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Original Article

Ultrasound-assisted catheter-directed thrombolysis versus anticoagulation alone for management of submassive pulmonary embolism

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ABSTRACT

Background: Patients with submassive pulmonary embolism (PE) are vulnerable to sudden deterioration, recurrent PE, and progression to pulmonary hypertension and chronic right ventricular (RV) dysfunction. Previous studies have suggested a clinical benefit of using ultrasound-assisted catheter-directed thrombolysis (USCDT) to invasively manage patients with submassive PE. However, there is sparse data comparing the clinical outcomes of these patients when treated with USCDT versus anticoagulation (AC) alone. We sought to compare the outcomes of USCDT versus AC alone in the management of submassive PE.

Methods: 192 consecutive patients who underwent USCDT for submassive PE between January 2013 and February 2019 were identified. ICD9/ICD10 codes were used to detect 2554 patients diagnosed with PE who did not undergo thrombolysis. Propensity matching identified 192 patients with acute PE treated with AC alone. Clinical outcomes were compared between the two groups. Baseline demographics, laboratory values, and pulmonary embolism severity index scores were similar between the two cohorts.

Results: There was a significant reduction in mean systolic pulmonary artery pressure (sPAP) in the USCDT group compared to the AC group (Δ11 vs Δ3.9 mmHg, $p < 0.001$). There was significant improvement in proportion of RV dysfunction in all patients, but the difference was larger in the USCDT group (Δ43.3% vs Δ17.3%, $p < 0.001$). Patients who underwent USCDT had lower 30-day (4.3% vs 10.5%, $p = 0.03$), 90-day (5.5% vs 12.4%, $p = 0.03$), and 1-year mortality (6.2% vs 14.2%, $p = 0.03$).

Conclusions: In patients with acute submassive PE, USCDT was associated with improved 30-day, 90-day, and 1 year mortality as compared to AC alone. USCDT also improved RV function and reduced sPAP to a greater degree than AC alone. Further studies are needed to verify these results in both short- and long-term outcomes.

Introduction

Acute pulmonary embolism (PE) is the third leading cause of cardiovascular death, accounting for an adjusted mortality rate of 3.5 per 100,000 persons in the USA in 2018 [1]. Approximately 40% of PEs are classified as submassive, as defined by signs of right ventricular (RV) strain in the absence of hemodynamic instability, and carry significant morbidity and mortality [2]. Patients with submassive PE are vulnerable to sudden clinical deterioration, development of recurrent PE, and progression to pulmonary hypertension and chronic RV dysfunction [2,3]. Previous studies have suggested clinical benefit of using ultrasound-assisted catheter-directed thrombolysis (USCDT) to invasively manage patients with high-risk submassive PE [4–6]. USCDT uses high-frequency (2.2 MHz), low-power (0.5 W per element) ultrasound

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with the capacity to disaggregate fibrin fibers and allow for increased thrombus permeability for thrombolytic drugs to reach plasminogen receptor sites and dissolve embolic clot. Although it is known that USCDT reduces thrombus burden, improves RV function, and reduces pulmonary hypertension in the short term, its effects on long-term clinical outcomes when compared to use of anticoagulation (AC) alone remains unclear [4–6]. We aimed to determine the short- and long-term clinical outcomes in a propensity matched analysis of patients with acute submassive PE who underwent USCDT versus AC alone. We also aimed to determine whether select patient populations with poor cardiopulmonary reserve would significantly benefit from USCDT compared to AC alone.

Methods

We retrospectively identified 192 consecutive patients through a cardiac catheterization database registry who underwent USCDT at our institution for acute submassive PE from January 2013 until February 2019. Submassive PE was defined as the presence of RV strain in the absence of hemodynamic instability, with RV strain being defined as: (1) computed tomography (CT) right ventricle: left ventricle (RV: LV) ratio ≥ 1; or (2) transthoracic echocardiogram RV hypokinesis, RV dilatation, and/or intraventricular septal bowing; or (3) simplified pulmonary embolism severity index (sPESI) ≥1. Patients were further classified as having high-risk submassive PE if they also had elevation in biomarkers (B-type natriuretic peptide >90 pg/mL, troponin >99th percentile) or syncope. We excluded patients with low-risk PE (no imaging or biomarker evidence of RV dysfunction) and those with massive PE (sustained systolic blood pressure < 90 mmHg for at least 30 min or requiring vasopressor support). Patients were also excluded if they were initially treated with systemic thrombolysis or surgical embolectomy that was unsuccessful. In evaluating patients, USCDT was contraindicated in the setting of prior intracranial hemorrhage, ischemic stroke within the past 6 months, central venous system neoplasm, major trauma, surgery, or head injury within the past 3 weeks. Our center relied on historical data for risk-assessment and did not routinely obtain cerebral imaging prior to offering USCDT. Using International Classification of Diseases (ICD) 9 and 10 Revision coding, we identified 2554 patients diagnosed with PE without an associated ICD code for thrombolysis during the same time period. The study variables for age, body mass index, gender, race, hypertension, hypersensitivity lung disease, diabetes, chronic kidney disease, coronary artery disease, congestive heart failure, smoking, chronic lung disease, pulmonary hypertension, prior deep vein thrombosis, prior pulmonary embolism, hypercoagulable state, cancer, and recent surgery were used to create a propensity score for each patient. Then the propensity score was used to match each USCDT case to a corresponding control (AC alone) using 1 to 1 matching. In order to identify a good quality matched cohort, we assessed patients dating back to 2013. USCDT was not offered at our institution prior to 2017, so those patients were treated with AC alone. Ultimately, there were 192 patients in the USCDT group and 192 patients in the control group. Patients were included if they met the above criteria, were age > 18 years old, and were hemodynamically stable.

