Original Article



# Ultrasound-facilitated catheter-directed thrombolysis is associated with improved survival and reduces hospital stay in acute pulmonary embolism: a propensity score-matched analysis

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**Background:** Systemic thrombolysis for intermediate-high and high-risk pulmonary embolism (PE) is limited by major bleeding risk. Ultrasound-facilitated catheter-directed thrombolysis (USAT) enables targeted fibrinolysis with lower thrombolytic doses, but comparative effectiveness data are often confounded by selection bias. We aimed to evaluate the safety and efficacy of USAT versus conventional therapy (anticoagulation or systemic thrombolysis) in a propensity score-matched cohort of patients managed within a multidisciplinary Pulmonary Embolism Response Team (PERT) pathway.

**Methods:** We performed a retrospective study of 230 consecutive patients within a multidisciplinary PERT pathway. Patients received USAT using the EkoSonic Endovascular System or conventional therapy consisting of anticoagulation or systemic lysis. One-to-one propensity score matching (PSM) was performed, adjusting for age, sex, Pulmonary Embolism Severity Index (PESI), chronic kidney disease, history of deep vein thrombosis, obesity, and baseline troponin. A doubly robust logistic regression (PSM plus regression adjustment) was used to account for residual imbalance in left heart failure.

**Results:** PSM yielded 81 matched pairs. USAT was associated with significantly lower in-hospital mortality (2.5% *vs.* 17.3%, P=0.003) and shorter hospital stay (13.0 *vs.* 17.5 days, P=0.008). Doubly robust post-match logistic regression confirmed USAT as an independent predictor of survival (adjusted odds ratio 0.17, P=0.007). Regarding safety, USAT had significantly fewer International Society on Thrombosis and Hemostasis (ISTH) major bleeding events (1.2% *vs.* 11.1%, P=0.02), whereas clinically relevant non-major bleeding was more common (17.3% *vs.* 1.2%, P<0.001). In exploratory subgroup analysis of obese patients (body mass index >30 kg/m$^2$), USAT showed a similar mortality signal (3.1% *vs.* 33.3%, P=0.02).

**Conclusions:** USAT was associated with lower in-hospital mortality and shorter hospital stay compared with conventional therapy. USAT was also associated with fewer major bleeding events, whereas clinically relevant non-major bleeding was more frequent. Exploratory subgroup analysis in obese patients suggested a

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similar mortality signal.

**Keywords:** Right ventricular dysfunction; Pulmonary Embolism Response Team (PERT); EkoSonic Endovascular System (EKOS); ultrasound-facilitated catheter-directed thrombolysis (USAT); hemodynamic; bleeding risk

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## Introduction

Acute pulmonary embolism (PE) represents a major global health issue, classified as the third leading cause of cardiovascular mortality, following myocardial infarction and stroke (1). Although outcomes for low-risk PE have improved with the use of direct oral anticoagulants, the management of patients with intermediate to high-risk PE remains an ongoing clinical challenge. These patients, characterized by hemodynamic stability with evident right ventricular (RV) dysfunction and myocardial injury, encounter a significant risk of early clinical deterioration and hemodynamic collapse (2).

### Highlight box

**Key findings**

- Ultrasound-facilitated catheter-directed thrombolysis (USAT) within a multidisciplinary Pulmonary Embolism Response Team (PERT) pathway was associated with lower in-hospital mortality (2.5% *vs.* 17.3%) and shorter hospital stay compared with conventional therapy.
- USAT demonstrated a lower rate of major bleeding compared with conventional treatments (1.2% *vs.* 11.1%).

**What is known and what is new?**

- Previous randomized trials established that USAT effectively reverses right ventricular (RV) dilation and reduces pulmonary vascular resistance; however, these studies were not powered to detect differences in survival.
- This real-world matched analysis suggests that the hemodynamic benefits of USAT may translate into lower in-hospital mortality and shorter hospital stay. Exploratory subgroup analysis suggested a similar mortality signal in obese patients.

**What is the implication, and what should change now?**

- Targeted fibrinolysis with USAT may bridge the therapeutic gap for intermediate-high and high-risk patients by preventing hemodynamic collapse while minimizing systemic bleeding risk.
- These data support consideration of early multidisciplinary evaluation and selective use of USAT in patients with evident RV dysfunction, while emphasizing the need for prospective validation.

Historically, the therapeutic options consisted of standard anticoagulation, which might be inadequate to reverse significant RV strain, and systemic thrombolysis. The PEITHO trial showed that systemic fibrinolysis lowered the risk of hemodynamic collapse, but was associated with an increased bleeding risk including a 2% incidence of intracranial hemorrhage (ICH) (3). As a result, current guidelines limit systemic thrombolysis to high-risk, hemodynamically unstable patients, leaving a therapeutic gap for the intermediate-risk group that needs RV unloading without the bleeding risks of systemic therapy (1).

