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Is time to thrombolytic therapy a predictor of mortality in patients with severe PE

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BACKGROUND AND OBJECTIVE

Venous thromboembolism (VTE) which comprises pulmonary embolism (PE) and deep vein thrombosis (DVT) has been a public health concern for several years. VTE accounts for an estimated 60,000 to 100,000 deaths per year in the United States. Specifically, patients who present with an acute PE, it has been estimated 25% of these patients have sudden death as the first symptom.[2]

Clinical presentation of an acute PE can manifest as nonspecific symptoms which may include: chest pain, cough, hemoptysis, dyspnea, tachypnea, shortness of breath, wheeze, and some patients may present in cardiopulmonary arrest.[1,2] Severe acute PE can be classified as either massive or submassive PE. A patient with a massive PE would present with signs and symptoms of shock and persistent arterial hypotension. Patients with submassive PE present with hemodynamic stability but positive biomarkers (troponin and BNP) and right ventricular dysfunction.[3] Patients who present with PE are at higher risk of death and adverse outcomes with increasing severity of illness and thrombolytic therapy is indicated in massive PE and may be frequently utilized in submassive PE. Prior studies have identified APACHE II score and need for mechanical ventilation as predictors of mortality in ICU patients, while thrombolytic therapy was identified as protective, however, the urgency of thrombolytic therapy administration has not been evaluated in severely ill patients.[5] The purpose of this study is to evaluate if time to thrombolytic therapy can be used as a predictor of mortality in patients receiving intravenous thrombolysis for severe acute PE.

DESIGN AND METHODS

Data Collection

- This study was a retrospective chart review of patients receiving intravenous alteplase for PE from March 2013 through August 2017.
- Patients who received intravenous alteplase for PE per a standard order set were identified from a database that underlies the electronic medical record (EMR).
- Data regarding risk factors for mortality in this patient population, including laboratory findings, vital signs and co-morbid conditions, were manually extracted from the EMR.

Study Groups

- Two study arms, survivors and non-survivors.

Statistical Analysis

- Mann Whitney U test was used for analyzing differences in survivors and nonsurvivors.
- Chi Sqare test was used for nominal risk factors for mortality.
- The Student T-test was used for continuous variables.
- If time-to-alteplase was found to be an independent predictor of mortality in univariate analysis, a multivariate linear regression analysis would be conducted to evaluate an association with mortality.

Definition

- Time to alteplase was defined as the time from ER admission to onset of drug administration, in minutes.

RESULTS

Table 1: Baseline characteristics (n=43)

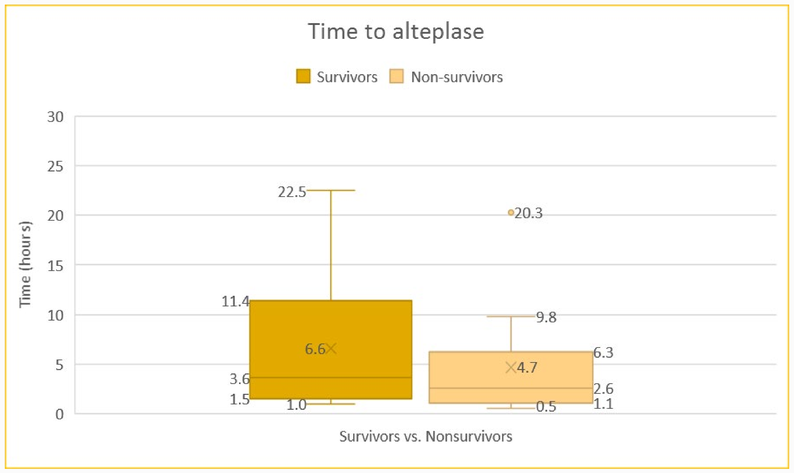
	n (%)
Mean age, years	61.8
Female	23 (53.5)
Mean weight, kg	100.6
Admitted from emergency department	33 (76.7)
Classified as massive PE	29 (67.4)
Received 100 mg alteplase	42 (97.7)
History of tobacco use	21 (48.8)
History of hypertension	24 (55.8)
Anticoagulation before alteplase	29 (67.4)

Table 2: Univariate analysis of predictors of death.