The epidemiological, clinical, laboratory, and procedural data were manually extracted from electronic health records. Race was based on self-identification. Comorbid conditions were identified based on patient problem lists and notes. The PESI score is a risk stratification tool that has been externally validated to determine the mortality and outcome of patients with newly diagnosed PE [7]. The PESI score was used in the propensity matching and was calculated in the following manner: (1) one point given per year of age, (2) 10 points for male gender, (3) 30 points for history of cancer, (4) 10 points for history of heart failure, (5) 10 points for history of chronic lung disease (CLD), (6) 20 points for heart rate ≥ 110 beats per minute (bpm), (7) 30 points for systolic blood pressure < 100 mmHg, (8) 20 points for respiratory rate ≥ 30 breaths per minute, (9) 20 points for temperature < 36 °C, (10) 60 points for altered mental status, and (11) 20 points for oxygen saturation < 90%. Myocardial infarction was defined as a troponin level above the 99th percentile along with new electrocardiogram changes or new wall motion abnormalities on echocardiogram. Acute kidney injury was defined according to the "Kidney Disease: Improving Global Outcomes" criteria for creatinine [8]. Electronic health records were used to manually extract 30-day, 90-day, and 1-year outcomes. CT scans were independently reviewed by G.M. and S.S. for the presence of RV strain. Echocardiographic variables were manually extracted and included RV dysfunction, RV dilatation, tricuspid annular plane systolic excursion (TAPSE), tricuspid regurgitation jet velocity, inferior vena cava (IVC) diameter, interventricular septum profile, and systolic pulmonary artery pressure (sPAP). RV dysfunction on echocardiogram was determined by a cardiologist, in adherence to the American Society of Echocardiography guidelines [9]. In general, RV dysfunction is defined as fractional area change (FAC) <35%, TAPSE <1.7 cm, pulsed Doppler S wave <9.5 cm/s, pulsed Doppler myocardial performance index >0.43, or tissue Doppler myocardial performance index >0.54. The following parameters were further used to grade RV dysfunction: RV FAC (mild 25–35%, moderate 18–24%, and severe <17%), and/or TAPSE (mild-moderate 1.0–1.6 cm, severe <1.0 cm).

The primary endpoints included all-cause mortality, recurrent PEs, and bleeding at 30 days, 90 days, and 1 year post-therapy. Bleeding severity was classified using the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) [10] bleeding criteria, where severe is defined as either intracranial hemorrhage or bleeding that causes hemodynamic compromise, moderate is defined as bleeding requiring blood transfusion but no hemodynamic compromise, and mild as bleeding that does not meet criteria for either severe or moderate. Secondary endpoints included changes in sPAP and RV function following therapy.

There was proper ethical oversight, the study was approved by the Institutional Review Board (IRB# 11289), and informed consent was waived.

In our institution, patients with acute submassive PE are evaluated by the multi-disciplinary Pulmonary Embolism Response Team (PERT), which includes members from interventional cardiology, interventional radiology, cardiothoracic surgery, vascular surgery, and pulmonary hypertension services. The team is activated if there is evidence of RV strain by CT, echocardiogram, and/or sPESI score ≥ 1 along with biomarker elevation or syncope. An algorithm developed from the European Society Guidelines [3] is followed, and those with high-risk submassive PE are considered for USCDT. Patients who receive USCDT typically undergo the procedure within 24 h of arrival.

Patients who are chosen for USCDT are then taken to the cardiac catheterization laboratory or interventional radiology laboratory. Femoral or internal jugular venous access is obtained, and a pigtail catheter is advanced into the appropriate pulmonary artery using CT findings to identify the clot location. Based on the clot location, an EkoSonic catheter (EKOS Corp, Bothell, WA, USA) is placed across the heaviest clot burden for ultrasound-assisted thrombolysis. Unilateral or bilateral catheters may be inserted into the pulmonary arteries, depending on the location and burden of clots. The majority of patients required bilateral catheters (Videos 1–3). An immediate infusion of 2 mg of tissue plasminogen activator at a concentration of 10 mg/250 mL 0.9% normal saline is then administered per catheter, followed by initiation of lytic infusion at rate of 0.5 mg/h to 1 mg/h for a total dose of 24 mg. The dose may be adjusted per the operator's discretion in special cases (obesity, extremity low body weight, etc.). During lytic infusion, patients receive additional low intensity heparin infusion to maintain partial thromboplastin time in a range of 40–55 s as part of the treatment protocol. After completion of lytic infusion, the catheters are removed at bedside and patients are switched to high-intensity unfractionated heparin and then long-term anticoagulation.

The group comparisons were performed using chi-square tests for non-sparse categorical variables, Fisher exact tests for sparse categorical

variables, 2-sample *t*-tests for normally distributed numerical variables, and Wilcoxon rank sum tests for non-normally distributed numerical variables. Non-normally distributed numerical variables were summarized as medians. Statistical analyses were considered significant if $p < 0.05$. A time-to-event analysis was performed using Kaplan-Meier curves, where significance was calculated using the log-rank test.

Table 1
Baseline characteristics.

