Journal of Thrombosis and Thrombolysis
https://doi.org/10.1007/s11239-022-02640-6

# Post-thrombolytic coagulopathy and complications in patients with pulmonary embolism treated with fixed-dose systemic alteplase

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Accepted: 9 February 2022


## Abstract

**Background** Alteplase treatment can cause a systemic coagulopathy although the incidence and contributory factors are unknown in pulmonary embolism (PE). Fixed-dosing of alteplase for PE may lead to interpatient variability in drug exposure and influence post-thrombolytic coagulopathy (PTC). While changes in fibrinogen and INR have been used to describe PTC, no universal PTC definition is available.

**Objectives** Evaluate the incidence of PTC after alteplase treatment for PE, the effect of patient weight and blood/plasma volume and the association with bleeding complications.

**Methods** We conducted a retrospective cohort study of patients treated with alteplase for massive or high-risk submassive PE. Demographics, alteplase dosing, laboratory assessment of coagulopathy, and bleeding events were collected. The primary endpoint was incidence of PTC defined as an international normalized ratio (INR) > 1.5 or fibrinogen < 170 mg/dL. Secondary outcomes included correlation between coagulopathies and alteplase dose normalized to actual body weight (ABW), ideal body weight (IBW), plasma volume (PV), and estimated blood volume (EBV). Bleeding events in patients with and without PTC were compared.

**Results** 125 patients met criteria for inclusion in the study. PTC occurred in 35.3% of patients, with INR >1.5 in 21.8% and fibrinogen <170 mg/dL in 26%. Alteplase dose >50 mg was associated with increased odds of PTC (OR 6.5, CI 2.1-19.9). Dose normalized to ABW and EBV correlated weakly with absolute increase in post-alteplase INR (r =0.20, p =0.06 and r =0.21, p =0.057 respectively) and to percent change in INR (r =0.20, p = 0.058 and r =0.21, p =0.048 respectively). Dose/ABW, dose/PV, and dose/EBV each correlated moderately with absolute decrease in fibrinogen (r =-0.53, -0.49, and -0.47 respectively, p <0.001 for each) and percent change in fibrinogen (r = -0.55, -0.49, and -0.49 respectively, p < 0.001 for each). Dose/IBW correlated weakly with absolute and percent decrease in fibrinogen (r = -0.32, p =0.013 and r =-0.33, p =0.011). Patients with bleeding were more likely to have PTC (58.3% vs. 28.6%, p= 0.05) and a bleeding event was predictive of PTC (OR 5.33, 1.32-23.99).

**Conclusions** PTC is prevalent in patients with PE. PTC is influenced by alteplase dose and exposure parameters (ABW, IBW, PV, EBV) and may contribute to the bleeding risk.

**Keywords** Alteplase · Coagulopathy · Pulmonary embolism · Tissue plasminogen activator · Thrombolytic

**Abbreviations**

ABW Actual Body Weight

This manuscript is not under review elsewhere and there is no prior publication of manuscript contents. We presented preliminary analysis of this data at the 4th Annual PERT Consortium Pulmonary Embolism Symposium in 2018.

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Published online: 23 March 2022

| | |
|---|---|
| AIS | Acute Ischemic Stroke |
| AMI | Acute Myocardial Infarction |
| aPTT | activated Partial Thromboplastin Time |
| CI | Confidence Interval |
| EBV | Estimated Blood Volume |
| ECMO | Extracorporeal Membrane Oxygenation |
| IBW | Ideal Body Weight |
| INR | International Normalized Ratio |
| ISTH | International Society on Thrombosis and Haemostasis |
| OR | Odds Ratio |
| PE | Pulmonary Embolism |
| PTC | Post-Thrombolytic Coagulopathy |
| PV | Plasma Volume |
| sPESI | Simplified Pulmonary Embolism Severity Index |

**Key Points**

- Incidence of post-thrombolytic coagulopathy (PTC) in PE and its association with hemorrhagic complications is unknown.
- PTC was prevalent and associated with dose, body weights, and blood/plasma volume.
- Patients with bleeding were more likely to have PTC and a bleeding event was predictive of PTC.
- Our study provides a foundation for future prospective trials to further evaluate patient-tailored alteplase dose regimens and overall strategies to optimize the risk/benefit of alteplase for the treatment of PE.

Massive and high-risk submassive pulmonary embolism (PE) is a medical emergency associated with significant morbidity and mortality [1]. Systemic thrombolysis has been shown to improve clinical outcomes including early hemodynamic stabilization, improvement in right ventricular function, and survival [2, 3]. Routine use of thrombolytics for PE is limited by an increased risk of hemorrhage [3]. Alteplase is a recombinant tissue plasminogen activator and the most commonly used thrombolytic for treatment of high-risk PE. The ideal alteplase regimen to achieve effective and safe thrombolysis in PE remains unknown.