Ultrasound-facilitated catheter-directed thrombolysis (USAT) has emerged as a promising strategy to bridge this gap. The technology employs high-frequency, low-power ultrasound to induce acoustic streaming, which reversibly disaggregates fibrin and enhances the permeation of thrombolytic agents into the clot (4). This mechanism is further supported by recent European consensus statements on percutaneous interventions (5). This mechanism allows for effective thrombus resolution using reduced dosages of recombinant tissue plasminogen activator (rt-PA), theoretically minimizing systemic bleeding risks. Randomized and prospective trials, including ULTIMA (6), SEATTLE II (7), and OPTALYSE-PE (8), have established the efficacy of USAT in reversing RV dilation and reducing pulmonary vascular resistance.

Despite these favorable hemodynamic outcomes, the conversion of surrogate imaging endpoints into definitive patient-centered outcomes, particularly survival and hospital length of stay (LOS), continues to be a point of debate. The published clinical trials were not powered to detect mortality differences, and subsequent real-world analyses have yielded conflicting results. While some observational data suggest USAT may facilitate earlier recovery and reduce LOS compared to systemic anticoagulation (9), other studies report no significant mortality benefit and raise concerns regarding procedural costs and bleeding complications (10,11).

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Given the rapid adoption of USAT within Pulmonary Embolism Response Team (PERT) protocols, there is a critical need to evaluate its real-world effectiveness using rigorous methodology to account for baseline imbalances.

The objective of this study was to evaluate the safety and efficacy of USAT compared to conventional therapy in a large, real-world cohort of patients with acute PE. To rigorously account for baseline differences in disease severity and comorbidities, we utilized propensity score matching (PSM) to isolate the specific impact of the intervention on survival, hospital resource utilization, and bleeding outcomes. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-2026-0468/rc).

## Methods

### *Study design and patient cohort*

We performed a retrospective, single-center comparative cohort study involving consecutive adult patients with acute PE treated at RWTH University Hospital Aachen, Germany from August 2017 to December 2023. Patients were identified from the institutional PERT registry and electronic health records. The patients were divided into two groups: the USAT Group, which included patients who had ultrasound-facilitated catheter-directed thrombolysis with the EkoSonic Endovascular System (EKOS), and the Conventional Group, which comprised patients treated with standard anticoagulation (unfractionated or low-molecular-weight heparin) or systemic thrombolysis. Allocation to systemic lysis within this group followed institutional standards based on European Society of Cardiology (ESC) guidelines (1), specifically reserving systemic therapy for patients presenting with hemodynamic instability or high-risk features. It is noteworthy that during the same study period, surgical embolectomy was performed in only a small minority of patients (n=3) who presented with absolute indications for open surgery, such as thrombus-in-transit or paradoxical embolism. This study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Ethics Committee of the Medical Faculty of RWTH Aachen University (No. EK 25-286). Due to the retrospective nature of the study, the requirement for informed consent was waived.

### *PERT*

All patients were assessed and treated according to a structured PERT pathway. The PERT was made up of experts in cardiology, thoracic surgery, intensive care medicine, and cardiac surgery, which allowed for quick, thorough evaluations by multiple specialists. Treatment decisions, including the allocation to catheter-directed therapy versus conventional care, were made by consensus, integrating clinical severity, imaging findings, biomarker profiles, bleeding risk, and comorbidities (12).

### *Treatment protocols: ultrasound-facilitated catheter-directed thrombolysis (USAT)*

USAT was performed using the EKOS Endovascular System (Boston Scientific, Marlborough, MA, USA). Procedures were primarily performed in a hybrid operating room by experienced interventional cardiac or thoracic surgeons, supported by an attending anesthesiology team. This setup was utilized to ensure immediate capability for veno-arterial extracorporeal membrane oxygenation (VA-ECMO) cannulation or conversion to open surgical embolectomy in the event of precipitous hemodynamic collapse, highlighting the integral role of the cardiothoracic surgeon within the multidisciplinary team. Catheters were positioned in the pulmonary arteries under fluoroscopic guidance. Thrombolysis was administered using rt-PA (alteplase) combined with continuous high-frequency ultrasound. The protocol followed a low-dose, slow-infusion strategy consistent with the SEATTLE II trial (7): alteplase was infused at 1 mg/h per catheter (total dose up to 24 mg over 12–24 hours). Systemic anticoagulation with unfractionated heparin was maintained during the procedure. Conventional therapy was defined as standard-of-care anticoagulation alone or systemic thrombolysis followed by anticoagulation, according to the treating team and PERT recommendation. Patients in the conventional group received therapeutic anticoagulation initiated immediately upon diagnosis, consisting of intravenous unfractionated heparin [adjusted to partial thromboplastin time (PTT) 60–80 seconds] or weight-adjusted low-molecular-weight heparin, in accordance with ESC guidelines (1). Details on systemic thrombolysis dosing regimens were not consistently captured in the registry dataset.

