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Safety and efficacy of catheter-directed therapy versus anticoagulation alone in a higher-risk acute pulmonary embolism population

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Abstract
There is little data comparing safety and efficacy outcomes in patients with pulmonary embolism (PE) receiving catheter directed therapies (CDT) compared to a similar-risk cohort of PE patients receiving anticoagulation alone. 1094 patients with acute PE were studied. CDT and conservatively-managed patients were compared using propensity score matching to assess safety outcomes, which included bleeding and acute kidney injury at 2 and 7 days after PE diagnosis. Efficacy outcomes included change in vital signs over 72 h and in-hospital mortality. PE patients with RV strain who underwent CDT (n = 76) had more bleeding at 2 days (additional 1.04 g/dL loss, 95% CI − 1.48 to − 0.60, p < 0.001) and 7 days (additional 1.36 g/dL loss, 95% CI − 1.88 to − 0.84, p < 0.001) compared to those receiving anticoagulation alone (n = 303). There was a significant increase in creatinine at 2 days (additional 0.22 mg/dL elevation, 95% CI 0.02 to 0.42, p = 0.03), but not at 7 days (additional 0.12 mg/dL elevation, 95% CI − 0.11 to 0.35, p = 0.30). In-hospital mortality for patients receiving CDT versus anticoagulation alone was similar (OR 1.21, 95% CI 0.53 to 2.77; p = 0.65). In patients with baseline abnormal vital signs who received CDT versus anticoagulation alone, heart rate, respiratory rate and oxygen requirement improved significantly faster and to levels closer to normal (p ≤ 0.001). CDT was associated with a small but increased risk of bleeding, but no significant worsening of renal function. CDT may be associated with more rapid improvements in heart rate, respiratory rate, and oxygen requirement.

Keywords Anticoagulation · Endovascular therapy · Pulmonary embolism · Propensity score

Highlights

- Catheter-directed therapy (CDT) for pulmonary embolism (PE) is increasingly common
- Safety and efficacy outcomes were assessed for higher risk PE patients receiving CDT versus anticoagulation alone
- CDT patients experienced slightly more early bleeding than conservatively-managed patients
- CDT may be associated with more rapid improvement of heart rate, respiratory rate, and oxygen requirement

Introduction

Acute pulmonary embolism (PE) is a potentially life-threating sequela of venous thrombosis. Patients diagnosed with acute PE present with a wide spectrum of signs and symptoms, including shortness of breath and hypoxemia, chest pain, syncope, right heart failure, and sudden death [1]. The true incidence of PE is difficult to assess given that many patients are either asymptomatic or die prior to presentation, but has been estimated at 60 to 70 cases per 100,000[2].

Patients with PE are traditionally classified as low-, intermediate-, or high-risk depending on the degree of abnormal

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hemodynamic, laboratory and imaging parameters. Treatment options differ significantly depending on this classification [3]. Registry data indicate that in-hospital mortality for patients with high-risk (or "massive") PE is between 15 and 60% [3–5]. Low-risk PE does not typically cause right ventricular (RV) dysfunction, hypotension, or cardiac biomarker elevation, and is associated with a < 1% mortality rate. Intermediate-risk (or "submassive") PE is a less well-defined entity that encompasses patients without hypotension but with evidence of RV dysfunction and/or cardiac biomarker elevation [3].

Commonly used risk stratification tools for acute PE include parameters such as shock or hypotension, risk scores such as the simplified pulmonary embolism severity index (sPESI), RV enlargement or dysfunction, and elevated cardiac biomarkers [6–8]. Improvement in these parameters is predicated on both patient factors and the choice of therapy chosen, and the acute safety and efficacy of catheter-directed therapies (CDT) compared to anticoagulation alone is still poorly defined. The aim of this study is to provide further definition to the safety and efficacy profiles of CDT compared to anticoagulation alone in a higher risk acute PE population.

Methods

Adult patients diagnosed with acute PE at an urban academic medical center were examined in this retrospective cohort study (University of Chicago Hospital, Chicago, IL, USA). Clinical data, including the diagnosis of acute PE and all available vital sign (VS), laboratory, and imaging data, were extracted from the electronic health record (EPIC; Verona, WI) by the University's Clinical Research Data Warehouse. Patients with incomplete clinical data were excluded. 87 PE patients referred for CDT and 1007 conservatively managed patients with complete data were identified (Fig. 1).