Alteplase is a fibrin-specific thrombolytic with targeted activity at the site of the thrombus and preserves the systemic coagulation system [4]. Experiences in treatment of acute myocardial infarction (AMI) and ischemic stroke (AIS) found that fibrinolytic activity of alteplase frequently leads to a systemic coagulopathy associated with major bleeding [5, 6]. Alteplase dosing for massive or high-risk submassive PE differs from other indications in that it lacks adjustment for interpatient differences in weight or other factors affecting drug exposure. Fixed-dose alteplase, without regard to patient weight or other measures of volume of distribution, may lead to significant interpatient variability in drug exposure and influence the incidence of post-thrombolytic coagulopathy (PTC). To date, there is a paucity of literature characterizing alteplase-associated coagulopathy in the setting of PE. Previous publications focused on decreased fibrinogen, elevated fibrinogen degradation products, and INR after alteplase administration, but a universal definition of the PTC is not available [7, 8]. The incidence and severity of PTC in PE and its association with hemorrhagic complications is unknown.

We conducted a retrospective analysis of patients with PE treated with fixed-dose alteplase to evaluate the incidence of coagulopathy, the influence of patient-specific weights and estimated blood/plasma volume (EBV) on PTC, and the correlation between PTC and bleeding complications.

## Methods

### Study Design

We conducted a retrospective cohort study of patients treated with alteplase for massive or high-risk submassive pulmonary embolism from 2012 to 2019 at a 670-bed tertiary care center. Eligible patients were identified through the hospital's Pulmonary Embolism Program database and cross-referenced with alteplase utilization reports. All patients required radiographic confirmation of PE and met criteria for massive or high-risk submassive PE.[7]

Patient exclusion criteria included cardiac arrest prior to or within 24 h after alteplase administration, treatment with extracorporeal membrane oxygenation (ECMO), and absence of coagulopathy laboratory tests. Patients with pre-alteplase INR >1.5 were excluded from the post-alteplase INR assessment and those with pre-alteplase fibrinogen < 170 mg/dL were excluded from the fibrinogen assessment, Pertinent demographic and clinical variables were collected by database extraction and manual chart review and compiled in a REDCap® database. The Institutional Review Board of Allina Health approved this study without the need for informed consent.

## Treatment

Immediately upon suspicion of PE, therapeutic unfractionated heparin (UFH) was initiated at guideline-recommended dosing [9]. The decision to treat with alteplase was based on clinical severity criteria and if the risk of bleeding was sufficiently low as dictated by absolute and relative

contraindications from established guidelines [9]. Heparin infusion was stopped prior to alteplase initiation. Alteplase dosing (standard fixed-dose of 100 mg infusion over 2 h or reduced dose of 10 mg bolus then 40 mg infused over 2 h) was selected at the discretion of the attending physician according to the hospital's treatment protocol. Per institutional guidelines, a complete blood count, International Normalized Ratio (INR), activated partial thromboplastin time (aPTT), and fibrinogen are recommended prior to alteplase initiation and within 2 h after infusion completion. Trending results over time was not standardized and left to the treating physician's discretion. The aPTT was measured every 1-2 h after alteplase until it was less than 2 times the upper limit of normal, then heparin was resumed at pre-alteplase dosing without a bolus. Subsequently, heparin was titrated to target aPTT equivalent to a heparin anti-Xa of 0.3-0.7 IU/mL with oral anticoagulation initiated upon clinical stability.

## Outcomes and Definitions

The primary study endpoint was incidence of PTC, defined as a documented elevation of INR >1.5 or a fibrinogen <170 mg/dL without an alternative cause. Additionally, changes in fibrinogen and aPTT within 24 h of alteplase administration were evaluated. Secondary outcomes included correlation between each component of PTC and alteplase dose normalized to (divided by) actual body weight (ABW), ideal body weight (IBW), plasma volume (PV), and estimated blood volume (EBV). Measured body weight on the day alteplase treatment was used for ABW. IBW was calculated using the Devine formula. PV was estimated using patient weight and hematocrit. EBV was estimated using Nadler's formula. The total dose of alteplase was divided by ABW, IBW, PV, and EBV and plotted against peak INR, peak aPTT prior to heparin resumption, and nadir fibrinogen in the first 24 h after thrombolysis. An additional secondary outcome was incidence of bleeding (major, minor, and any) in patients with and without PTC within 7 days of alteplase. Major bleeding was defined using ISTH criteria [10]. Minor bleeding was defined as any bleeding event that did not meet the definition of major bleeding.