	All (N = 384)	USCDT (N = 192)	Anticoagulation (N = 192)	*p*-value
I. Demographics				
Age	59.3 ± 15.1	58.9 ± 14.1	59.8 ± 16.1	0.55
BMI	34.2 ± 9.7	34.9 ± 8.7	33.5 ± 10.6	0.18
Male	188 (49.0%)	93 (48.4%)	95 (49.5%)	0.84
Race				
Black	141 (38.6%)	71 (40.3%)	70 (37.0%)	0.61
White	198 (54.2%)	91 (51.7%)	107 (56.6%)	
Other	26 (7.1%)	14 (8.0%)	12 (6.3%)	
II. Comorbidities				
Hypertension	225 (58.6%)	113 (58.9%)	112 (58.3%)	0.92
Hyperlipidemia	135 (35.2%)	65 (33.9%)	70 (36.5%)	0.59
Diabetes Mellitus	104 (27.1%)	47 (24.5%)	57 (29.7%)	0.25
Chronic Kidney Disease	45 (11.7%)	22 (11.5%)	23 (12.0%)	0.87
Coronary Artery Disease	30 (7.8%)	13 (6.8%)	17 (8.9%)	0.45
Congestive Heart Failure	24 (6.3%)	10 (5.2%)	14 (7.3%)	0.40
Smoking	173 (45.1%)	78 (40.6%)	95 (49.5%)	0.08
Chronic Lung Disease	51 (13.3%)	24 (12.5%)	27 (14.1%)	0.65
Pulmonary Hypertension	12 (3.1%)	5 (2.6%)	7 (3.6%)	0.56
Prior DVT	63 (16.4%)	28 (14.6%)	35 (18.2%)	0.34
Prior PE	54 (14.1%)	24 (12.5%)	30 (15.6%)	0.38
Hypercoagulable state	14 (3.6%)	5 (2.6%)	9 (4.7%)	0.28
Recent Surgery	32 (8.3%)	17 (8.9%)	15 (7.8%)	0.71
Cancer	75 (19.5%)	35 (18.2%)	40 (20.8%)	0.52
III. Initial vital signs				
Systolic blood pressure	127.8 ± 22.5	128.6 ± 23.6	126.9 ± 21.5	0.47
Diastolic blood pressure	77.2 ± 15.1	78.2 ± 15.8	76.3 ± 14.3	0.22
Heart rate	103.2 ± 18.9	106.6 ± 18.0	99.8 ± 19.1	<0.001
Respiratory rate	22.6 ± 7.5	22.8 ± 5.6	22.4 ± 9.0	0.02
	Median = 20.0	Median = 22.0	Median = 20.0	
Oxygen saturation	91.3 ± 7.2	90.9 ± 8.4	91.8 ± 5.9	0.21
	Median = 93.0	Median = 92.0	Median = 93.0	
Temperature	36.6 ± 0.7	36.6 ± 0.8	36.7 ± 0.6	0.17
	Median = 36.7	Median = 36.7	Median = 36.7	
Altered mental status	32 (8.4%)	10 (5.2%)	22 (11.5%)	0.03
Syncope	32 (8.6%)	21 (11.0%)	11 (6.1%)	0.09
PESI score	100.8 ± 32.0	101.4 ± 29.4	100.1 ± 34.5	0.70
IV. Initial laboratory values				
BNP level	336.9 ± 652.6	319.8 ± 659.9	357.0 ± 645.7	0.44
	Median = 162.5	Median = 165.0	Median = 149.0	
Troponin level	0.5 ± 2.0	0.5 ± 1.1	0.6 ± 2.6	<0.001
	Median = 0.1	Median = 0.2	Median = 0.1	
Peak troponin	1.3 ± 4.8	1.3 ± 4.7	1.2 ± 4.9	<0.001
	Median = 0.2	Median = 0.3	Median = 0.1	
V. CTPE findings				
RV strain	251 (65.4%)	152 (79.2%)	99 (51.6%)	<0.001
Intraventricular septum				
Normal	151 (45.1%)	46 (26.4%)	105 (61.4%)	<0.001
Flattened	121 (36.1%)	77 (44.2%)	44 (25.7%)	<0.001
Bowing	63 (18.8%)	51 (29.3%)	22 (12.9%)	<0.001
IVC contrast reflux	198 (51.6%)	123 (64.1%)	75 (39.1%)	<0.001
VI. Initial echocardiogram				
RV dysfunction				
Normal	114 (32.9%)	11 (6.7%)	103 (56.3%)	< 0.001
Mild	68 (19.7%)	34 (20.9%)	34 (18.6%)	0.69
Moderate	95 (27.5%)	71 (43.6%)	24 (13.1%)	< 0.001
Severe	69 (19.9%)	47 (28.8%)	22 (12.0%)	< 0.001
TAPSE (cm)	1.76 ± 0.43	1.63 ± 0.38	1.89 ± 0.44	<0.001
TR Jet velocity (cm/s)	292.9 ± 57.5	306.1 ± 58.7	281.3 ± 53.7	<0.001
Systolic PAP (mmHg)	43.9 ± 14.1	48.0 ± 13.9	40.2 ± 13.3	<0.001
IVC diameter				
Normal, >50% variation	156 (53.2%)	48 (34.8%)	108 (69.7%)	<0.001
Dilated, >50% variation	73 (24.9%)	36 (26.1%)	37 (23.9%)	0.76
Dilated, <50% variation	64 (21.8%)	54 (39.1%)	10 (6.5%)	<0.001
Intraventricular septum				
Normal	153 (55.8%)	49 (35.5%)	104 (76.5%)	<0.001
Flattened	121 (44.2%)	89 (64.5%)	32 (23.5%)	<0.001

USCDT, ultrasound-assisted catheter-directed thrombolysis; BMI, body mass index; DVT, deep venous thromboembolism; PE, pulmonary embolism; PESI, pulmonary embolism severity score; BNP, brain natriuretic peptide; RV, right ventricle; IVC, inferior vena cava; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; PAP, pulmonary artery pressure.