Using ICD-9/10 codes, patients with PE as a primary hospital diagnosis were identified. Both PE-protocol computed tomography (CT) scans and invasive pulmonary angiography were acceptable means of diagnosis of acute PE in this study. Acute PE of at least segmental location was required to be included, and estimation of PE chronicity was determined by the radiologist reading the individual study. Each CT report was also reviewed manually by the authors to exclude chronic PE or distal (i.e. subsegmental) acute PE. It was required that the CT report include "acute pulmonary embolism." Any report that included "chronic pulmonary embolism" or "acute on chronic pulmonary embolism" was excluded. Each diagnostic study was time-stamped so that correlations could be made with subsequent VS and laboratory values. CT and echocardiographic data were used to assess for the presence of RV strain at baseline. Patients in both arms were characterized as having RV strain if the ratio of RV to LV size was > 0.9 by CT scan or if there was RV dysfunction noted in the echocardiography report.

All laboratory values and VS including heart rate, respiratory rate, blood pressure, and oxygen saturation for each patient during the hospitalization were extracted from the medical record. Pertinent laboratory tests include creatinine, hemoglobin, NTpro-BNP and troponin. In an effort to best represent the acuity of patient illness, the most abnormal value for each VS was recorded as part of the baseline

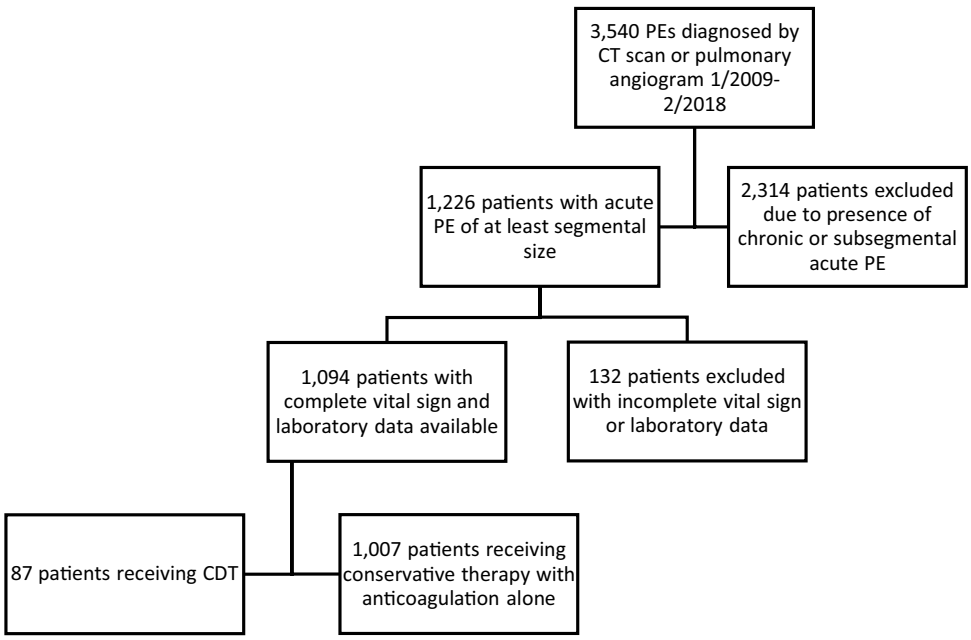

Fig. 1 Consort diagram. Patients with ICD 9 and ICD 10 codes for pulmonary embolism were queried, and patient charts were only extracted if there was confirmed pulmonary embolism on CT scan or pulmonary angiogram. Each radiology report was manually inspected for the presence of acute PE of at least segmental location. Only patients with complete VS and laboratory data were included. *CDT* catheter-directed therapy, *CT* computed tomography, *ICD-9/10* International Classification of Disease-9th or 10th Revision, *PE* pulmonary embolism

characteristics. This included the highest heart rate, lowest systolic blood pressure (SBP) and diastolic blood pressure, highest respiratory rate, and lowest oxygen saturation, and highest oxygen requirement in the preceding 24 h before PE diagnosis.