## Statistical Analyses

Descriptive statistics for relevant continuous and categorical variables were computed and reported as medians with interquartile ranges and frequencies. Paired t-tests were performed for changes from pre-alteplase to post-alteplase maximum INR, first aPTT, and minimum fibrinogen value. We removed all patients who had a pre-alteplase INR >1.5 or a fibrinogen <170 mg/dL. Pearson correlation coefficients and 95% confidence intervals were computed between alteplase dose normalized to ABW, IBW, PV, and EBV and the percent/absolute difference, and nadir/peak values for fibrinogen, INR, and aPTT values. Kendall rank correlation coefficients were computed between alteplase dose normalized to ABW, IBW, PV, and EBV for those patients with post-alteplase fibrinogen <170 mg/dL, INR >1.5, and aPTT >35 s within 24 h. Differences in patient characteristics and outcomes between those patients with and without in-hospital bleeding complications were tested using t-tests, Mann-Whitney, Chi-squared tests, and Fisher's exact tests as appropriate. We conducted t-tests and Chi-squared tests with computed odds ratios and 95% confidence intervals to compare the clinical and patient characteristics between those with and without PTC. Logistic regression was used to test differences in post-thrombolytic coagulopathy, with adjusted odds ratios and 95% confidence intervals. The final model was decided on using previous clinical knowledge of association with outcome and a 0.2 p-value cutoff in initial analysis. These variables were further controlled using a backward elimination method. All statistical analyses were conducted using R software version 3.6.1 (The R Foundation for Statistical Computing, Vienna, Austria.) For all analyses, $P<0.05$ was considered significant.

## Results

Overall, 148 patient encounters were identified in which alteplase was used in the management of massive or high-risk submassive PE. Of those, 23 patients were excluded, 7 due to cardiac arrest and 16 due to no coagulopathy assessment. Twenty-five patients were censored from the pre and post-alteplase fibrinogen assessment due to values below 170 mg/dL or no assessment while 10 patients were censored from the INR assessment. Patients included in the analysis were predominantly male, obese, with comorbid conditions, and had a median age of 60 (Table 1). The majority of patients presented with high-risk submassive PE and met additional criteria for elevated risk per sPESI score. All patients received a fixed-dose of alteplase with the majority receiving 50 mg. One patient received a dose of 90 mg due to a hemorrhagic complication leading to early discontinuation of 100 mg infusion. In-hospital mortality was 4.8%. Four of 6 patients who died in the hospital presented with massive PE, and three patients had advanced neoplastic process as the cause of death. No cases of recurrent pulmonary embolism or clinical decompensation related to heparin infusion interruption for alteplase administration were observed in our patients.

**Table 1** Baseline characteristics of all study participants

| Patient Characteristics | All Patients (n = 125) |
|---|---|
| Female, n (%) | 57 (45.6%) |
| Age, median (IQR), y | 60 (53-71) |
| ABW, median (IQR), kg | 105.0 (87.3-127.5) |
| IBW, median (IQR), kg | 68.4 (57-75.3) |
| EBV, median (IQR), L | 5.75 (5.12-6.52) |
| PV, median (IQR), L | 3.55 (3.09-3.92) |
| BMI, median (IQR), $kg/m^2$ | 34.1 (30.1-41.4) |
| History of cancer, n (%) | 38 (30.4%) |
| History of COPD, n (%) | 6 (4.8%) |
| History of heart failure, n (%) | 27 (21.6%) |
| PE severity: | |
| Massive | 27 (21.6%) |
| High-Risk Submassive | 98 (78.4%) |
| sPESI ≥1*, n (%) | 113 (91.1%) |
| Shock Index*: | |
| All, median (IQR) | 0.82 (0.70-0.90) |
| > 1, n (%) | 18 (15.8%) |
| Alteplase dose: | |
| 50 mg | 104 (83.2%) |
| 100 mg | 20 (16.0%) |
| Other | 1 (0.8%) |
| Mortality: | |
| In-hospital | 6 (4.8%) |
| PE-related | 2 (1.6%) |

*sPESI and Shock Index were calculated at presentation to the hospital. BMI = Body Mass Index, COPD = Chronic obstructive pulmonary disease, EBV = estimated blood volume, IBW = ideal body weight, IV= intravenous, L= liters, PE = pulmonary embolism, PV = plasma volume, sPESI = Simplified Pulmonary Embolism Severity Index

## Post-Thrombolytic Coagulopathy

Overall, PTC occurred in 41 patients or 35.3% of cohort with values measured (Table 2). A post-alteplase INR >1.5 or fibrinogen <170 mg/dL was prevalent individually, with a significant proportion of patients having more severe derangements than our criteria (Table 2). Median baseline INR prior to alteplase was 1.1 (1.1, 1.2) for patients without

**Table 2** Coagulopathy parameters after alteplase

| Coagulopathy Parameter | n# | Pre-Alteplase Value | Post-Alteplase Timing | Incidence*, n (%) |
|---|---|---|---|---|
| PTC | 116 | ---- | ---- | 41 (35.3%) |
| INR | 110 | 1.2 (1.1, 1.3) | 2.5 h (1.5, 3.5) | >1.5 = 24 (21.8%)<br>>2 = 6 (5.5%) |
| Fibrinogen | 100 | 418 mg/dL (361, 487) | 2.6 h (1.7, 3.5) | <170 mg/dL = 26 (26%)<br><100 mg/dL = 10 (10%) |
| aPTT | 117 | 47.5 s (30–67) | 1.9 h (1, 2.7) | >35 s = 38 (53.5%)<br>>50 s = 17 (14.5%)<br>>80 s = 5 (4.3%) |

aPTT = activated partial thromboplastin time, INR = International Normalized Ratio, PTC = post-thrombolytic coagulopathy, s = seconds. Pre-alteplase value and post-alteplase timing are reported as medians with interquartile range. #number of patients with a post-alteplase assessment. *percent of patients of which had the parameter measured post-alteplase

PTC and 1.2 (1.1, 1.3) for patients with PTC (p = 0.01) while the median baseline fibrinogen was 415 mg/dL (369, 477) versus 418 (297, 506) (p = 0.87). The median percent change in INR was +9.1 (7.7, 27.3). The median percent change in fibrinogen was -31.5% (-54.5, -12.5) with 65% of patients experiencing a reduction of 25% or more.