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### *Data collection and outcomes*

Baseline characteristics, vital signs, laboratory biomarkers including B-type natriuretic peptide (BNP) and cardiac troponin, and imaging parameters were extracted from medical records. The primary endpoint was the In-hospital all-cause mortality. While the secondary endpoints were the Length of hospital stay (LOS) and hemodynamic efficacy (change in RV/LV ratio). Safety outcomes included acute kidney injury (AKI) and other in-hospital complications, which were defined according to institutional clinical criteria. Bleeding outcomes were adjudicated according to the standardized definitions proposed by the International Society on Thrombosis and Hemostasis (ISTH) (13). Major bleeding was defined as fatal bleeding, symptomatic bleeding in a critical organ (including intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal bleeding), bleeding causing a hemoglobin decrease of ≥2 g/dL, or leading to transfusion of ≥2 units of packed red blood cells. Clinically relevant non-major (CRNM) bleeding was defined as overt bleeding that did not meet criteria for major bleeding but required medical intervention, unscheduled physician contact, temporary cessation of anticoagulation, or resulted in patient discomfort or impairment of daily activities (14).

### *Statistical analysis and PSM*

To account for baseline differences between treatment groups, a PSM approach was applied. Propensity scores were estimated using a logistic regression model including age, sex, Pulmonary Embolism Severity Index (PESI) risk class, chronic kidney disease, history of deep vein thrombosis, obesity, and baseline troponin as covariates. Patients were matched 1:1 using nearest-neighbor matching without replacement, with a caliper width of 0.2 standard deviations of the logit of the propensity score, yielding 81 matched pairs. Covariate balance before and after matching was assessed using standardized mean differences (SMD). In the matched cohort, continuous variables were compared using non-parametric tests as appropriate, and categorical outcomes were compared using exact or chi-square tests. Survival was analyzed using Kaplan-Meier curves and compared using the log-rank test. Residual imbalance was noted for history of left heart failure. To account for residual confounding, we performed a doubly robust logistic regression in the matched cohort (PSM plus regression adjustment), entering treatment group and left heart failure status as covariates to calculate adjusted odds ratios (aORs) for in-hospital mortality. A two-sided P value <0.05 was considered statistically significant. All statistical analyses were performed using R Statistical Software (R Foundation for Statistical Computing, Vienna, Austria).

## Results

### *Baseline characteristics and PSM*

A total of 230 patients were identified (Conventional: n=102; USAT: n=128). Prior to matching, significant baseline differences were observed, reflecting selection bias in real-world clinical practice. The Conventional group presented with a significantly higher burden of comorbidities, including chronic kidney disease (20.6% *vs.* 7.8%; P=0.009) and a higher prevalence of high-risk PESI stratification (25.5% *vs.* 4.7%; P<0.001). Conversely, obesity [body mass index (BMI) >30 kg/m$^2$] was more prevalent in the USAT group (25.0% *vs.* 11.8%; P=0.02) (*Table 1*).

Following 1:1 PSM, 162 patients were retained (n=81 per group). Within the conventional group, 74 patients (72.5%) received anticoagulation alone and 28 patients (27.5%) underwent systemic thrombolysis. The matching procedure improved balance in key demographic and PE severity variables, including age, sex, PESI risk class, baseline troponin T levels, and RV/LV ratio (*Table 1*). Covariate balance before and after matching is illustrated in *Figure 1*. However, residual imbalances remained in selected comorbidities and laboratory parameters, most notably a history of left heart failure, which was more prevalent in the matched conventional cohort compared with the USAT cohort (23.5% *vs.* 4.9%; P=0.001). Mild residual differences in BNP levels and echocardiographic RV dysfunction were also observed after matching (*Table 1*). Despite these residual differences, overall baseline risk stratification and PE severity markers were well balanced between groups. Importantly, in a doubly robust post-match logistic regression model adjusting for left heart failure, USAT remained independently associated with lower in-hospital mortality, indicating that the observed survival difference was not solely explained by these residual imbalances.

