

**TITLE:** Compassionate Use of Tissue Plasminogen Activator (tPA) in the Setting of Acute Respiratory Distress Syndrome (ARDS) due to COVID-19 in the United States: A Markov Decision Analysis

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Running title: Markov Prediction of *Tissue Plasminogen Activator (tPA) to Treat ARDS*

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## ABSTRACT:

**Background:** COVID-19 threatens to quickly overwhelm our existing critical-care infrastructure in the United States. Systemic tissue plasminogen activator (tPA) has been previously demonstrated to improve PaO<sub>2</sub>/FiO<sub>2</sub> (mmHg) when given to critically-ill patients with acute respiratory distress syndrome (ARDS). It is unclear to what extent tPA may impact population-based survival during the current United States COVID-19 pandemic.

**Methods:** A decision analytic Markov state transition model was created to simulate the life critically-ill COVID-19 patients as they transitioned to either recovery or death. Two patient groups were simulated (50,000 patients in each group); 1) Patients received tPA immediately upon diagnosis of ARDS, 2) Patients received standard therapy for ARDS. Base case critically-ill COVID-19 patients were defined as having a refractory PaO<sub>2</sub>/FiO<sub>2</sub> of < 60 mmHg (compassionate use criteria). Transition from severe to moderate to mild ARDS, recovery and death were estimated. Markov model parameters were extracted from existing ARDS/COVID-19 literature.

**Results:** Use of tPA was associated with reduced mortality (47.6% [tPA] vs. 71.0% [No tPA]) for base case patients. When extrapolated to the projected COVID-19 eligible for compassionate-use tPA in the United States, peak mortality (deaths/100,000 patients) was reduced for both optimal social distancing (70.5 [tPA] vs. 75.0 [No tPA]) and no social distancing (158.7 [tPA] vs. 168.8 [No tPA]) scenarios.

**Conclusions:** Compassionate use of tPA may improve recovery of ARDS patients, thereby reducing COVID-19 related mortality and ensuring sufficient resources to manage this pandemic.

Keywords: COVID-19; Acute Respiratory Distress Syndrome (ARDS); Tissue Plasminogen Activator (tPA); Pulmonary Failure; Fibrinolysis; Markov

## INTRODUCTION:

The COVID-19 pandemic has quickly spread throughout the world and threatens to overwhelm our critical care bed supply in the United States in the

upcoming weeks[1-3]. As of March 25<sup>nd</sup> 2020, there were 435,000 cases of confirmed cases of COVID-19, expanding at an exponential rate with 40,000 patients in the past 24 hours, and 20,000 deaths[4]. Estimates for the final death toll of COVID-19 if appropriate social distancing measures fail range from 200,000 to over 1,500,000 just in the United States[3]. Such a dire projection, requires urgent, thoughtful and creative action amongst clinicians.

Compassionate use of therapeutics targeted at attenuating acute respiratory distress syndrome (ARDS) as a sequelae COVID-19 related mortality is of high interest[5, 6] and promising therapeutics may be invaluable for mitigating a large burden of advanced disease. A phase I clinical trial for compassionate use in ARDS in 2001 reported significant improvements in PaO<sub>2</sub>/FiO<sub>2</sub> when systemic tissue plasminogen activator (tPA) was given for patients with severe ARDS[7]. The mechanism of this finding is theorized to involve the dissolution of the extensive fibrin burden in the microcirculation and airway spaces in ARDS. There is growing evidence that lethal COVID-19 ARDS is associated with disseminated intravascular fibrin deposition[8, 9]. Consequently, there is revived interest in exploring the role of tPA in reducing ARDS related mortality for COVID-19 patients who are eligible for compassionate use therapeutics. A multicenter group from the United States has proposed that tPA could be an invaluable tool to reduce severe ARDS related to COVID-19 and act as a salvage technique to rescue patients when mechanical ventilation was not available[10]. This investigator cohort has set forward a treatment plan for the impending crisis.