The incidence of PTC was significantly more common in patients treated with >50 mg as compared to those who received 50 mg of alteplase (76.5% vs. 23.9%, p = 0.0001)

**Table 3** Dose Normalization in Patients with PTC and No PTC

| Normalized Dose | No PTC (n = 75) | | PTC (n = 41) | | |
|---|---|---|---|---|---|
| | **Median (IQR)** | **Range** | **Median (IQR)** | **Range** | **p** |
| Dose/ABW | 0.47 (0.39-0.59) | 0.23 - 1.20 | 0.58 (0.49-0.90) | 0.32 - 1.43 | 0.001 |
| Dose/IBW | 0.73 (0.65-0.88) | 0.58 - 1.91 | 0.88 (0.73-1.33) | 0.61 - 2.20 | 0.002 |
| Dose/EBV | 8.4 (7.5-10.1) | 5.0 - 21.5 | 9.9 (8.9-15.9) | 6.9 - 26.6 | 0.001 |

ABW = actual body weight, EBV = estimated blood volume, IBW = ideal body weight, IQR = interquartile range, PTC = post-thrombolytic coagulopathy

**Table 4** Dose Normalized to ABW, IBW, PV and EBV for all patients for various coagulopathy parameters

| Normalized Dose | r | 95% CI | p |
|---|---|---|---|
| Absolute change in INR: | | | |
| Dose/ABW | 0.20 | (-0.009, 0.396) | 0.06 |
| Dose/IBW | 0.15 | (-0.065, 0.348) | 0.172 |
| Dose/PV | 0.18 | (-0.04, 0.383) | 0.108 |
| Dose/EBV | 0.21 | (-0.065, 0.348) | 0.057 |
| Percent Change in INR: | | | |
| Dose/ABW | 0.20 | (-0.007, 0.398) | 0.058 |
| Dose/IBW | 0.16 | (-0.052, 0.359) | 0.138 |
| Dose/PV | 0.19 | (-0.035, 0.388) | 0.099 |
| Dose/EBV | 0.21 | (0.002, 0.405) | 0.048 |
| Peak INR Post-Alteplase: | | | |
| Dose/ABW | 0.26 | (0.08, 0.424) | 0.005 |
| Dose/IBW | 0.20 | (0.014, 0.368) | 0.036 |
| Dose/PV | 0.23 | (0.038, 0.399) | 0.019 |
| Dose/EBV | 0.25 | (0.071, 0.416) | 0.007 |
| Absolute Change in Fibrinogen: | | | |
| Dose/ABW | -0.53 | (-0.692, -0.32) | < 0.001 |
| Dose/IBW | -0.32 | (-0.53, -0.071) | 0.013 |
| Dose/PV | -0.49 | (-0.665, -0.262) | < 0.001 |
| Dose/EBV | -0.47 | (-0.645, -0.243) | < 0.001 |
| Percent Change in Fibrinogen: | | | |
| Dose/ABW | -0.55 | (-0.702, -0.339) | < 0.001 |
| Dose/IBW | -0.33 | (-0.537, -0.08) | 0.011 |
| Dose/PV | -0.49 | (-0.667, -0.266) | < 0.001 |
| Dose/EBV | -0.49 | (-0.658, -0.263) | < 0.001 |
| Nadir Fibrinogen Post-Alteplase: | | | |
| Dose/ABW | -0.38 | (-0.538, -0.2) | < 0.001 |
| Dose/IBW | -0.34 | (-0.503, -0.154) | < 0.001 |
| Dose/PV | -0.39 | (-0.548, -0.201) | < 0.001 |
| Dose/EBV | -0.39 | (-0.544, -0.209) | < 0.001 |
| Peak aPTT Post-Alteplase: | | | |
| Dose/ABW | 0.21 | (0.031, 0.378) | 0.022 |
| Dose/IBW | 0.09 | (-0.097, 0.264) | 0.354 |
| Dose/PV | 0.15 | (-0.043, 0.324) | 0.131 |
| Dose/EBV | 0.17 | (-0.017, 0.336) | 0.075 |

ABW = actual body weight, EBV = estimated blood volume, IBW = ideal body weight, PV = plasma volume, PTC = post-thrombolytic coagulopathy. Absolute and percent change was the difference in the last laboratory value before alteplase and the peak/nadir value within 48 h after alteplase

Absolute and percent change in aPTT were not assessed due to therapeutic heparin treatment being common prior to alteplase. Pearson correlation coefficient categories: <0.2 – very weak, 0.2-0.4- weak, 0.4-0.6- moderate, 0.6-0.8- strong

and in patients whose dose was ≥0.6 mg/kg as compared to < 0.6 mg/kg (53.3% vs. 23.8%, p = 0.003). Doses exceeding 50 mg (odds ratio (OR) 6.5, confidence interval (CI) 2.1-19.9) were associated with PTC. Logistic regression analysis identified dose/EBV (OR 1.25, CI 1.10-1.46), baseline INR prior to alteplase (OR 1.84, CI 1.30-2.85), and any bleeding event following alteplase treatment (OR 5.33, CI 1.32-23.99) as independent predictors of PTC.