### *Hemodynamic and biomarker response*

In the USAT cohort, treatment resulted in a rapid and significant reduction in RV strain. Multivariable linear

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**Table 1** Baseline demographic characteristics of the study population before and after propensity score matching

| Variable | Before matching | | | After matching | | | |
|---|---|---|---|---|---|---|---|
| | Conventional (n=102) | USAT (n=128) | P value | Conventional (n=81) | USAT (n=81) | SMD | P value |
| Demographics | | | | | | | |
| Age (years) | 65.7±16.5 | 64.0±14.2 | 0.16 | 64.4±16.7 | 65.4±13.5 | 0.065 | 0.83 |
| Female sex | 52 (51.0) | 45 (35.2) | 0.02 | 37 (45.7) | 36 (44.4) | 0.025 | >0.99 |
| Obesity (BMI >30 kg/m$^2$) | 12 (11.8) | 32 (25.0) | 0.02 | 12 (14.8) | 13 (16.0) | 0.034 | >0.99 |
| Comorbidities | | | | | | | |
| Hypertension | 16 (15.7) | 17 (13.3) | 0.74 | 8 (9.9) | 11 (13.6) | 0.115 | 0.63 |
| Diabetes mellitus type 2 | 22 (21.6) | 18 (14.1) | 0.19 | 17 (21.0) | 9 (11.1) | 0.272 | 0.13 |
| CAD | 5 (4.9) | 4 (3.1) | 0.52 | 4 (4.9) | 1 (1.2) | 0.215 | 0.37 |
| Left heart failure | 9 (8.8) | 6 (4.7) | 0.28 | 19 (23.5) | 4 (4.9) | 0.550 | 0.001 |
| COPD | 0 (0.0) | 2 (1.6) | 0.50 | 0 (0.0) | 1 (1.2) | 0.158 | >0.99 |
| Active cancer history | 5 (4.9) | 11 (8.6) | 0.41 | 5 (6.2) | 9 (11.1) | 0.176 | 0.40 |
| History of DVT | 37 (36.3) | 67 (52.3) | 0.02 | 34 (42.0) | 37 (45.7) | 0.075 | 0.75 |
| CKD | 21 (20.6) | 10 (7.8) | 0.009 | 10 (12.3) | 8 (9.9) | 0.079 | 0.80 |
| Nicotine abuse | 8 (7.8) | 15 (11.7) | 0.39 | 0 (0.0) | 1 (1.2) | 0.158 | >0.99 |
| Clinical presentation | | | | | | | |
| Cardiac arrest (resuscitated) | 6 (5.9) | 3 (2.3) | 0.18 | 10 (12.3) | 7 (8.6) | 0.121 | 0.61 |
| Shock at admission | 3 (2.9) | 6 (4.7) | 0.73 | 3 (3.7) | 4 (4.9) | 0.061 | >0.99 |
| PESI risk stratification | | | | | | | |
| Low risk | 45 (44.1) | 61 (47.7) | 0.69 | 43 (53.1) | 38 (46.9) | 0.124 | 0.53 |
| Intermediate risk | 31 (30.4) | 61 (47.7) | 0.009 | 28 (34.6) | 37 (45.7) | 0.228 | 0.20 |
| High risk | 26 (25.5) | 6 (4.7) | <0.001 | 10 (12.3) | 6 (7.4) | 0.166 | 0.43 |
| Laboratory values | | | | | | | |
| Troponin T (ng/L) | 69.0 [33.0–172.0] | 49.0 [24.0–114.5] | 0.03 | 92.0 [44.0–210.0] | 97.0 [45.0–166.0] | 0.049 | 0.92 |
| BNP (ng/L) | 2,700 [1,131–7,950] | 2,800 [1,400–5,250] | 0.90 | 2,714.0 [1,124.0–5,133.0] | 2,365.0 [1,153.0–3,666.0] | 0.284 | 0.07 |
| AST (U/L) | 51.0 [30.0–113.0] | 30.5 [23.8–50.0] | <0.001 | 53.5 [29.0–84.0] | 30.0 [23.0–50.0] | 0.370 | 0.009 |
| ALT (U/L) | 47.0 [25.0–94.0] | 29.0 [17.8–55.0] | <0.001 | 47.0 [26.0–73.0] | 30.0 [17.0–54.2] | 0.093 | 0.08 |
| Imaging parameters | | | | | | | |
| RV/LV ratio (CT) | 1.6±0.3 | 1.6±0.3 | >0.99 | 1.6±0.3 | 1.6±0.3 | 0.035 | 0.72 |
| RV dysfunction on echo | 68 (66.7) | 75 (58.6) | 0.26 | 17 (21.0) | 8 (9.9) | 0.311 | 0.08 |

Data are presented as mean ± SD, median [IQR], or n (%) as appropriate. Balance between the matched cohorts was assessed using the standardized mean difference, with values <0.10 generally considered to indicate a negligible difference between groups. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CT, computed tomography; DVT, deep vein thrombosis; IQR, interquartile range; LV, left ventricular; PESI, pulmonary embolism severity index; RV, right ventricular; SD, standard deviation; SMD, standardized mean difference; USAT, ultrasound-facilitated catheter-directed thrombolysis.