For patients who received CDT, treatment included infusion-catheter directed thrombolysis via a Cragg-Macnamara catheter (Medtronic, Minneapolis, MN), ultrasound-assisted thrombolysis (USAT) (EKOS®, Boston Scientific, Marlborough, MA), rheolytic thrombectomy (Angiojet™, Boston Scientific, Marlborough, MA), or a combination of these therapies. When catheter-directed thrombolytics were given, a 2 mg alteplase bolus per catheter was generally given, followed by 0.5 mg/h (if bilateral catheters placed) or 1 mg/h (if one-sided involvement requiring only one catheter) for ~ 24 h so that the total dose of alteplase delivered was typically ~ 25 mg (USAT n = 46, Cragg-McNamara/tPA n = 14, mechanical thrombectomy alone n = 11, combination of mechanical and pharmacologic therapy n = 11, infusion catheter not otherwise specified n = 2). Patients who received conservative therapy received unfractionated heparin, low molecular weight heparin, or argatroban as initial therapies before being transitioned to a vitamin K antagonist or a direct oral anticoagulant (DOAC).

Confounder adjustment was performed using propensity score matching (PSM) weights, which was restricted only to patients with RV strain in both cohorts to minimize confounding. The weighting applied to individual patients is analogous to the probability that they would have been selected as part of a matched pair if a 1:1 matching approach was used. This results in the ability to retain all study patients in the analysis, although some patients will have low weights. This method has been shown to improve covariate balance, provide more accurate variance estimation, and be more efficient than 1:1 pair matching [9]. It has also been shown to provide the lowest bias when studying rare binary outcomes as compared to other methods [10].

Eleven variables were used for PSM: age, length of hospitalization before PE diagnosis, location of diagnosis, need for mechanical ventilation within 24 h prior to diagnosis, and the most abnormal value of seven different VS in the 24 h before diagnosis: heart rate, SBP, diastolic blood pressure, respiratory rate, oxygen saturation, oxygen flow, and temperature. These variables were chosen because they were available for nearly every patient. Troponin and NTpro-BNP values were not used for PSM due to the large amount of missing values around the time of PE diagnosis.

To further define the risk profile of this PE cohort in the context of the 2019 ESC guidelines, patients were assigned to one of four risk profiles (High-risk, Intermediate-high-risk, Intermediate-low-risk, and Low-risk) based on the presence and combination of shock or hypotension, an sPESI ≥ 1, evidence of RV dysfunction, or elevated cardiac biomarkers [1].

Study outcomes

To assess safety of CDT, the endpoints were the change in hemoglobin at two and seven days, as well as a change in creatinine at two and seven days, after propensity matching analysis. An assessment of outcomes at two days was chosen based on a heavily-cited previously published CDT study [11]. An assessment of outcomes at seven days was chosen arbitrarily to ensure that enough patients were still hospitalized with available vital sign and laboratory data. TIMI major bleeding, including intracranial bleeding or any fatal bleeding, was also included to assess safety [12]. Any head CT scans within 30 days of diagnosis of PE were included in the analysis. For efficacy endpoints, in-hospital mortality, the need for mechanical ventilation, and hospital length of stay after PE diagnosis were examined, as well as four physiologic parameters with indicated cutoffs for high-risk and intermediate-high-risk patients to create a cohort of patients of similar illness: change in oxygen requirement (in patients with baseline FiO_2 requirement > 21%), change in respiratory rate (in patients with baseline respiratory rate ≥ 22 breaths/min), change in heart rate (in patients with baseline heart rate > 90 beats per minute), and change in SBP (in patients with baseline SBP ≤ 100 mmHg). Patient demographics, VS, and laboratory parameters were described using Wilcoxon rank sum tests for continuous variables, and chi square (or Fisher's exact tests when needed) for categorical variables. A p value of < 0.05 was considered statistically significant for all analyses. Continuous and categorical variables are presented as mean ± SD unless indicated otherwise. For safety outcomes, after propensity matching analysis, multivariate linear regression models were used for continuous outcomes, and multivariate logistic regression models were used for binary outcomes. VS trajectories between the high-risk and intermediate-high-risk patients in each of the two groups over the initial 72 h after PE diagnosis were compared using a mixed-effects regression model to account for repeated observations over time. Quadratic regression plots were generated which create a best-fit line of the VS data. The p values represent differences in the linear trajectories over time.

Results

Baseline characteristics

From January 2009 to February 2018, 1094 patients were diagnosed with acute PE of at least segmental location.