The fixed doses of alteplase administered were retrospectively normalized with pre-specified exposure parameters: ABW, IBW, PV, and EBV. The median dose normalized to ABW, IBW, and EBV were significantly greater in patients with PTC compared to those without (Table 3). Dose/ABW and dose/EBV showed the best correlations with peak INR (Table 4; Fig. 1). No exposure parameter correlated with post-alteplase INR >1.5. Alteplase Dose/ABW, Dose/PV, and Dose/EBV each correlated moderately with absolute and percent change in fibrinogen with dose/ABW demonstrating the strongest correlation (Table 4). Fibrinogen nadir after alteplase correlated weakly with all exposure parameters (Fig. 1). Dose/PV was the only exposure parameter to correlate with a post-alteplase fibrinogen <170 mg/dL, albeit weakly.

## Other Coagulopathy Parameters

Prolongation of aPTT was common after alteplase but prior to heparin resumption, although severe derangements were rare (Table 2). According to the hospital treatment protocol, heparin was held prior to the 2-hour alteplase initiation, and not resumed until at least 1 h after the alteplase completion. The median first aPTT after alteplase, and before resuming therapeutic heparin, was 37 s (IQR 32-46). The median pre-alteplase aPTT just prior to alteplase was 47.5 s (30, 67) when residual heparin effect could be present. Post-alteplase aPTT peak values weakly and positively correlated with alteplase dose/ABW only (Table 4). No exposure parameter correlated with any post-alteplase aPTT greater than the upper limit of normal (35 s).

## Thrombolytic-Associated Hemorrhage

Fifteen patients (12%) experienced 17 hemorrhagic complications within 7 days of alteplase administration. Five patients (4%) experienced a major bleeding event while 10 experienced minor bleeding (8.0%). Eight bleeding events (47.1%) occurred within 24 h of alteplase, one of which was major. Overall, 16 events (94.1%) occurred on systemic anticoagulation and 9 events (52.9%) were related to an invasive procedure. Patients with bleeding complications had a higher incidence of PTC (58.3% vs. 28.6%, p= 0.05). INR ≥1.5 and fibrinogen <170 mg/dL occurred in a higher proportion of patients who bled (41.7% vs. 26%, p = 0.31 and 40% vs. 24.4%, p = 0.28, respectively). Bleeding events were predictive of PTC with odds ratio of 5.33 (1.32–23.99, p= 0.022). More than one risk factor (systemic anticoagulation, PTC, invasive procedure) were present in 10 bleeding episodes (59%). See Supplemental Table 1 for complication details.

## Discussion

Despite its short half-life, alteplase can induce a coagulopathy, including reductions in fibrinogen and prolongation of INR and aPTT times, which may persist for 24-48 h [5, 6, 11–14]. Literature evaluating coagulopathy after alteplase is predominantly in the setting of AMI and AIS with a paucity of literature in the setting of PE beyond percent change in fibrinogen [13, 14]. Our study provides a contemporary, real world population of patients with massive and high-risk submassive PE, treated with alteplase that was assessed for PTC and other parameters of coagulopathy. PTC is not universally defined. Early studies focused on "early fibrinogen degradation coagulopathy" after alteplase and more recent studies evaluating INR [7, 8]. We expanded the definition of PTC to encompass both significant derangements in INR and fibrinogen as they can be mutually exclusive, and both potentially confer risk.

Enhanced plasmin-mediated cleavage of fibrin can lead to secondary fibrinogen depletion in patients treated with alteplase, regardless of indication. In our study, fibrinogen degradation was a common manifestation of coagulopathy (31.5% median reduction). Our results align with fibrinogen measurements from clinical outcomes trials of alteplase for PE (33–72% reduction) [15–23]. The variability in percent reduction in the trials and incidence falling on the lower end of the range can be attributed to differing assessment times and dosing. In our cohort, 65% of patients experienced a reduction in fibrinogen of 25% or more, a threshold associated with bleeding in AIS [12]. This outcome was not previously assessed in the setting of PE but studies of AIS found a lower incidence of 20.2% [12]. Historical PE trials rarely reported the incidence of overt and severe hypofibrinogenemia [16, 20]. Overt hypofibrinogenemia was prevalent in our cohort of PE patients with 26% of patients experienced a post-alteplase fibrinogen <170 mg/dL and severe hypofibrinogenemia (<100 mg/dL) occurring in 10% of patients, which was more common than studies in AMI and AIS [5, 12].

