 25-50 mg), with an infusion duration of 6 hours (IQR: 4-10 hours) in the low-dose IV tPA cohort. A distinctive finding was the high requirement for repeated infusions; nearly 59% of patients required a second 25 mg dose, suggesting that a single bolus may be insufficient for a significant portion of IHR PE patients. The Pulmonary Embolism Response Team (PERT) algorithm in acute PE related to reductions in all-cause mortality, major or clinically relevant bleeding, length of hospital stay, but higher utilization rates of advanced therapies.[10] In the PERT Consortium Registry between the years 2028 and 2024, trends for utilization of CDT, STT, surgical embolectomy, and extracorporeal membrane oxygenation (ECMO) in large series of patients with acute PE enrolled at 51 sites were analyzed, and an age-, sex-, and PE risk-matched population from the US Nationwide Inpatient Sample was also used for comparison. The HR and IR status were documented in 13.7% and 62.5% of patients respectively. The CDTs were utilized in 23.1% of overall PE patients, and CDL with USAT, MT and CDL without USAT were documented in 32.2%, 58.1% and 5.3% of those, respectively. Surgical embolectomy, STT and ECMO were also noted in 1.1%, 5.6% and 1.1% of patients, respectively. There were significant trends of increase in CDT over time, with an increase in MT and a decrease in CDL. In comparison to the US Nationwide Inpatient Sample population, patients enrolled in the PERT Consortium registry had a lower in-hospital mortality and a shorter hospital length of stay.[6] Similarly, Medicare records confirmed the increase in the rate of CDT over time, and this was mainly related to increases in MT.[7] Time trends of PE treatments from Germany also demonstrated an increase in the utilization of CDT for HR patients. Although utilization of CDT decreased with aging, in-hospital case-fatality rates showed a higher benefit from CDT in octogenarians.[8]

In the ERASE PE (Bern Acute Pulmonary Embolism Registry) single-center cohort study investigating the safety and effectiveness of USAT with low-dose tPA according to the decision of the local PE response team in IHR and HR patients, RV overload and pulmonary artery mean pressure was reduced in 88% of patients. Mortality, embolic stroke, bleeding, and recurrent PE rates were 3.2%, 0.3%, 7.9%, and 1.0%, respectively.[9]

Comparisons of MT and CDL in a systematic review and meta-analysis showed comparable all-cause mortality, in-hospital stay, re-hospitalizations, and bleeding rate in PE.[49] In a nationwide analysis on patients with HR PE, in-hospital mortality, major bleeding, and 30-day urgent readmission rates were not different among the CDL, MT, or both CDL and MT cohorts.[50] A meta-analysis on patients with IR and HR PE revealed that CDT vs. STT was associated with a 60% reduction in in-hospital mortality, a 49% reduction in 30-day mortality, a 54% reduction in 1-year mortality, a 57% reduction in stroke, a 29% reduction in 30-day readmission, a 39% reduction in major bleeding, but a 2.5 times higher rate of hemoptysis and 2.52 times higher rates of ECMO utilization.[51] Another systematic review and network meta-analysis on patients with IR or HR PE, CDT vs. STT was associated with a 57% reduction in all-cause mortality, a 39% reduction in major bleeding, and a 56% reduction in intracranial hemorrhage.[52] The last systematic review and meta-analysis on patients with PE at IR to HR confirmed the superiority of CDT over STT in terms of reductions in major bleeding, in-hospital mortality, and recurrent PE rates.[53] Earlier vs. delayed CDTs was also associated with a significantly higher 90-day survival in IR and HR PE cohorts.[54]

In the study, the majority of USAT procedures were performed bilaterally, and the mean adjuvant tPA dose range was higher, and the infusion duration was also longer than those in currently available other low-dose/slow-infusion USAT trials.