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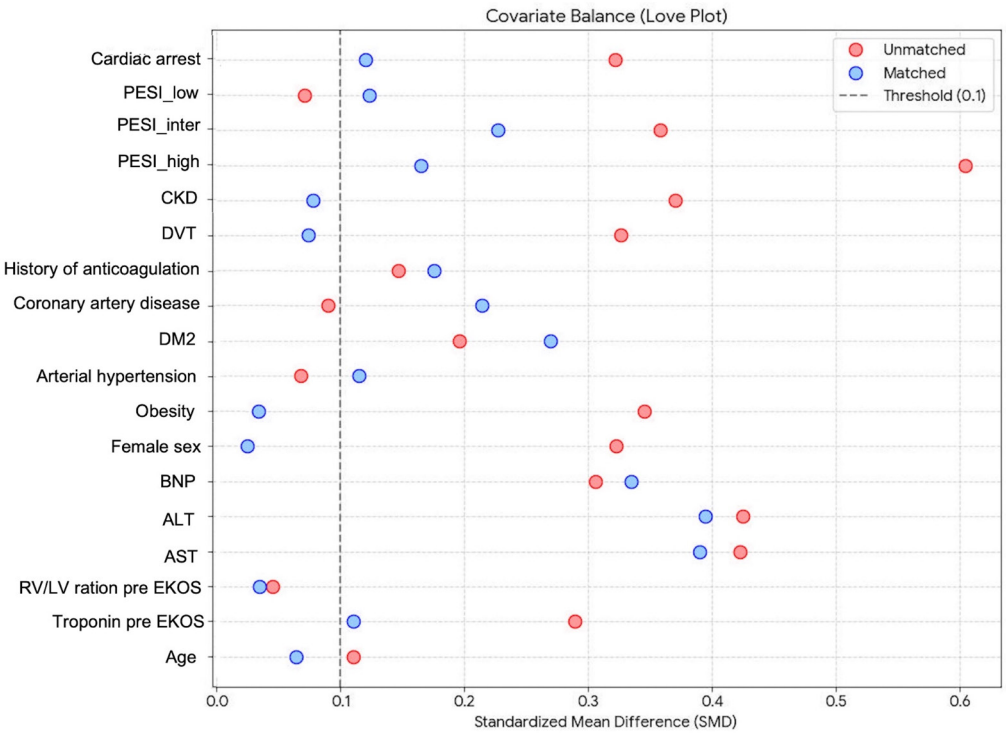



**Figure 1** Covariate balance before and after propensity score matching. SMDs are shown for baseline demographic characteristics, comorbidities, laboratory parameters, and risk stratification variables in the unmatched cohort (red circles) and after 1:1 propensity score matching (blue circles). The dashed vertical line indicates the predefined threshold for adequate balance (SMD <0.10). After matching, most covariates achieved acceptable balance, although residual imbalance remained for history of left heart failure and selected laboratory markers. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; CKD, chronic kidney disease; DM2, diabetes mellitus type 2; DVT, deep vein thrombosis; EKOS, EkoSonic Endovascular System; LV, left ventricle; PESI, Pulmonary Embolism Severity Index; PRE, preoperatively; RV, right ventricle; SMD, standardized mean difference.

regression identified baseline RV/LV ratio as the strongest independent predictor of therapeutic efficacy. Patients with severe RV dilation (ratio >1.5) exhibited the most profound reverse remodeling (coefficient 0.91, P<0.001). Conversely, high-risk PESI status was associated with a blunted anatomical response (P=0.045). Importantly, obesity (BMI >30 kg/m$^2$) was not associated with a reduced hemodynamic response (P=0.68), suggesting that the efficacy of USAT is maintained regardless of body mass index (*Table 2*). The relationship between baseline RV/LV ratio and magnitude of RV recovery is illustrated in Figure S1.

### *Clinical outcomes in the matched cohort*

USAT was associated with a statistically significant reduction in in-hospital mortality. In the matched analysis, the mortality rate was 2.5% (2/81) in the USAT group compared to 17.3% (14/81) in the conventional group (P=0.003). Kaplan-Meier survival analysis (*Figure 2*) demonstrated a significant divergence in survival curves early in the hospital course (Log-Rank P=0.002), suggesting that USAT may prevent early death due to RV failure or hemodynamic collapse (*Table 2*). To account for the residual post-matching imbalance in left heart failure, we performed a doubly robust logistic regression in the matched cohort (PSM plus regression adjustment), including treatment group and left heart failure as covariates. In this adjusted model, USAT treatment remained independently associated with lower in-hospital mortality (aOR 0.17, 95% CI: 0.05–0.61, P=0.007), while left heart failure was confirmed as an independent predictor of mortality (aOR 5.28, 95% CI: 1.93–14.46, P=0.001).