INR elevations >1.5, another common manifestation of coagulopathy, occurred in 21.8% of patients and >2 in 5.3%.

Assessment of PT or INR after alteplase is rare in outcomes studies of PE. The only PE trial to assess PT or INR found a paradoxical reduction in PT at 2 h which returned to near baseline values in 24 h [17]. Our findings of INR prolongation align more closely with a PTC study of AIS patients where 7.4% patients experienced an INR >1.5, although our prevalence was 4-fold greater [7]. The mechanism of INR rise is less clear than fibrinogen depletion. Severe hypofibrinogenemia may prolong PT/INR but did not universally explain the INR rise in our cohort. An alternative mechanism of INR rise may be plasmin-mediated depletion of coagulation factor V, a factor with activity that affects INR [24].

Although alteplase improves outcomes in high-risk PE, the optimal dosing has not been established. FDA approved, guideline recommended dosing for PE is a fixed dose of 100 mg infused intravenously over 2 h which is an extrapolation from the AMI indication [9, 16, 25]. Alternative dosing strategies have been explored, including fixed-dose 50 mg or 0.6 mg/kg, in attempt to reduce complications related to thrombolysis but their role in treatment remains to be determined [21, 26, 27]. The 50 mg dosing strategy was most prevalent in our study due to our institutional preference for lower dosing in submassive PE, the predominant presentation is this population. To date, coagulopathy with 50 mg dosing has not been assessed in patients with PE, nor has it been compared to 100 mg. PTC was more common in patients treated with 100 mg as opposed to 50 mg, which corresponded to a greater than 6-fold increase in risk.

We hypothesized that normalizing fixed-dose of alteplase to estimates of EBV and PV, along with commonly used dosing weights for medication, may better predict changes in coagulopathic parameters with PTC serving as a sign of excessive thrombolysis. During and after infusion, alteplase distributes primarily to the vascular space with an estimated initial volume of distribution that approximates plasma volume which does not proportionally rise with increasing body weight [29, 30]. Our study found a weak, negative correlation with nadir fibrinogen levels and a weak, positive correlation with peak INR when plotted against rising values of dose normalized to all four parameters (ABW, IBW, PV, and EBV). Of the normalization parameters assessed, increasing dose/ABW and dose/EBV had consistently the strongest correlation to changes in fibrinogen and INR as well as nadir/peak. Logistic regression analysis identified dose/EBV to be an independent predictor of PTC.

The reported rates of major hemorrhagic complications associated with systemic alteplase in PE patients vary from 0.8 to 20.6%, although minor bleeding rates of up to 33% have also been reported [2, 31]. In our patient cohort, complication rates were relatively low, possibly due to the predominant use of the reduced-dose regimen and close attention to the systemic anticoagulation around the time of alteplase administration. Major bleeding occurred in 4% patients, while minor bleeding was noted in 8.0%. There was no mortality associated with bleeding complications, and the single case of ICH that occurred on post-TPA day 5 was likely related to oral anticoagulation. The relationship between PTC and bleeding in PE has not been previously evaluated. In AMI and AIS, percent change in fibrinogen, an absolute decrease ≥200 mg/dL, nadir less than 200 mg/dL, and a 25% reduction in fibrinogen have all correlated with hemorrhagic events [5, 6, 12]. Changes in INR have not been previously evaluated. In our study, patients with bleeding complications had nearly twice the incidence of PTC. While bleeding events were predictive of PTC, the majority of them occurred in the setting of full systemic anticoagulation and invasive procedures. Only 1 (0.8%) major hemorrhage occurred within 24 h of alteplase administration, and no PTC was noted in cases of bleeding occurring after post-alteplase day 3. These observations suggest that, in addition to the PTC, systemic anticoagulation and invasive procedures are playing a role in the development of hemorrhagic complications, especially at the later stages of patient's recovery.

Our study has limitations consistent with other retrospective, single center studies. To limit confounders we excluded patients with cardiac arrest or ECMO. In addition, we censored patients who had a severely elevated coagulopathy parameter prior to alteplase from analysis of that specific parameter. However, other confounding factors could be present. Our sample size is relatively small compared to the prospective clinical trials for thrombolysis in PE, but this is, to our knowledge, the first real-world study focusing on coagulopathy after alteplase for PE. Assessment of INR, fibrinogen, and aPTT pre- and post-alteplase was driven by our institutional guidelines and order set but was ultimately up to the treating physician therefore not all patients had all laboratory assessments, and not all of the 125 patients were included in the analysis of each coagulopathic parameter. In addition, there were variable practices for serial monitoring post-alteplase; therefore, nadir and peak values may have been more extreme but unmeasured. Lower absolute doses of alteplase could have lead to lower rates of PTC. While the present study is most applicable to centers who use alteplase doses of 50 mg, our comparison to 100 mg suggests a dose-response. Our ability to assess the effect of PTC on clinical outcomes was limited by a low bleeding rate. We could not control for differences in post-alteplase anticoagulation, but the vast majority of patients were resumed on therapeutic anticoagulation within 2-6 h of alteplase. The PE-related mortality was low but we did not assess for correlation between alteplase dosing, PTC, and efficacy outcomes. Future studies to explore tailored dosing strategies

for PE to reduce PTC and improve alteplase safety must also assure efficacy is maintained.