Eighty-four of these patients underwent CDT and 1007 received conservative therapy with anticoagulation alone. Three patients with submassive PE were referred for CDT but did not receive CDT; two were found not to have significant PE by pulmonary angiogram and one patient refused the procedure. These patients were still included in the CDT group in an intention-to-treat fashion, and omission of these patients would not have changed any of the primary outcomes. Unadjusted baseline characteristics between the two groups of patients were significantly different: more patients who received CDT compared to anticoagulation alone had NT-proBNP levels > 500 mg/dL (51% versus 16%, $p < 0.0001$), troponin T levels ≥ 0.03 mg/dL (44% vs. 16%, $p < 0.0001$), lower SBP (99 mmHg versus 107 mmHg, $p < 0.001$), and higher respiratory rate (28 versus 24 breaths/min, $p < 0.001$). RV dysfunction was more common in PE patients who underwent CDT versus anticoagulation alone (87% versus 30%, $p < 0.001$). CDT patients more often required mechanical ventilation (15% versus 6.9%, $p = 0.006$), and had higher baseline hemoglobin (12.7 versus 10.8 g/dL, $p < 0.001$) and creatinine (1.0 versus 0.9 mg/dL, $p < 0.001$) values (Table 1). Patients referred for CDT were high-risk or intermediate-high-risk in 69% of cases, compared to 22% of the PE patients who received conservative therapy (Table 2). After adjustment using the propensity matching methods described above, patients were well-matched (Table 3) and the standardized mean difference (SMD) of the eleven different variables used for matching was < 0.1 between groups (Supplemental Fig. 1).

Safety endpoints

PE patients with RV strain who underwent CDT ($n = 76$) versus receiving anticoagulation alone ($n = 303$) had more significant hemoglobin loss at two days (additional 1.04 g/dL loss, $p < 0.001$) and seven days (additional 1.36 g/dL loss, $p < 0.001$) (Table 4). Fourteen of the patients who received CDT received a transfusion after the procedure. Seven (50%) of these patients had access site bleeding. The remainder of patients required blood transfusions due to acute on chronic anemia, gastrointestinal bleeding, or gynecological bleeding. The mean transfusion requirement of 2.8 units of packed red blood cells (PRBCs) during the admission for these patients. This included one patient who required 11 units of PRBCs in the setting of extracorporeal membrane oxygenation for ongoing shock. There were no intracranial hemorrhages in either group within the first 30 days after PE diagnosis. There was an increase in creatinine at two days (additional 0.22 mg/dL elevation, $p = 0.03$), but not at seven days (additional 0.12 mg/dL elevation, $p = 0.30$) for patients who received CDT compared to anticoagulation alone. One patient required new initiation of hemodialysis during the hospitalization, and this was the same patient who had profound shock requiring extracorporeal membrane oxygenation and initiation of continuous renal replacement therapy.

Efficacy endpoints

In patients with baseline abnormal VS who received CDT versus anticoagulation alone, there was more rapid improvement in heart rate, respiratory rate, and oxygen requirement over 72 h (Fig. 2). The p values of these quadratic fit plots represent differences in the linear trajectories of the curves over time. All VS had p values < 0.001, indicating significantly different trajectories. These trajectories favor CDT for heart rate, respiratory rate and oxygen requirement. SBP improved in both groups over 72 h, but was slower to improve in the CDT group. There were 14 (16%) in-hospital deaths in the CDT arm, and 66 (6.6%) deaths in the conservatively-treated arm. After PSM, in-hospital mortality for patients receiving CDT versus anticoagulation alone was similar (OR 1.21, 95% CI 0.53 to 2.77, $p = 0.65$). There was no significant difference in the need for mechanical ventilation after PE diagnosis between the two groups (OR 1.63; 95% CI 0.85 to 3.16, $p = 0.15$). There was also no difference in length of stay (hours after PE diagnosis) for acute PE patients with baseline RV strain undergoing CDT versus anticoagulation alone (95% CI − 59.7, 12.2; $p = 0.20$).

Discussion

This study of management in patients with acute, higher-risk PE suggests an acceptable safety profile of CDT compared to conservative treatment with anticoagulation alone, and that CDT may be more effective in the rapid restoration of normal physiology. Other studies, including SEATTLE II and ULTIMA, have shown that CDT is superior to anticoagulation with regards to improvement in pulmonary artery pressures [11] and RV dilatation [4]. Additionally, these studies show that CDT is safe from a bleeding perspective, carries a low rate of major complications, and is associated with shorter stays in the intensive care unit [13–15]. Propensity matching analyses have been used to compare in-hospital outcomes between PE patients who receive CDT versus systemic thrombolysis, and patients who received CDT had significantly lower in-hospital mortality and less intracranial hemorrhage [16]. Despite this data, the treatment of submassive PE remains controversial [17]. There is currently no data to suggest a significant decrease in mortality in intermediate-risk PE patients who receive CDT versus anticoagulation alone [18].