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**Table 2** Comparison of outcomes in the propensity score-matched cohort

| Outcome | Conventional (n=81) | USAT (n=81) | SMD | P value |
|---|---|---|---|---|
| Primary outcome | | | | |
| In-hospital mortality | 14 (17.3) | 2 (2.5) | 0.508 | 0.003 |
| Secondary outcomes | | | | |
| Length of stay (days) | 17.5±19.8 | 13.0±18.9 | 0.232 | 0.008 |
| ISTH major bleeding | 9 (11.1) | 1 (1.2) | 0.419 | 0.02 |
| ISTH CRNM bleeding | 1 (1.2) | 14 (17.3) | 0.576 | <0.001 |
| Hemodynamic efficacy | | | | |
| Post-treatment RV/LV ratio | 1.0±0.1 | 1.0±0.2 | 0.134 | 0.46 |
| Reduction in RV/LV ratio (delta) | 0.6±0.2 | 0.5±0.3 | 0.231 | 0.63 |
| Post-intervention shock | 8 (9.9) | 6 (7.4) | 0.088 | 0.58 |

Data are expressed as n (%) or mean ± standard deviation. CRNM, clinically relevant non-major; ISTH, International Society on Thrombosis and Hemostasis; LV, left ventricular; RV, right ventricular; SMD, standardized mean difference; USAT, ultrasound-facilitated catheter-directed thrombolysis.

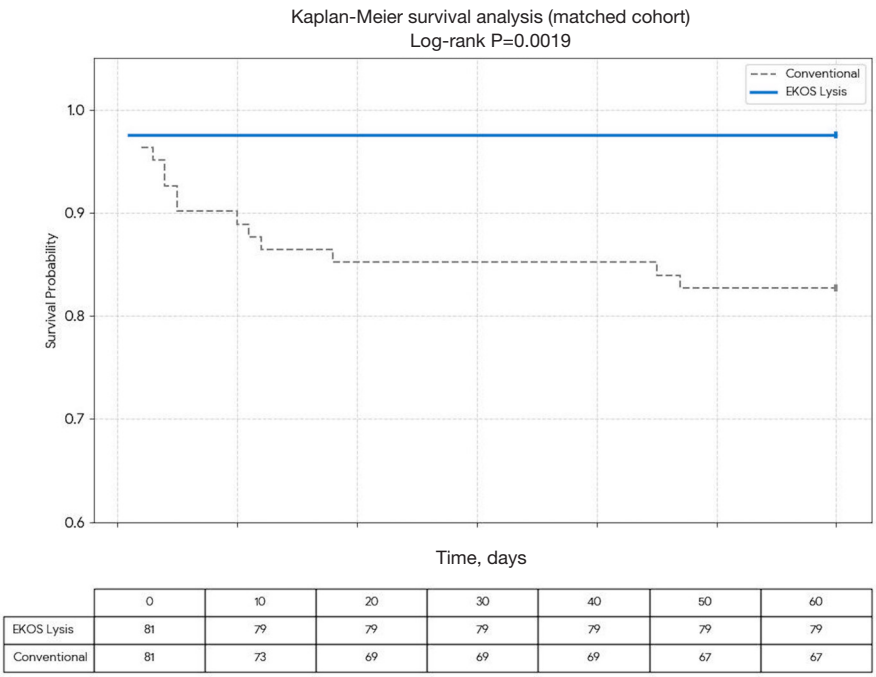



**Figure 2** Kaplan-Meier survival curves comparing in-hospital mortality. EKOS, EkoSonic Endovascular System.

### *Resource utilization and safety*

Patients treated with USAT had a significantly shorter length of hospital stay compared to the matched conventional group (13.0±18.9 *vs.* 17.5±19.8 days; P=0.008). When bleeding events were classified according to ISTH criteria, EKOS-treated patients had significantly fewer major bleeding events (1.2% *vs.* 11.1%, P=0.02), but a higher rate of CRNM bleeding (17.3% *vs.* 1.2%, P<0.001) (*Table 2*). Within the conventional treatment group, post-

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**Table 3** Subgroup analysis of clinical outcomes and safety profile in obese patients

| Outcome | Obese control (n=12) | Obese USAT (n=32) | P value |
|---|---|---|---|
| Mortality | 4 (33.3) | 1 (3.1) | 0.02 |
| Length of stay (days) | 18.3±14.6 | 11.4±8.0 | 0.13 |
| ISTH major bleeding | 3 (25.0) | 1 (3.1) | 0.06 |
| ISTH CRNM bleeding | 1 (8.3) | 10 (31.3) | 0.24 |