Results

A total of 384 patients with acute submassive PE were included in this study: 192 patients underwent USCDT and 192 propensity-matched patients received AC alone. The mean age for the entire cohort was 59.3 ± 15.1 years old, 49.0% were male, 54.2% were White, and 38.6% were Black. There were no differences in age, gender, race, comorbidities, or PESI score between the two cohorts (Table 1). Patients who underwent USCDT had higher initial heart rate, respiratory rate, initial troponin level, and peak troponin level, although the differences in values were not clinically significant. Most patients had RV strain present by either CT scan or echocardiography. RV strain was present in 65.4% of all patients via CT and RV dysfunction was present in 67.1% of all patients on echocardiography. Patients who underwent USCDT were more likely to have RV strain via CT scan, and more likely to have moderate or severe RV dysfunction on initial echocardiogram, a bias towards a potentially higher risk population (Table 1).

Table 2
Outcomes.

	All (N = 384)	USCDT (N = 192)	Anticoagulation (N = 192)	*p*-value
I. In-hospital outcomes				
In-hospital death	14 (3.7%)	5 (2.6%)	9 (4.7%)	0.27
Length of stay	7.6 ± 6.9 Median = 5.0	6.9 ± 5.4 Median = 5.0	8.3 ± 8.1 Median = 5.0	0.64
Intracranial hemorrhage	2 (0.5%)	0 (0.0%)	2 (1.1%)	0.23
Cardiac arrest	6 (1.6%)	3 (1.6%)	3 (1.6%)	1.00
Ventricular arrhythmia	6 (1.6%)	3 (1.6%)	3 (1.6%)	1.00
Myocardial infarction	10 (2.6%)	2 (1.0%)	8 (4.2%)	0.06
Stroke	3 (0.8%)	1 (0.5%)	2 (1.0%)	0.62
Acute kidney injury	54 (14.1%)	19 (9.9%)	35 (18.3%)	0.02
Intubation/ventilation	19 (5.0%)	9 (4.7%)	10 (5.2%)	0.81
Inotropic support	8 (2.1%)	4 (2.1%)	4 (2.1%)	1.00
Bleeding	34 (8.9%)	19 (9.9%)	15 (7.9%)	0.48
Access site hematoma	10 (3.0%)	10 (5.2%)	0 (0.0%)	0.006
Pseudoaneurysm	5 (1.5%)	5 (2.6%)	0 (0.0%)	0.08
IVC filter placed	36 (9.4%)	16 (8.3%)	20 (10.5%)	0.47
II. 30-day outcomes				
Death	27 (7.6%)	7 (4.3%)	20 (10.5%)	0.03
Intracranial hemorrhage	2 (0.6%)	1 (0.6%)	1 (0.6%)	1.00
Bleeding	14 (4.1%)	6 (3.7%)	8 (4.4%)	0.74
Recurrent VTE	8 (2.3%)	3 (1.8%)	5 (2.8%)	0.73
III. 90-day outcomes				
Death	30 (9.3%)	8 (5.5%)	22 (12.4%)	0.03
Intracranial hemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
Bleeding	13 (4.4%)	8 (5.7%)	5 (3.3%)	0.32
Recurrent VTE	10 (3.4%)	7 (5.0%)	3 (2.0%)	0.20
IV. 1-year outcomes				
Death	32 (10.7%)	8 (6.2%)	24 (14.2%)	0.03
Intracranial hemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
Bleeding	17 (6.2%)	6 (4.8%)	11 (7.2%)	0.41
Recurrent VTE	5 (1.8%)	3 (2.4%)	2 (1.3%)	0.67
V. Follow up echocardiogram				
RV dysfunction				
Normal	134 (57.3%)	81 (50.0%)	53 (73.6%)	0.001
Mild	46 (19.7%)	37 (22.8%)	9 (12.5%)	0.10
Moderate	50 (21.4%)	41 (25.3%)	9 (12.5%)	0.042
Severe	4 (1.7%)	3 (1.9%)	1 (1.4%)	0.80
TAPSE (cm)	2.16 ± 1.9	2.20 ± 2.2	2.95 ± 0.47	<0.001
TR jet velocity (cm/s)	271.6 ± 51.5	274.0 ± 54.3	266.3 ± 44.3	0.13
Systolic PAP (mmHg)	36.8 ± 12.2	37.0 ± 12.4	36.3 ± 11.7	0.57
IVC diameter				
Normal, >50% variation	163 (78.4%)	119 (78.3%)	44 (78.6%)	0.97
Dilated, >50% variation	31 (14.9%)	19 (12.5%)	12 (21.4%)	0.17
Dilated, <50% variation	14 (6.7%)	14 (9.2%)	0 (0.0%)	0.04
Intraventricular septum				
Normal	169 (85.8%)	130 (89.0%)	39 (76.5%)	0.048
Flattened	28 (14.2%)	16 (11.0%)	12 (23.5%)	0.048

USCDT, ultrasound-assisted catheter-directed thrombolysis; IVC, inferior vena cava; VTE, venous thromboembolism; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; PAP, pulmonary artery pressure.

The rates of in-hospital death, cardiac arrest, need for mechanical ventilation, and bleeding were similar between the two cohorts (Table 2). Patients who underwent USCDT had lower rates of acute kidney injury (9.9% vs 18.3%, $p = 0.02$) and lower rates of myocardial infarction (1.0% vs 4.2%, $p = 0.06$), although the latter was not statistically significant. Rates of bleeding, intracranial hemorrhage, recurrent venous thromboembolism (VTE), including PE, were similar among the two groups (Table 2). In those who underwent USCDT, 5.2% developed access site hematomas and 2.6% developed venous pseudoaneurysms. The form of AC on discharge was similar between the two cohorts. In the control group, 46.4% of patients were discharged on direct oral anticoagulants (DOACs) ($n = 44/192$ apixaban, 30/192 rivaroxaban, 15/192 other), 37.0% on warfarin, and 16.7% on lovenox. In the intervention group, 46.4% of patients were discharged on DOACs ($n = 53/192$ apixaban, 28/192 rivaroxaban, 8/192 other), 44.3% on warfarin, and 9.4% on lovenox. Patients who were placed on warfarin were bridged using heparin infusion or lovenox injection, were kept in the therapeutic range by our pharmacists, and followed up at an international normalized ratio (INR) clinic for regular checks.