In this retrospective study of acute PE patients who undergo CDT, we demonstrate that CDT is associated with slightly increased bleeding risk, but does not result in a

Table 1 Baseline characteristics of PE patients who received CDT versus conservative therapy before propensity matching

	CDT (N = 87)	Conservative treatment (N = 1007)	p value
Gender			0.92
Female, n (%)	50 (57%)	584 (58%)	
Male, n (%)	37 (43%)	423 (42%)	
Race			0.03
Black/African-American, n (%)	71 (82%)	690 (69%)	
White, n (%)	12 (14%)	267 (27%)	
Other, n (%)	4 (4.6%)	50 (5.0%)	
Age	57 (42, 71)	61 (47, 71)	0.40
Hours hospitalized prior to PE diagnosis	17 (5.9, 30)	21 (14, 73)	< 0.001
Body mass index	32 (26, 39)	28 (24, 34)	< 0.001
NT-proBNP	1,949 (830, 3,970)	664 (96, 2,678)	< 0.001
Troponin (high)	3 (0.06, 3)	0.04 (0.03, 3)	< 0.001
NT-proBNP > 500, n (%)	44 (51%)	157 (16%)	< 0.001
No NT-proBNP > 500	7 (8.1%)	127 (13%)	
No NT-proBNP measured	36 (41%)	723 (72%)	
Troponin ≥ 0.03, n (%)	38 (44%)	160 (16%)	< 0.001
No troponin ≥ 0.03	30 (34%)	397 (39%)	
No troponin measured	19 (22%)	450 (45%)	
RV dysfunction by echocardiography or CT	76 (87%)	303 (30%)	< 0.001
No RV dysfunction	11 (13%)	704 (70%)	
On ventilator (before PE diagnosis)	13 (15%)	69 (6.9%)	0.006
Location at PE diagnosis			< 0.001
Ward	17 (20%)	553 (55%)	
Intensive care unit	43 (50%)	214 (21%)	
Emergency Department	26 (30%)	240 (24%)	
Hemoglobin (baseline)	12.7 (10.4, 14.1)	10.8 (9.3, 12.6)	< 0.001
Creatinine (baseline)	1.0 (0.8, 1.3)	0.9 (0.7, 1.1)	< 0.001
	CDT (N = 87)	Conservative treatment (N = 1007)	p value
Systolic blood pressure (lowest)	99 (86, 118)	107 (96, 119)	< 0.001
Diastolic blood pressure (lowest)	61 (48, 71)	61 (52, 69)	0.81
Heart rate (highest)	112 (100, 127)	110 (95, 124)	0.32
Respirations (highest)	28 (23, 31)	24 (20, 29)	< 0.001
Oxygen flow (L/min) (highest)	3 (0, 6)	2 (0, 3)	< 0.001
Oxygen saturation (lowest)	91 (85, 93)	93 (90, 95)	< 0.001
Temperature (highest)	98.2 (97.5, 99.0)	98.4 (97.7, 99.3)	0.02
Heart rate ≥ 90 n(%)	78 (90%)	858 (85%)	0.26
Systolic BP ≤ 90 n(%)	24 (28%)	153 (15%)	0.003
On supplemental oxygen n(%)	61 (70%)	601 (60%)	0.04

Unless otherwise indicated, laboratory and VS values are medians and (x, x) represents IQR, where the value represents the 25th and 75th quartiles respectively. Otherwise, parentheses indicate % of patients

CDT catheter-directed therapy, *PE* pulmonary embolism, *SMD* standardized mean difference, *ICU* intensive care unit

significant decrease in renal function. Bleeding was more significant in the CDT group (additional 1 g/dL Hgb loss) and these patients received more blood transfusions. While in-hospital mortality was not different between the two groups after PSM, blood transfusions are associated with increased rates of infection and mortality in some groups of patients, and judicious administration of blood products is prudent [19–21].