Bleeding outcomes were classified according to ISTH definitions (13,14). Subgroup analysis is exploratory due to small sample size. Data are presented as n (%) or mean ± standard deviation, as appropriate. CRNM, clinically relevant non-major; ISTH, International Society on Thrombosis and Hemostasis; USAT, ultrasound-facilitated catheter-directed thrombolysis.

intervention shock occurred more frequently in patients treated with anticoagulation alone compared with those receiving systemic thrombolysis (16.2% *vs.* 3.6%). Detailed subgroup results are provided in Table S1.

### *Subgroup analysis: outcomes in obese patients*

Given the challenge of dosing systemic thrombolytics in obese patients, a dedicated subgroup analysis was performed on patients with BMI >30 kg/m$^2$. Among obese patients, USAT (n=32) was associated with significantly lower mortality compared to conventional therapy (n=12) (3.1% *vs.* 33.3%, P=0.02). Furthermore, USAT reduced the LOS in this subgroup by approximately 7 days (11.4 *vs.* 18.3 days), without an increase in bleeding events (*Table 3*).

## Discussion

### *Principal findings*

The principal finding of this propensity score-matched analysis is that USAT, when administered within a multidisciplinary PERT pathway, is associated with a significant reduction in in-hospital mortality compared to conventional therapy in patients with intermediate-high and high-risk PE. We noted a decrease in the mortality rate from 17.3% in the conventional group to 2.5% in the USAT group after adjusting for baseline severity, including the PESI and comorbidities. Furthermore, USAT treatment resulted in a significantly shorter LOS with significantly fewer major bleeding events, albeit with higher CRNM bleeding, suggesting that the lower cumulative dose of thrombolytic drugs used in USAT effectively reduces the bleeding risks linked to systemic thrombolysis.

Although PSM achieved good balance across most baseline covariates, residual imbalances in selected comorbidities and laboratory parameters persisted, most notably pre-existing left heart failure, which is a known predictor of adverse outcomes in acute PE. To address this potential confounding, we performed a doubly robust logistic regression in the matched cohort adjusting for left heart failure. Importantly, USAT treatment remained independently associated with lower in-hospital mortality even after this adjustment, confirming that the observed survival benefit is not solely explained by differences in baseline cardiac comorbidity. Residual differences in markers of right heart strain, including BNP levels and echocardiographic RV dysfunction, were also observed and should be considered when interpreting the matched comparisons.

### *Context and comparison with literature*

Our study provides real-world evidence that translates the hemodynamic benefits of USAT into a survival advantage. While many trials such as ULTIMA (6), and SEATTLE II (7) established that USAT rapidly reverses RV dilation, they were not powered to detect mortality differences. However, our finding of significantly reduced in-hospital mortality (2.5% *vs.* 17.3%) aligns with a recent systematic review and meta-analysis which found that catheter-directed thrombolysis combined with anticoagulation was associated with significantly lower in-hospital and 30-day mortality compared to anticoagulation alone (RR 0.41; P<0.001) (15). This agreement suggests that the hemodynamic bridge provided by USAT effectively stops the progression to obstructive shock in intermediate-high and high-risk populations.

Safety remains the primary concern in the pharmacological management of PE. The PEITHO trial reported that while systemic thrombolysis prevents hemodynamic decompensation, it carries a significant risk of major bleeding

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and ICH (3). A quasi-experimental study comparing USAT with anticoagulation in intermediate-high-risk patients observed a higher rate of bleeding in the USAT group (5.9% *vs.* 0.9%) (16). Bleeding events were classified according to ISTH criteria (13) to ensure standardized safety reporting and to avoid under- or over-estimation of hemorrhagic complications. ICH represents a specific subtype of major bleeding; however, individual bleeding subtypes, including ICH, were not separately and consistently captured in our dataset. Therefore, comparisons in this manuscript are based on overall ISTH-defined major bleeding, which encompasses a broader range of clinically significant events. These findings should be interpreted cautiously, given the retrospective design and the relatively small number of events. Importantly, subgroup analysis revealed that post-intervention shock within the conventional treatment group was more frequent in patients treated with anticoagulation alone than in those receiving systemic thrombolysis (Table S1), suggesting that lack of active reperfusion may contribute to persistent hemodynamic instability. In the matched cohort, EKOS-treated patients experienced significantly fewer ISTH major bleeding events, but a higher rate of CRNM bleeding compared with conventional therapy. The increased rate of CRNM bleeding likely reflects access-site hematomas and minor procedural blood loss inherent to catheter-based interventions, whereas life-threatening hemorrhage was reduced. This explains the higher overall bleeding signal observed when using a sensitive bleeding definition and aligns with contemporary ultrasound-facilitated catheter-directed thrombolysis safety (17).