Regarding longer term outcomes, patients who underwent USCDT had lower rates of 30-day mortality (4.3% vs 10.5%, $p = 0.03$), 90-day mortality (5.5% vs 12.4%, $p = 0.03$), and 1-year mortality (6.2% vs 14.2%, $p = 0.03$) as compared to AC alone (Fig. 1). Survival analysis using Kaplan-Meier log-rank test demonstrated significant mortality difference between the two cohorts, favoring USCDT-treated patients (Fig. 2). Univariate and multivariate subgroup analysis showed no difference in survival based on underlying comorbidities in those who received USCDT versus AC only. Patients who underwent USCDT had higher mean sPAP on initial echocardiogram (48.0 + 13.9 vs 40.2 + 13.3, $p < 0.001$), and more significant improvement in sPAP on follow-up echocardiogram done three to six months post-hospitalization (37 + 12.4 vs 36.3 + 11.7) (Fig. 3). There was significant improvement in proportion of RV dysfunction after both USCDT and AC, but the difference was larger in the group that received USCDT (Fig. 4). In a subgroup analysis of patients with poor cardiopulmonary reserve, there was no predictor of increased benefit with USCDT as compared to AC alone (Table 3).

In patients who underwent USCDT, there were a few notable differences about racial and sex differences in outcomes. Despite being similar in age and PESI scores and receiving USCDT, females had higher rates of RV dysfunction on follow-up echocardiogram. Death, bleeding, and recurrent VTE rates were similar among males and females (Online Table 1). Whites had a significantly higher survival rate at 30 days as compared to non-Whites (100% vs 91.8%, $p = 0.03$), although this difference was not sustained at 90-day or 1-year follow up (Online Table 2).

Discussion

In this retrospective, propensity matched study, patients who underwent USCDT for submassive PE had better long-term clinical and hemodynamic outcomes as compared to those who received AC alone. This was an overall sick cohort, with an average PESI score of 101 (Class III) and 47.4% of patients having moderate or severe RV dysfunction on presentation. Patients who underwent USCDT had higher initial sPAP and worse RV dysfunction, but better mortality rates on follow up. To our knowledge, this is the largest observational study of patients treated in routine clinical practice ("real world") evaluating outcomes of USCDT for submassive PE as compared to AC alone.

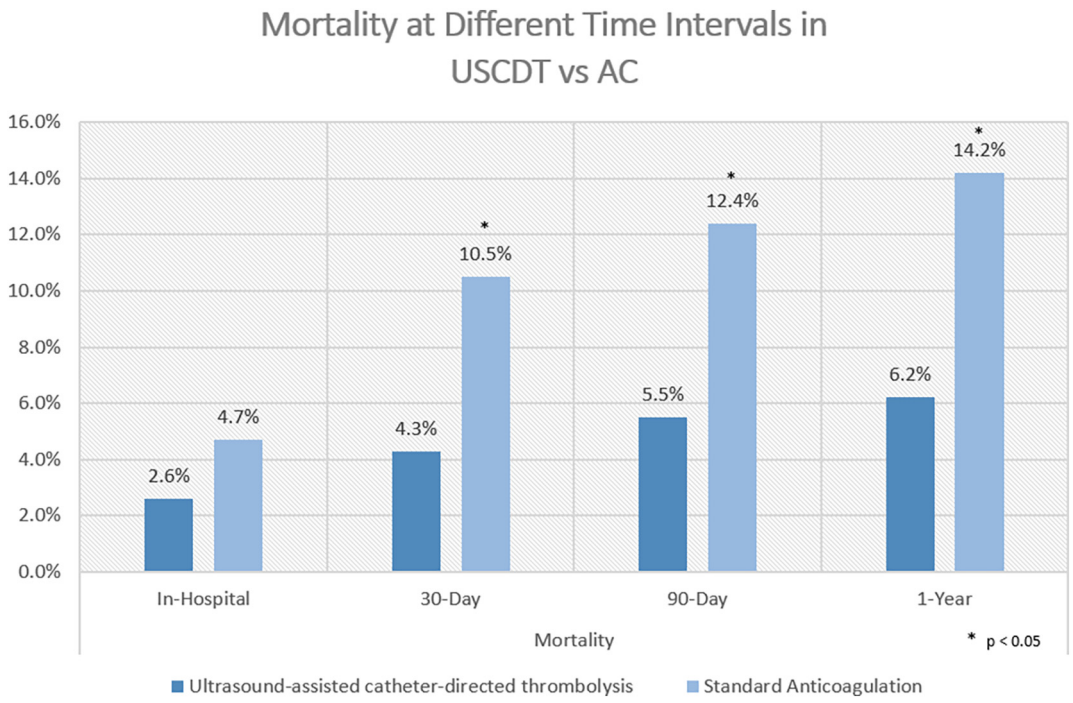

Fig. 1. Mortality at different time intervals in USCDT vs AC alone. Patients who underwent USCDT had lower rates of 30-day mortality (4.3% vs 10.5%, $p = 0.03$), 90-day mortality (5.5% vs 12.4%, $p = 0.03$), and 1-year mortality (6.2% vs 14.2%, $p = 0.03$) as compared to AC alone.
AC, anticoagulation; USCDT, ultrasound-assisted catheter-directed thrombolysis.