From a physiologic outcome perspective, high-risk and intermediate-high-risk PE patients with abnormal baseline VS (i.e. heart rate > 90 bpm, RR > 22 breaths/min, or FiO_2 requirement of > 21%) had more rapid improvement in these VS parameters if they received CDT compared to patients

Table 2 Risk profile of PE patients who received CDT versus medical therapy. Patients were classified according to the early mortality risk criteria as described in the 2019 ESC Guidelines. Parenthesis indicate percentage of patients within each group

Early Mortality Risk	CDT (N = 87)	Conservative treatment (N = 1007)
High	26 (30%)	167 (17%)
Intermediate-high	34 (39%)	96 (10%)
Intermediate-low	23 (26%)	498 (49%)
Low	4 (5%)	246 (24%)

CDT catheter-directed therapy

treated with anticoagulation alone. While SBP improved in both groups of patients, the rate of improvement in high-risk CDT patients was slower than that seen in conservatively-managed patients. This finding is surprising but may be due in part to the effects of sedation medications given during CDT procedures. With this exception, our data shows a potential benefit of CDT with regard to clinical improvement of VS in the short term. This is commensurate with what is known about improvements in RV dimension and pulmonary artery pressures in similar patients, as demonstrated in SEATTLE II (mean RV/LV diameter at 48 h decreased from 1.55 to 1.13, and mean pulmonary artery pressure decreased from 51 to 36.9 mmHg) [11, 14, 18].

Table 3 Baseline characteristics of PE patients with RV strain who received CDT versus medical therapy, after propensity matching

	CDT (N = 76)	Conservative treatment (N = 303)	SMD
Age (mean, sd)	57 (16)	57 (17)	0.011
Hours hospitalized prior to PE diagnosis	40 (59)	41 (66)	0.011
On ventilator (before PE diagnosis)	10 (14%)	11 (15%)	0.026
Location at PE diagnosis			
ICU	36 (49%)	36 (49%)	0.004
ED	20 (27%)	21 (28%)	0.018
Systolic blood pressure (lowest)	100 (21)	99 (19)	0.017
Diastolic blood pressure (lowest)	61 (18)	60 (15)	0.027
Heart rate (highest)	114 (19)	114 (23)	0.034
Respirations (highest)	28 (6)	28 (8)	0.033
Oxygen flow (L/min) (highest)	6 (10)	6 (10)	< 0.001
Oxygen saturation (lowest)	89 (8)	88 (13)	0.066
Temperature (highest)	98.2 (1.5)	98.2 (1.3)	0.009

Parentheses indicate standard deviation, or % of patients where indicated. SMD is the standardized mean difference, and is provided instead of a p value given propensity score matching was performed. An SMD of > 0.1 is considered an important difference between two groups, and all variables in this study have an SMD of < 0.1

CDT catheter-directed therapy, *PE* pulmonary embolism, *SMD* standardized mean difference

Table 4 Outcomes for PE patients treated with CDT versus anticoagulation alone, after propensity score matching

Continuous outcomes	Mean difference	95% CI	p value
Drop in hemoglobin at 2 days (g/dL)	− 1.04	− 1.48, − 0.60	< 0.001
Drop in hemoglobin 1 week (g/dL)	− 1.36	− 1.88, − 0.84	< 0.001
Increase in creatinine at 2 days (mg/dL)	0.22	0.02, 0.42	0.03
Increase in creatinine at 1 week (mg/dL)	0.12	− 0.11, 0.35	0.30
Binary outcomes	Odds ratio	95% CI	p value
In-hospital mortality	1.21	0.53, 2.77	0.65
Required mechanical ventilation	1.63	0.85, 3.16	0.15

Reported values represent mean difference in laboratory values or odds ratio where indicated. A p value < 0.05 is considered significant