In an emulated target trial analysis on in-hospital mortality prediction adjusted for all non-modifiable risk factors according to treatment strategy in patients with HR PE, the mortality risk ratios were largely in favor of any advanced recanalization strategy including STT, CDT, and surgical thrombectomy over veno-arterial ECMO alone.[55]

In the study, post-treatment systemic arterial pressures, RV function, RV/LV ratio, and PA diameters were similar between 2 treatment groups, but PASP and RA/LA ratio were significantly higher, and pleural effusion and pulmonary infarction were more frequent after USAT treatment. Low-dose IV t-PA was related to more marked reductions in heart rate and in RV/LV ratio, while USAT showed superiority in thrombus resolution. However, both treatment cohorts showed similar improvements in the oxygen saturation, TAPSE, and PASP. Adjustment for confounders also confirmed the superiority of USAT over IV tPA in the dissolution of clot but not for in-hospital mortality, PE recurrence and long-term mortality. These results seem to differ from the results of some meta-analyses favoring the CDT over STT in terms of all-cause mortality and bleeding outcomes. However, the low doses of tPA in STT and moderate-dose/slow-infusion tPA regimen in USAT cohorts might be associated with the absence of the difference in mortality and bleeding outcomes in the study. But, regardless of the selected reperfusion treatments, a higher PESI score independent predictor for in-hospital death or PE recurrence risks, whereas older age, male sex and a higher PASP at discharge predicted long-term survival.

In the recently published retrospective study, using unsupervised machine learning, 2 phenotypes were identified in IHR PE patients.[56] Cluster 1 (RV-failure phenotype) exhibited a younger age, lower systolic blood pressure, more severe RV dysfunction, higher thrombotic burden, and lower baseline TAPSE/PASP ratios, while Cluster 2 (comorbidity-dominant phenotype) comprised older patients with more cardiovascular/metabolic comorbidities but relatively preserved hemodynamics. Cluster 1 demonstrated a higher improvement in RV function after reperfusion therapies, while Cluster 2 was independently associated with a lower early mortality. However, the CDT-cluster interaction term was not statistically significant, and long-term survival was comparable between clusters.[56]These findings suggest that unsupervised machine learning may refine initial risk stratification and help guide tailored management decisions in patients at IHR.

With further validations regarding the efficacy and safety outcomes of low-dose IV tPA protocols, this approach might transform the care for IHR PE. Three ongoing trials in patients at IHR; reduced-dose intravenous thrombolysis for acute intermediate-high-risk pulmonary embolism: rationale and design of the pulmonary embolism international thrombolysis (PEITHO)-3, and low dose thrombolysis, USAT or heparin for intermediate high risk pulmonary embolism (STRATIFY) have been designed to assess the efficacy and safety of reduced-dose tPA regimen compared with standard anticoagulant therapy, and the USAT with low-dose, rapid-infusion tPA strategy vs. standard anticoagulation, respectively.[46,57]

Limitations, Clinical Implications, and Future Directions

This study has several limitations inherent to its retrospective, single-center design. Although IPW adjustment was employed to mitigate selection bias, unmeasured confounders may still influence the results. However, the relatively large sample size for a single-center study and the long-term follow-up provide robust real-world data on these competing reperfusion strategies. Innovative risk stratification algorithms taking into account obstructive burden, RV adaptive response to pressure strain, hemodynamic status, and bleeding risks may provide further insights regarding the tailored PE treatments in IHR. Prospective trial designs that permit comparisons among risk-based anticoagulant and full-dose or reduced-dose STT therapies, different doses and infusion regimens of tPA with USAT, and USAT vs. other CDTs might provide more relevant data for efficacy and safety concerns in this setting.

CONCLUSION

In patients with acute IHR PE, systemic low-dose IV tPA was associated with more pronounced early improvements in heart rate and RV/LV ratio, whereas USAT demonstrated clear superiority in thrombus resolution. After adjusting for confounders, these responses did not translate into differences in early or late clinical outcomes, including in-hospital mortality, PE recurrence, or long-term survival. The comparable safety and efficacy profiles suggest that both USAT and low-dose systemic regimens are viable reperfusion strategies in this setting. Ongoing randomized trials are expected to further refine the optimal selection of reperfusion strategies for this vulnerable patient population.

Ethics Committee Approval: This study was approved by the Ethics Committee of Kartal Kosuyolu Research and Education Hospital, Istanbul, Türkiye (Approval No: 2025/06/1093, Date: April 22, 2025).

Informed Consent: Due to the retrospective nature of the study, informed consent was not obtained from the patients.

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SUPPLEMENTARY MATERIAL

Procedural characteristics of USAT.