The higher rate of ISTH major bleeding observed in the conventional group must be interpreted in the context of that group's risk profile. The registry did not consistently capture systemic thrombolysis dosing details; however, systemic thrombolysis was generally reserved for high-risk presentations per institutional standards and ESC guidance (1). In our matched control cohort, 12.3% of patients were classified as PESI high risk and 3.7% presented with shock. Current ESC guidelines recommend systemic thrombolysis for such high-risk patients, providing a plausible explanation for the elevated major bleeding rate observed in this cohort. A recent contemporary review further highlighted that the role of systemic thrombolysis in acute PE remains limited by the lack of a consistently convincing net clinical benefit, particularly because any hemodynamic gain must be weighed against substantial bleeding risk in non-high-risk populations (18). By contrast, USAT achieved effective reperfusion with a significantly lower risk of major hemorrhagic events, likely due to the reduced thrombolytic dosage (7). Otherwise, our findings regarding the safety profile of USAT are strongly supported by the recently published ERASE PE (Bern Acute Pulmonary Embolism Registry) study (17). In this prospective study by Draxler *et al.*, they observed a low overall bleeding rate (7.9%) and low ICH risk (1.0%) (17). They also reported that the bleeding events were similar, supporting the finding that USAT is a safe reperfusion strategy with a favorable risk–benefit ratio (17). Finally, our observation of reduced LOS aligns with the findings of Johnson *et al.* (9), suggesting that faster hemodynamic recovery may lead to earlier discharge, potentially balancing the procedural costs of the intervention.

### *Subgroup analysis: outcomes in obese patients*

We performed an exploratory subgroup analysis in patients with obesity (BMI >30 kg/m$^2$), a population frequently associated with altered pharmacokinetics, higher thrombotic burden, and increased risk of adverse outcomes in acute PE. In this unadjusted comparison, USAT was associated with a marked survival advantage (mortality 3.1% *vs.* 33.3%, P=0.02). Notably, hemodynamic response to therapy was preserved in obese patients, as reflected by comparable improvement in RV/LV ratio (P=0.68), suggesting that ultrasound-facilitated catheter-directed delivery may contribute to effective thrombus resolution regardless of body habitus. This may represent an advantage over conventional therapy, including systemic fibrinolysis when used, where weight-based dosing is complicated by the trade-off between efficacy and bleeding risk in patients with high BMI (1).

Findings from large registry analyses, including data from the RIETE registry, suggest that obesity is not associated with worse clinical outcomes in patients with venous thromboembolism and may even be linked to lower mortality, consistent with the concept of an "obesity paradox" (19,20). However, data specifically addressing catheter-directed therapies in obese patients remain limited, highlighting the relevance of our findings. The substantially lower mortality observed in our PERT-managed USAT cohort suggests that a standardized, low-dose USAT strategy may mitigate obesity-associated risk. From a safety perspective, exploratory ISTH-based bleeding analysis in obese patients demonstrated a numerical reduction in major bleeding in EKOS-treated patients, albeit with higher rates

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of CRNM bleeding; these findings should be interpreted cautiously given small sample size.

As this subgroup analysis was performed in the unmatched cohort, results should be considered hypothesis-generating and warrant confirmation in larger dedicated studies.

### *Limitations*

This study has limitations inherent to its retrospective design. Although PSM was used to account for confounders, residual unmeasured confounding cannot be excluded. Residual imbalance in certain baseline variables persisted despite matching, particularly left heart failure and selected laboratory markers, which may introduce residual confounding despite doubly robust adjustment. Bleeding outcomes were adjudicated retrospectively based on chart review, which may rely on the accuracy of documentation regarding minor access-site events. Finally, while a residual imbalance in left heart failure history remained after matching, our multivariable adjustment confirmed that the survival benefit of USAT was independent of this comorbidity.

## Conclusions

In a propensity-matched real-world cohort, USAT was associated with significantly lower in-hospital mortality and shorter LOS compared with conventional therapy, as well as a significant reduction in major bleeding events, albeit with higher rates of CRNM bleeding. Exploratory subgroup analysis in obese patients suggested a similar mortality signal. Our findings support consideration of early USAT use in patients with evident RV dysfunction within a multidisciplinary PERT pathway to facilitate rapid hemodynamic recovery and improve survival.

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## Footnote

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Ethics Committee of the Medical Faculty of RWTH Aachen University (No. EK 25-286). Due to the retrospective nature of the study, the requirement for informed consent was waived.

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