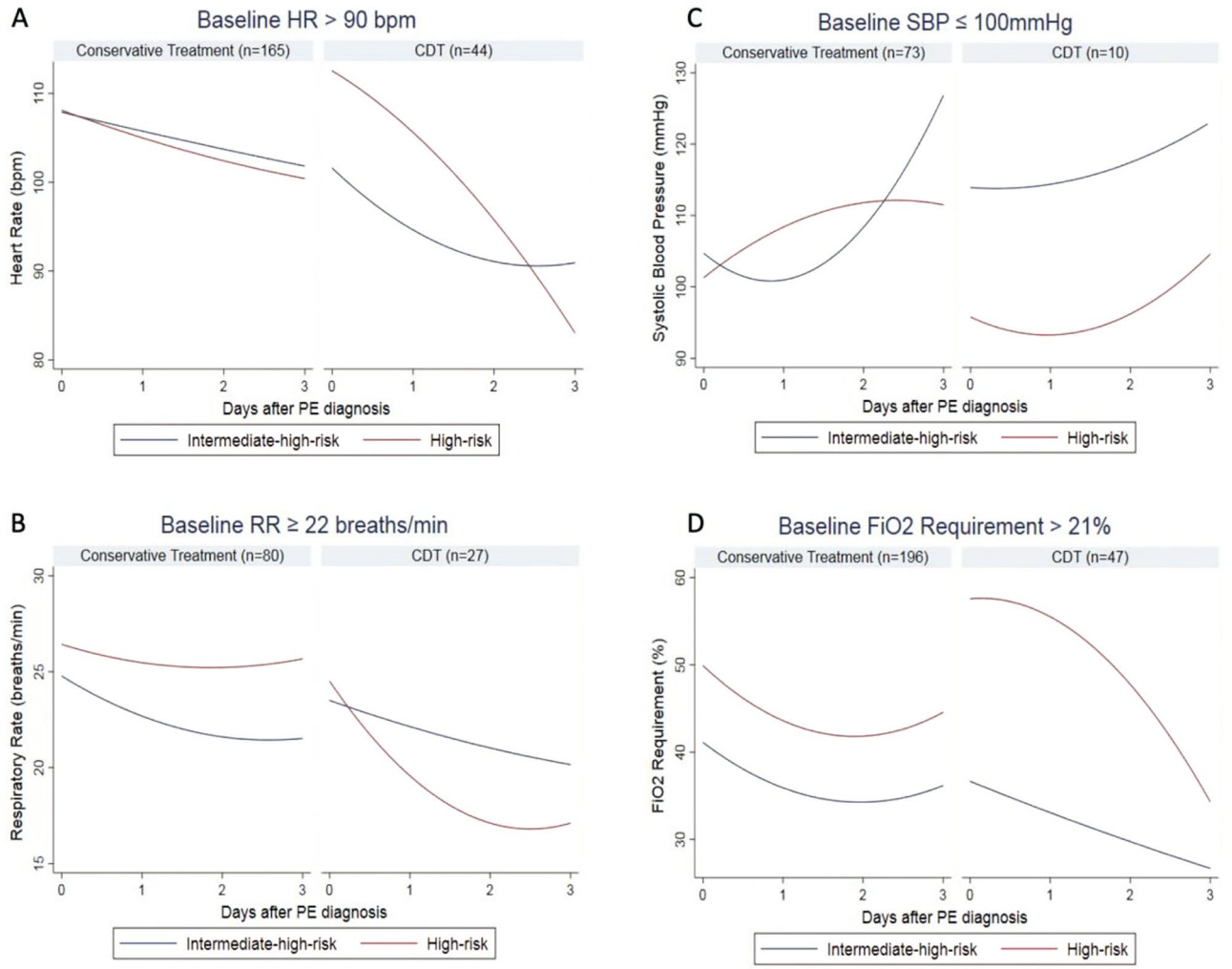

Fig. 2 Comparison of vital signs in PE patients receiving conservative treatment or CDT, from diagnosis through day three of hospitalization. **A** Change in heart rate with baseline heart rate > 90 bpm, $p < 0.001$. **B** Change in respiratory rate in patients with baseline respiratory rate ≥ 22 breaths per minute, $p < 0.001$. **C** Change in SBP in patients with baseline SBP ≤ 100mmHg, $p < 0.001$. **D** Change in FiO_2 requirement ($\%FiO_2$) in patients with baseline FiO_2 requirement > 21%, $p < 0.001$. Note that some of the quadratic regression plots for SBP start above the specified cutoff value. This is because these lines represent a best-fit curve, and while the initial SBP values were < 100mmHg, subsequent values after diagnosis were higher and resulted in a best-fit curve above 100 mmHg. *CDT* catheter-directed therapy, *HR* heart rate, *SBP* systolic blood pressure, *RR* respiratory rate