## Conclusions

Our study is the first to evaluate the incidence and predictors of PTC in PE. We corroborate an association between PTC and bleeding events previously identified in AIS and AMI but found a higher incidence in this PE cohort. Higher doses of alteplase conferred greater risk and the correlation analysis suggests an opportunity to explore tailored dosing strategies using ABW or EBV to minimize PTC and bleeding risk. Our study is limited by its relatively small sample size and the influence of our institution-specific treatment protocols for pulmonary embolism. We hope our study provides a foundation for future prospective, multi-center trials to further evaluate patient-tailored alteplase dose regimens, other factors associated with PTC, bleeding-related complications, and overall strategies to optimize the risk/benefit of alteplase for the treatment of massive and high-risk submassive PE.

**Acknowledgements** Not applicable

**Author contributions** All co-authors have made a substantial contribution to the design, data collection and analysis of the research, drafting of the manuscript, have reviewed and accepted the contents of the manuscript prior to its submission, and agree to be accountable for all aspects of the work. M Lillyblad provided conceptualization, methodology, design, clinical interpretation, and writing, review, and editing of the submitted manuscript. G Qadri contributed to methodology, design, clinical interpretation, and writing, review, and editing of the submitted manuscript. B Weise contributed to methodology, design, clinical interpretation, and writing, review, and editing of the submitted manuscript. C Smith performed data collection, analysis, and writing, review, and editing of the submitted manuscript. C St. Hill contributed to study development, scientific interpretation, and writing, review, and editing of the submitted manuscript. D Tierney contributed to methodology, design, clinical interpretation, and writing, review, and editing of the submitted manuscript. R Melamed contributed to methodology, design, clinical interpretation, and writing, review, and editing of the submitted manuscript.

**Funding** This research was unfunded.

**Availability of data and material** data is available upon request.

**Code availability** not applicable.

**Conflict of interest** No conflicts of interest exist for the above mentioned authors.

**Ethics approval** This research study was conducted retrospectively from data obtained for clinical purposes. We consulted with the IRB of Allina Health who determined that our study did not need ethical approval. An IRB official waiver of ethical approval was granted from the IRB.

**Consent to participate** not applicable.

**Consent for publication** not applicable.

**Guarantor statement** Matthew Lillyblad accepts official responsibility for the overall integrity of the manuscript.

**Names of collaborators** Not applicable.

**Financial/nonfinancial disclosures** The authors have no disclosures to report.

**Role of the sponsors** Not applicable.

**Other contributions** The authors would like to thank Barite Dawud for her contributions to the manuscript.

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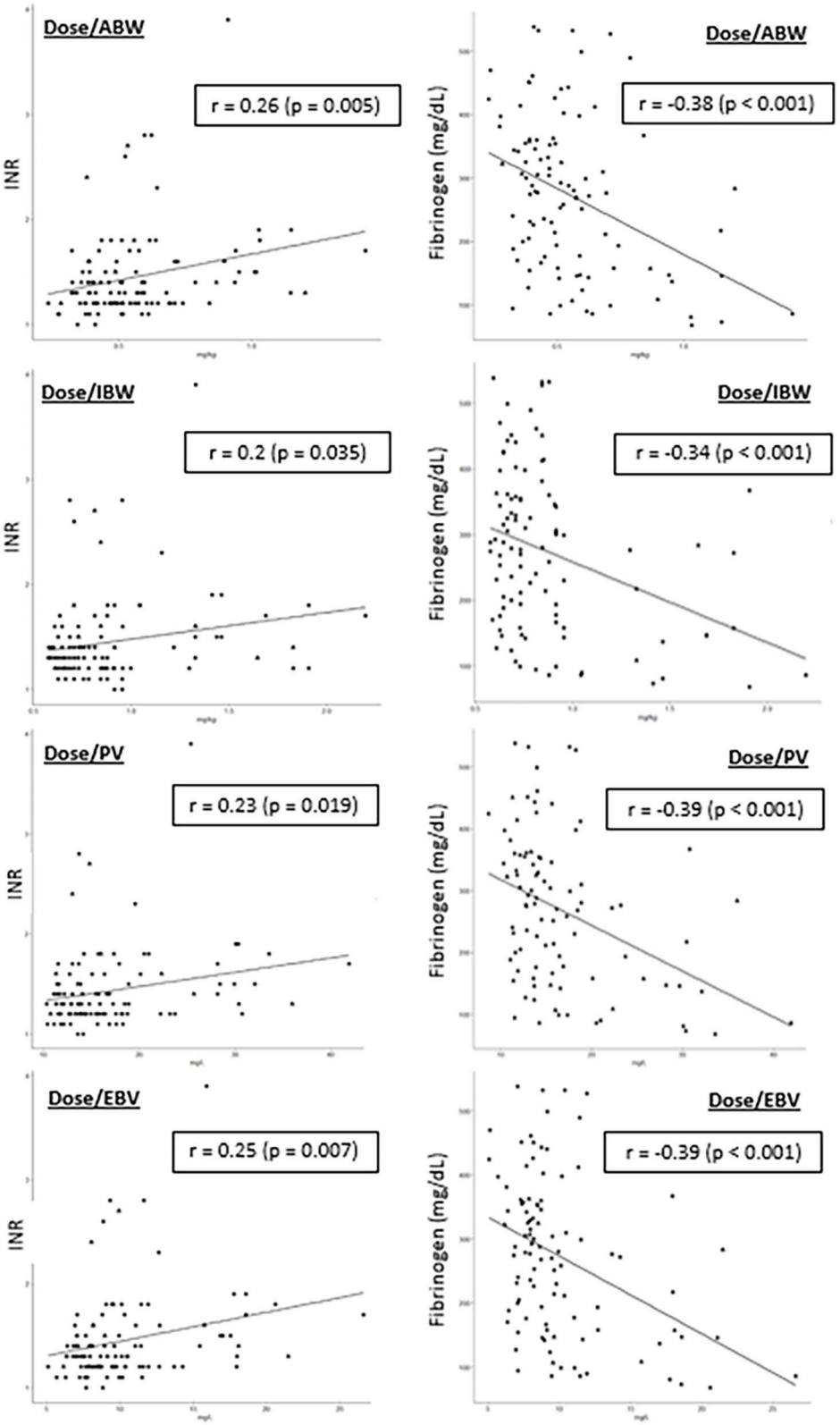