The previously reported short- and long-term survival in patients with submassive PE is sparse and limited [11]{Alotaibi, 2018 #11}. Anticoagulation has been the standard treatment, aimed to slow thrombus progression in the early phase and to reduce thrombus recurrence in the long term. Although early recognition and treatment has improved short-term outcomes, it is estimated that 5-year mortality post-PE is still about 25% [12]. Systemic thrombolytics can achieve faster pulmonary reperfusion, but this treatment is reserved for those with hemodynamic compromise given the significantly increased risk of bleeding, particularly intracranial hemorrhage. USCDT was introduced as a method to deliver thrombolytic therapy directly into the pulmonary circulation, thus lowering the systemic bleeding risk. The major aim was to reduce pulmonary thrombus burden and subsequent hemodynamic consequences that lead to RV dysfunction. Unknown is the specific impact on mortality, with limited long-term outcome data in patients with submassive PE who undergo USCDT. Only two studies compared mortality in patients who undergo USCDT versus AC alone. In ULTIMA (Ultrasound Accelerated Thrombolysis of Pulmonary Embolism), a total of only 59 patients were randomized to USCDT versus AC alone, and there was no statistical difference in 90-day mortality between the two small cohorts [4]. Avgerions et al. had the largest retrospective analysis, evaluating 128 patients who underwent either CDT or AC alone for submassive PE, and found no difference in 90-day all-cause mortality or major adverse events between the two groups [13]. In this current study of 394 patients, we show that there is a sustained improvement in survival at 30 days, 90 days, and 1 year in patients who received USCDT. A notable difference between our study and that of Avgerions et al.'s is the matching of baseline characteristics. The rate of recurrent

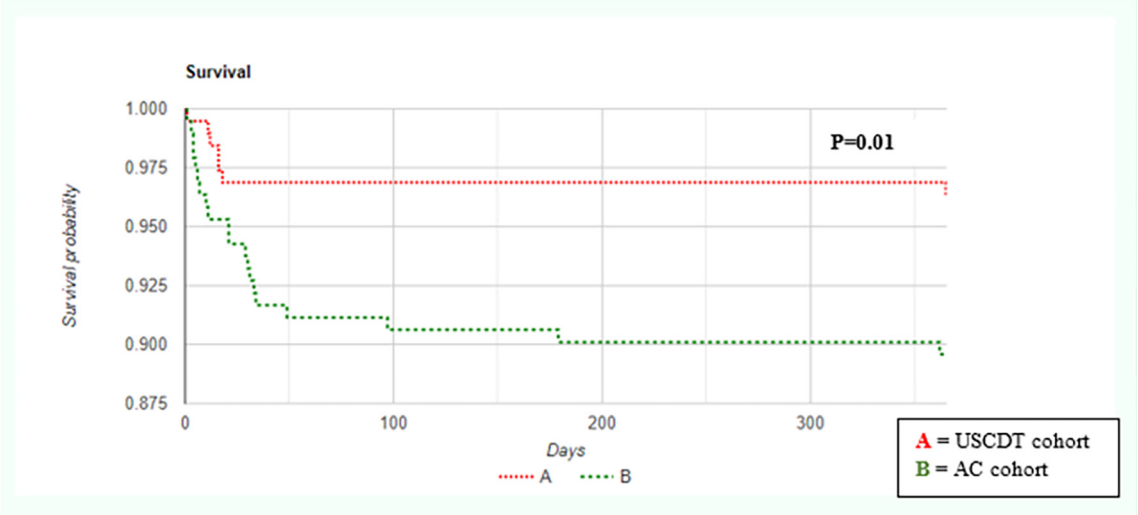

Fig. 2. Survival analysis using Kaplan-Meier log-rank test demonstrated significant mortality difference between the two cohorts, favoring USCDT-treated patients.
AC, anticoagulation; USCDT, ultrasound-assisted catheter-directed thrombolysis.