Strengths and limitations

One particular strength of this retrospective study is the use of PSM weights, which allows for a more accurate comparison between these groups. The authors used propensity score matching weights because this method has been shown to minimize bias better than simple matching in small datasets with binary outcomes[10]. In the critical care literature, Kitsios et al. published a systematic review and found that PSM analyses were generally consistent with randomized trials [22]. Lastly, using PSM allowed us to include significantly more patients in the analysis. Another strength of our study was the focus on patients with acute PE of at least segmental size. No chronic PEs or subsegmental PEs were included in this analysis. While ICD-9/10 codes were used as an initial screen for patients with PE, all CT reports flagged as positive were manually inspected. Further, to strengthen the PSM modeling we limited the analysis of safety endpoints (bleeding and renal function) to patients with RV dysfunction at the time of PE diagnosis. It should be noted that for the VS trajectory outcomes, PSM could not be used, as there were too few patients in each subgroup to perform adequate modeling. Instead, regression modeling was applied to patients with respiratory rate > 22 breaths per minute, heart rate > 90 beats per minute, SBP < 100 mmHg, and for patients requiring supplemental oxygen.

Our study has several limitations. First, while the authors feel that PSM is an overall strength of this analysis, PSM

cannot replace true randomization in a retrospective study, and thus our analysis is subject to confounding, especially by indication. PSM cannot account for all factors contributing to a physician's perception of bleeding risk and patient frailty when deciding whether or not to refer to CDT. While PSM may adjust for some degree of confounding bias, it is possible there is residual confounding, which could alter our results.

Another limitation is that this study was designed using ICD codes to define patients with acute PE, which may have excluded some patients who suffered a PE during their hospitalization but were not identified due to coding errors. However, in an attempt to further characterize degree of illness in patients who were identified in this manner, we used readily available data that was present for almost all patients (heart rate, SBP, diastolic blood pressure, respiratory rate, oxygen saturation, oxygen flow, temperature, age, length of hospitalization before PE diagnosis, location of diagnosis, need for mechanical ventilation within 24 h prior to diagnosis). These variables (at numerous time points) were present for nearly all patients, whereas other variables that are commonly used for risk-stratification were not. Only 64% of patients had cardiac biomarkers drawn around the time of PE diagnosis; thus, proper classification of patients into intermediate-high-risk and intermediate-low-risk groups may have been affected. It is also not known if some patients were on vasoactive agents at baseline or after the intervention. These agents would clearly have impacted VS data, making some patients appear more stable than they may have been. With retrospective studies such as this, correlating changes in clinical parameters to the timing of intervention (CDT or anticoagulation alone) is difficult. In our study, the median time from diagnosis to CDT was 5 h, and therefore the authors feel that changes in vital signs are reflective of the intervention. This relatively short time-frame suggests that CDT was not employed as a rescue effort after many hours or days of worsening vital signs.

The lack of some comorbidity data (especially prior VTE and cancer history) is a limitation. However, in spite of these significant limitations, the acuity of illness of patients in each cohort is reflected by sPESI scores of at least 2 (HR > 110 bpm, $SpO_2 < 90\%$), which correlates to a high mortality rate at 30 days [7].

Echocardiographic data was not useful for purposes of this study as patients did not reliably undergo echocardiograms close enough to the time of PE diagnosis or again during the hospitalization. While CT data were available on almost every patient, a ratio of right to left ventricular size from CT was purposefully not included as a baseline parameter. PE-protocol CT scans are typically not gated to the cardiac cycle and thus right ventricular measurements would not be uniformly measured appropriately at end-diastole. As with any retrospective study, there exists the potential for unmeasured selection and confounding biases that could favor the results in any direction, but we feel that PSM significantly reduced this probability. PSM could not be performed on the individual mortality risk groups, however, as the number of patients in each subgroup was too small. For the same reason, PSM could not be used to compare outcomes for the individual types of CDT.

Lastly, our results are limited to in-hospital parameters only. Data such as follow-up imaging studies (i.e. echocardiogram and ventilation-perfusion scans), 6-min walk distance, biomarker and quality of life surveys weeks to months after discharge would add important information.

Conclusions

CDT compared to anticoagulation alone for acute, higher-risk PE may be associated with a faster normalization of heart rate, respiratory rate, and oxygen requirement over the first 72 h of hospitalization, at the cost of a minor increase in bleeding. While CDT has a reasonable safety profile, a well-powered randomized trial is still needed to further address whether CDT is superior to anticoagulation alone for the treatment of intermediate-risk PE.

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Author contributions AP, JP, KC, and MC had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the analysis. AM, AS, JF, JB, AS, SN contributed substantially through study design and data collection. All authors have provided AP with permission to be named in the manuscript.

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Data availability All data is available upon request.

Declarations

Conflict of interest There are no relevant conflicts of interest or competing interests.

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