**Fig. 1** Correlation of peak INR and nadir fibrinogen to dose normalized to ABW, IBW, PV and EBV for all patients

**Supplement Table 1** Contributory factors to bleeding events

| Patient | Severity | Dose | AC* Intensity | Fibrinogen | INR | Invasive Procedure | Day | Comments |
|---|---|---|---|---|---|---|---|---|
| 1 | Minor | 50 mg | Anti-Xa 0.67 | 362 | 1.2 | No | 1 | Gingival bleeding |
| 1 | Major | 50 mg | Anti-Xa 0.48 | NM | 1.3 | Yes | 3 | Hematuria related to Foley catheter placement requiring RBC transfusion and bladder irrigation |
| 2 | Minor | 100 mg | Anti-Xa 0.97 | NM | 1.2 | No | 5 | IV site hematoma |
| 3 | Minor | 50 mg | Anti-Xa 0.52 | <60 | 2.7 | No | 3 | Vaginal and rectal bleeding (menstrual period and recent flare of ulcerative colitis) |
| 4 | Minor | 100 mg | aPTT 67 | NM | 1.5 | Yes | 1 | Oropharyngeal bleeding due to intubation |
| 5 | Major | 100 mg | aPTT 146 | 132 | 1.4 | Yes | 2 | Retroperitoneal hematoma after coronary angiogram prior to alteplase |
| 6 | Minor | 50 mg | aPTT 68 | 113 | 1.8 | Yes | 1 | IV site bleeding |
| 7 | Major | 50 mg | aPTT 154 | 147 | 1.4 | Yes | 1 | Groin site bleeding after coronary angiography |
| 8 | Minor | 50 mg | aPTT 113 | NM | NM | Yes | 6 | Neck hematoma with recent central venous line on heparin |
| 9 | Minor | 50 mg | aPTT 54 | 506 | 1.5 | No | 1 | Epistaxis on IV heparin |
| 10 | Major | 50 mg | aPTT 33 | NM | 1.3 | No | 5 | Re-admitted 5 days after alteplase (2 days after discharge) with small temporal lobe ICH on rivaroxaban |
| 11 | Major | 50 mg | aPTT 142 | 450 | 1.2 | No | 4 | Iliacus hematoma on IV heparin |
| 12 | Minor | 50 mg | aPTT 113 | 306 | 1.2 | No | 1 | Epistaxis on IV heparin |
| 12 | Minor | 50 mg | aPTT 95 | NM | 1.7 | No | 6 | Hematuria and upper extremity hematoma on IV heparin |
| 13 | Minor | 50 mg | aPTT 235 | <60 | 2.4 | Yes | 2 | Upper extremity hematoma at IV site |
| 14 | Minor | 50 mg | aPTT 116 | NM | 1.2 | No | 1 | Gingival bleeding on IV heparin |
| 15 | Minor | 50 mg | aPTT 30 | NM | 1.2 | Yes | 1 | Upper extremity hematoma at IV site |

ICH = intracranial hemorrhage, RBC = red blood cell, IV = intravenous. *at the time of the bleeding event

Major bleeding: Fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 2 g/dl or more, or leading to transfusion of two or more units of red blood cells, all within 7 days from the time of intervention

Minor bleeding: any bleeding episode within 7 days from the time of intervention that did not qualify for the major bleeding definition

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