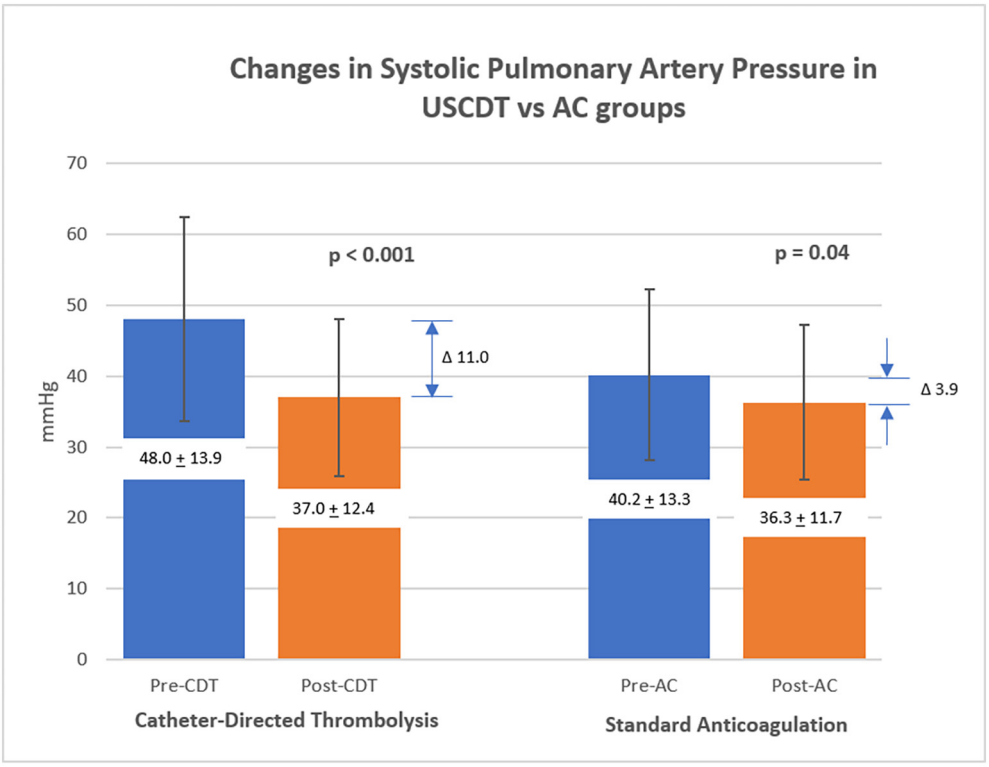

Fig. 3. Changes in systolic pulmonary arterial pressure in USCDT vs AC alone. Patients who underwent USCDT had higher mean sPAP on initial echocardiogram (48.0 + 13.9 vs 40.2 + 13.3 mmHg, $p < 0.001$), and more significant improvement in sPAP on follow-up echocardiogram done three to six months post-hospitalization (37 + 12.4 vs 36.3 + 11.7 mmHg).
AC, anticoagulation; sPAP, systolic pulmonary artery pressure; USCDT, ultrasound-assisted catheter-directed thrombolysis.

VTE was significantly higher in Avgerions et al.'s CDT cohort, which may suggest a more vulnerable patient group. To ultimately address this question on a large scale, the HI-PEITHO study has been approved to randomize patients with submassive PE to USCDT or AC alone, but is still in its early phase of recruiting centers (ClinicalTrials.gov ID: NCT04790370).

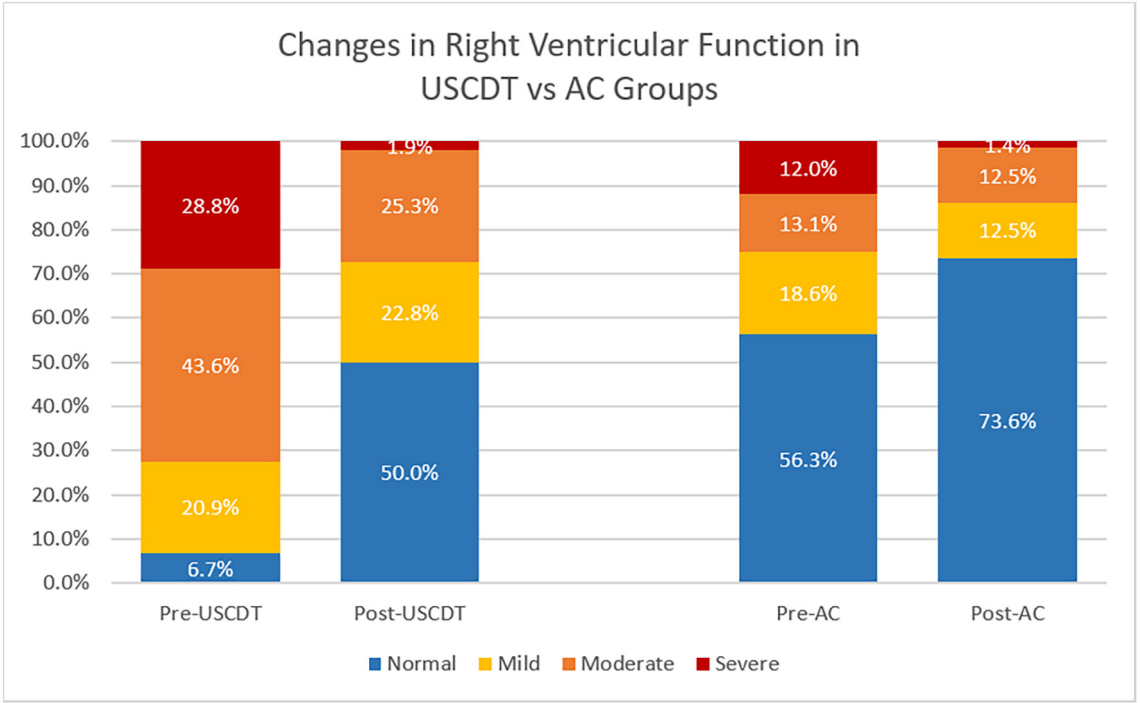

Fig. 4. Changes in right ventricular function in USCDT vs AC alone. There was significant improvement in proportion of right ventricular dysfunction after both USCDT and AC, but the difference was larger in the group that received USCDT.
AC, anticoagulation; USCDT, ultrasound-assisted catheter-directed thrombolysis.

Table 3
Univariable log-rank test results for 1-year mortality.

Predictor	*p*-value
Hypertension	0.383
Smoking	0.316
Diabetes	0.740
CAD	0.930
CHF	0.316
CLD	0.188
PH	0.243
Prior DVT	0.478
Prior PE	0.444

CAD, coronary artery disease; CHF, congestive heart failure; CLD, chronic lung disease; PH, pulmonary hypertension; DVT, deep venous thrombosis; PE, pulmonary embolism.