Measure	Survivors N= 28	Non-survivors N = 15	P-value
Baseline Scr (mg/dL)	1.36	1.83	<0.01
Median sPESI score	2	3	0.025
RVSP (mmHg)	50	61.5	<0.01
BNP (pg/mL)	40,20	22,769	0.04
Time to alteplase (hours)	94	139	≥0.05
Classification of PE			**Mortality Rate (%)**
Massive	15	14	46.4%
Submassive	12	1	6.7%

*Scr = serum creatinine, sPESI = simplified PE severity index, RVSP = right ventricular systolic pressure.

Figure 1: Box and whisker plot of time to alteplase between survivors and nonsurvivors.



- Outliers > 30 hours have been removed, however, this does not change the outcome of figure 1.

DISCUSSION AND LIMITATIONS

Discussion

- Alteplase is an effective treatment option for patients presenting with acute massive PE but increases risk of major bleeding events and death from complications.
- Severity of symptoms at presentation increase a patients risk for death.[4] Few studies have examined how time to alteplase administration in acute PE affects a patient's risk for death.
- Patients with massive PE were at higher risk of death than patients with submassive PE.
- Out of 43 patients our study found no difference between time to administration of alteplase and mortality in patients diagnosed with massive PE.
- No direct predictors of death were identified in patients who had multiple comorbidities, a history of smoking and coagulopathy.
- Higher baseline serum creatinine, sPESI score, and RSVP were statistically significant for predicting death in patients. ($p < 0.01$, $p = 0.025$, & $p < 0.01$ respectively). These identified risk factors for death were more likely indicative of illness severity rather than specific risk factors related to alteplase administration.

Limitations

- Single site and small sample size, n=43.
- Hospital admitted patients that developed a PE may skew the results.
- BNP values was found to be a statistically significant biomarker but only 17 of 43 patients had BNP measured.

CONCLUSION

Time-to-alteplase administration was not a risk factor for mortality in our patient population; however, the population may have been too small to detect clinically meaningful differences. Larger studies should consider time from symptom onset to alteplase administration and time from presentation to administration as potential predictors for mortality. Future studies could evaluate more patient specific risk factors, symptom presentation and laboratory values as well as different alteplase dosing for predictors of death in patients with acute PE.

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AUTHOR DISCLOSURES

Authors of this presentation have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.

This study was a retrospective chart review of patients receiving intravenous alteplase for PE from March 2013 through August 2017.

- Patients who received intravenous alteplase for PE per a standard order set were identified from a database that underlies the electronic medical record (EMR).
- Data regarding risk factors for mortality in this patient population, including laboratory findings, vital signs and co-morbid conditions, were manually extracted from the EMR. Differences in characteristics were compared between hospital survivors and non-survivors.
- Time to alteplase was defined as the time from ER admission to onset of drug administration, in minutes.
- Differences between survivors and non-survivors were compared using the Mann-Whitney U test.
- Nominal risk factors for mortality were compared using the chi square test while other continuous variables were compared using the student t-test.
- If time-to-alteplase was found to be an independent predictor of mortality in univariate analysis, a multivariate linear regression analysis would be conducted to evaluate an association with mortality.

- Alteplase can be an effective treatment option for patients presenting with acute ischemic stroke, but there has been significant controversy over its safety and efficacy after a prolonged period of time has passed from onset of symptoms[4].
- Saver, et al published a trial in 2013 examining the time to treatment with intravenous tissue plasminogen activator and resulting outcomes. Through this large retrospective trial of nearly 58,000 patients, a faster administration of treatment was associated with decreased mortality, reduced symptomatic intracranial hemorrhage, increased independent ambulation at discharge and increased discharge to home rate[5].
- No difference was found between time to administration of alteplase and mortality. This is limited by the number of available patients receiving the treatment medication, as well as the single site collection. This may also be limited by those patients who experienced prolonged asymptomatic periods prior to administration of alteplase. Health care contact may have been made, but there is a potential for the PE to be undetected. Only upon a later rapid decompensation of the patient was a PE suspected. There were a large portion of patients who had multiple comorbidities, smoking history, as well as an excessive weight that resulted in PE, but were not direct predictors of death.
- By identifying potential risk factors for mortality associated with PE, health care providers in the acute and critical care settings can provide a higher level of care by anticipating potential needs and appropriately utilizing available treatment options.

Time-to-alteplase administration was not associated with mortality in our patient population; however, the population may have been too small to detect clinically meaningful differences. Patients with massive PE were at higher risk of death than patients with submassive PE and other identified risk factors for death were more likely indicative of illness severity rather than specific risk factors related to alteplase administration. Larger studies should consider time from symptom onset to alteplase administration and time for presentation to administration as potential predictors for mortality.