	USAT n = 205		
Bilateral, n (%)	170 (82.9%)		
tPA dose, mg Unilateral Bilateral	27.4 ± 14.5 38.5 ± 13.6		
Infusion duration, hours	25.2 ± 6.6		
Pulmonary pressures before USAT		Pulmonary pressures after USAT	
PASP, mm Hg	56.2 ± 15.1	PASP, mm Hg	40.2 ± 12.6
PADP, mm Hg	17.5 ± 7.2	PADP, mm Hg	12.7 ± 5.6
PAMP, mm Hg	30.9 ± 8.5	PAMP, mm Hg	22.6 ± 7.5

Abbreviations: tPA: Tissue plasminogen activator, PASP: Pulmonary artery systolic pressure PADP: Pulmonary artery diastolic pressure, PAMP: Pulmonary artery mean pressure

Thrombolytic dosing regimens.

	All, n = 124
tPA dose, mg	50 (25-50), 47.6 ± 24.8
tPA infusion duration, hours	6 (4-10)
tPA infusion rate, mg/hours	6 (4-10)
Requirement following the 1st infusion 2nd Infusion (50 mg) 3rd Infusion (75 mg) 4th Infusion (100 mg)	 73 (58.9%) 24 (19.3%) 14 (11.3%)
tPA dose groups 25mg 50mg 75mg 100mg	 51 (41.1%) 49 (39.5%) 10 (8%) 14 (11.3)

Supplementary Table 1. Weighted Linear Regression for RV/LV_2.

Variables	**Estimate**	**95% CI**	***P***
IV tPA	0.071	(−0.033 – 0.175)	0.184
PESI	0.001	(−0.001 – 0.004)	0.220
Age (per year)	−0.000	(−0.004 – 0.003)	0.814
Gender (female)	−0.052	(−0.158 – 0.054)	0.334
RV/LV_1	0.039	(−0.230 – 0.308)	0.778

Supplementary Table 2. Weighted Linear Regression for ΔRV/LV.

Variables	**Estimate**	**95% CI**	***P***
IV tPA	**−0.053**	**(−0.164 – 0.058)**	**0.356**
PESI	**−0.001**	**(−0.003 – 0.002)**	**0.460**
Age (per year)	**0.001**	**(−0.003 – 0.005)**	**0.666**
Gender (female)	**0.094**	**(−0.019 – 0.206)**	**0.103**

Supplementary Table 3. Weighted Linear Regression for QS_2.

Variables	**Estimate**	**95% CI**	***P***
IV tPA	**1.920**	**0.768 – 3.072**	**0.0012**
PESI	**−0.013**	**(−0.037 – 0.012)**	**0.323**
Age (per year)	**−0.045**	**(−0.087 – −0.003)**	**0.038**
Gender (female)	**−0.180**	**(−1.311 – 0.951)**	**0.755**
QS_1	**0.498**	**0.410 – 0.586**	**<0.001**

Supplementary Table 4. Weighted Linear Regression for ΔQS

Variables	**Estimate**	**95% CI**	***P***
IV tPA	**−3.314**	**−4.634 – −1.994**	**<0.001**
PESI	**0.015**	**−0.015 – 0.045**	**0.310**
Age (per year)	**0.070**	**0.020 – 0.120**	**0.006**
Gender (female)	**0.666**	**−0.659 – 1.990**	**0.325**

Supplementary Table 5. Weighted Linear Regression for $TAPSE_2$.

Variables	**Estimate**	**95% CI**	***P***
IV tPA	**−0.014**	**−0.094 – 0.066**	**0.727**
PESI	**−0.001**	**−0.003 – 0.001**	**0.443**
Age (per year)	**0.000**	**−0.003 – 0.004**	**0.779**
Gender (female)	**−0.040**	**−0.120 – 0.041**	**0.335**
$TAPSE_1$ (cm)	**0.420**	**0.318 – 0.521**	**<0.001**

Supplementary Table 6. Weighted Linear Regression for ΔTAPSE

Variables	**Estimate**	**95% CI**	***P***
IV tPA	**−0.021**	**−0.113 – 0.071**	**0.666**
PESI	**0.001**	**−0.001 – 0.004**	**0.268**
Age (per year)	**0.001**	**−0.003 – 0.005**	**0.773**
Gender (female)	**−0.020**	**−0.133 – 0.093**	**0.685**