RV dysfunction following acute PE can lead to hemodynamic collapse and death. This is clinically recognized as sustained hypotension in those with massive PE. The systemic consequences of PE lay on a spectrum of hemodynamic sequela, and submassive PE serves as a potential precursor of hemodynamic compromise with biomarker and/or imaging evidence of RV strain. Despite being defined as hemodynamically stable, patients with submassive PE carry a 5–25% mortality rate [14]. The RV, being a thin-walled chamber, is accustomed to contracting against a highly compliant, low-pressure system (pulmonary arteries and arterioles). In submassive PE, the RV compensates until the pressure in the pulmonary vasculature typically exceeds 40 mmHg [14]. Pulmonary artery pressures rise from the resistance caused by obstructing emboli and vasoconstriction caused by hypoxia. Following Laplace's law, the RV dilates causing under filling, resulting in the coronary arteries becoming underperfused, and development of RV ischemia [15]. The ischemic RV develops worse contractility leading to RV dilatation, reduced LV output, and cardiogenic shock [16]. Therefore, intervention that reduces pulmonary artery pressures and RV dilatation early may prevent adverse RV remodeling. USCDT has been shown to be effective in timely reduction of sPAP and improving RV function in patients with submassive PE. In our cohort, severe RV dysfunction was reduced from 28.8% to 1.9%, and moderate dysfunction was reduced from 43.6% to 25.3% in those who received USCDT (Fig. 4). This is further supported by reduced rates of intraventricular septal flattening (64.5% vs 11.0%) and dilated IVC diameters (65.1% vs 21.7%) following USCDT treatment. This is consistent with data from ULTIMA [4], SEATTLE II [5], and PERFECT [6]. There was also improvement in rates of RV dysfunction in patients who received AC alone, but the degree of improvement was significantly less than in the USCDT group (Fig. 4).

The development of chronic thromboembolic pulmonary hypertension (CTEPH) in patients with PE has significant consequences. CTEPH arises from pulmonary emboli that do not resolve and lead to chronic obstruction of the pulmonary vasculature with subsequent high pulmonary vascular resistance [17]. It is estimated to occur in 2–4% of patients with acute PE [18,19]. When left untreated, it carries a poor prognosis, with limited therapeutic options of surgical embolectomy through pulmonary endarterectomy and percutaneous balloon pulmonary angioplasty [20,21]. Factors known to increase risk of development of CTEPH include recurrent unprovoked PE, large perfusion defects, initial sPAP >50 mmHg, and persistent pulmonary hypertension on echocardiogram performed 6 months after PE is detected [22]. Increased awareness of the burden of CTEPH has resulted in the creation of PERT teams that aim to identify high-risk submassive PE patients and offer early invasive treatment. In our study, patients who underwent USCDT or AC-alone both had a significant reduction in their follow-up sPAP. However, patients who underwent USCDT had higher initial sPAP (48.0 ± 13.9 vs 40.2 ± 13.3 mmHg, $p < 0.001$) and a more significant reduction in sPAP on follow up ($\Delta 11.0$ vs 3.9 mmHg, $p < 0.001$). This is expected, as patients with increased risk for long-term consequences are those targeted for intervention. Prior studies have also reported similar findings [4,5]. ULTIMA demonstrated a significant decrease in sPAP ($\Delta 12.3 \pm 10.0$ mmHg, $p < 0.001$), diastolic ($\Delta 3.2 \pm 7.8$ mmHg, $p = 0.049$), and mean pulmonary artery pressures ($\Delta 5.7 \pm 7.6$ mmHg, $p < 0.001$) at 18 h after initiation of USCDT; and SEATTLE II reported an absolute difference of -14.4 ± 15.4 mmHg in sPAP following USCDT [5].

There were a few notable differences in outcomes based on race and sex in patients who underwent USCDT. Whites had a significantly higher 30-day survival rate as compared to non-Whites, although this difference was not noted on longer follow up. The reason for this finding is unclear, but may be related to social determinants of health and access to early follow up. The survival difference based on race in patients presenting with acute PE has been evaluated in several large studies, with Whites universally having improved early survival [23–25]. In our study, this racial survival difference was also noted in patients who receive USCDT. There are limited data on sex differences in patients with acute PE, but one study of 1428 patients did demonstrate that severe cases with massive embolism were more commonly seen in women compared to men (14.6% vs 9.2%, $p < 0.001$) and 30-day PE-related mortality was significantly higher in women than men (5% vs 2.8%, $p = 0.04$) [26]. In our analysis, there was no difference in mortality based on sex in those who underwent USCDT, but rather RV function. Females had higher rates of RV dysfunction on follow-up echocardiogram, despite being similar in age, PESI score, and receiving USCDT. This may suggest that females are more susceptible to long-term adverse RV consequences, for unclear reasons. Finally, we hypothesized that USCDT may provide more benefit to patients with increased risk factors for CTEPH, particularly those with underlying CLD or CHF. However, our subgroup analysis did not identify any increased benefit of USCDT in patients with any underlying comorbidity, but we may have been limited by small numbers.

There is sparse direct comparison of USCDT versus AC alone in submassive PE. In our propensity matched analysis of 394 patients, we show that those who underwent USCDT had improved reduction in sPAP, RV dysfunction, and mortality rates as compared to the use of AC alone.

Limitations

Despite several strengths of this study, there are notable limitations. This is a single center retrospective study, which relies on previously documented information to be reliably present on presentation. Although propensity matching was performed for baseline characteristics and presenting PESI scores, patients who underwent USCDT did appear to have higher rates of RV dysfunction and sPAP on initial echocardiogram.

Conclusions

In patients with acute submassive PE, USCDT may be associated with improved 30-day, 90-day, and 1-year mortality as compared to AC alone. USCDT also improves RV function and reduces sPAP to a greater degree than AC alone. Large randomized prospective trials are needed to confirm these findings.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jjcc.2022.04.008.

Declaration of competing interest

The following are disclosures from co-authors:

1. Sara Hegab is a consultant to Bayer.
2. Reem Ismail is a speaker bureau for Bayer.

All other authors report no relevant financial disclosure.

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