However, it remains unclear to what extent the potential PaO<sub>2</sub>/FiO<sub>2</sub> improvement of tPA would reduce ICU bed requirements and population-based mortality for the COVID-19 crisis. Long-term randomized clinical trial not practical in the midst of the current pandemic. However, in our unprecedented setting, a decision analytic Markov model may offer guidance. Markov models use existing published data to project the movement of patients through simulated health states over time[11]. Markov models have previously been used by our group, and have been increasingly applied to model healthcare challenges for which trial data may be lacking for the foreseeable future[12-15]. As such a Markov model was created to estimate the impact of compassionate use systemic tPA on ARDS/COVID-19 patients in addition to a more aggressive use for interventions at an earlier state of disease progression.

## **METHODS:**

A decision analytic Markov state transition model was created to simulate the life critically-ill COVID-19 as they transitioned to either recovery or death. Two patient groups were simulated 1) patients received tPA immediately upon diagnosis of ARDS, or 2) patients received standard therapy for ARDS. Medical decision-making software was utilized for the creation and computation of the model (DATA 3.5, TreeAge Software Inc, Williamstown, MA). Base case patients were defined as having a PaO<sub>2</sub>/FiO<sub>2</sub>(P/F) of < 60 mmHg, as this approximates

the initial (within 7 days) PaO<sub>2</sub>/FiO<sub>2</sub> of current ARDS/COVID-19 patients who would be eligible for compassionate use of therapeutics.

*Decision Model Structure (Figure 1):*

100,000 patients were modeled in the two arms of the decision model (50,000 patients in each arm). The model began following the admission of a simulated ARDS/COVID-19 patient to the ICU. Patients in the tPA arm received therapy within 7 days of admission, while patients in the No tPA received standard ARDS treatment. Patients were followed as they transitioned through severe/moderate/mild ARDS, recovery and death. Seven-day cycle lengths were used until all patients died or recovered.

*State Transition Probabilities (Table 1):*

Transition probabilities were extracted from existing, published literature using MEDLINE electronic search. As has been previously described by Naugler et al, transition probabilities for various times periods were converted into rates per cycle with the actuarial method for 7-day cycle probabilities, as such[16]:

$$P = 1 - \exp^{-rt}$$

$$\text{Standard rate} = \ln(1-P)/t$$

$$\text{Seven day transition probability} = 1 - \exp^{[7]\ln(1-P)/t}$$

(*P* = probability of event; *exp* = base of natural logarithm; *r* = rate of event occurring; *t* = time period in days; *ln* = natural logarithm).

*Systemic tPA PaO<sub>2</sub>/FiO<sub>2</sub> Improvement:*

Natural history of ARDS was extracted from Bellani et al[17]. To estimate improvement of PaO<sub>2</sub>/FiO<sub>2</sub> following tPA, results from Hardaway et al were applied [18]. It was assumed that patient's response to tPA followed a normal distribution in regard to probability of transitioning from severe to moderate to mild ARDS. Standard scores were calculated using:

$$z = (X - \mu) / \sigma$$

(*z* = standard score; *X* = PaO<sub>2</sub>/FiO<sub>2</sub> cut-off value (100 mmHg and 200 mmHg); *μ* = mean PaO<sub>2</sub>/FiO<sub>2</sub> following treatment; *σ* = standard deviation).

Standard scores were converted to percentiles using table for one-sided standard normal distribution. The calculated transition probabilities were assumed to be independent of the initial ARDS class.

Mortality rate following systemic tPA was extrapolated from the GUSTO-I trial, whereby tPA use was associated with a 0.6% death or non-fatal debilitating stroke rate[19].

Our group has previously used the presented approach to transition probability creation in Markov decision analysis to estimate the impact of weight loss interventions for renal, and liver transplant candidates[12-15].

#### *COVID-19 Imperial College Response Team Projection:*

The Imperial College has recently published their projection of COVID-19 critical-care bed utilization in various scenarios; no social distancing and optimal social distancing[20]. The impact of tPA on mortality was extrapolated (standard method) upon these projections to create population-based mortality estimates. Two scenarios were modeled: 1) tPA given to only patients eligible for compassionate use therapeutics and 2) all patient who presented to ICU with ARDS. Estimates for Model 1 were extracted from the Wuhan COVID-19 experience[6].

#### **RESULTS:**

##### *State Transitions:*

Patients were followed as they cycled through the model (Figure 2a and 2b). For base case patients, all patients began in the severe (compassionate use) ARDS health state, and transitioned through ARDS health states (mild, moderate, and severe), and then to either recovery or death. Compared to patients who did not undergo tPA, patient who received compassionate use tPA therapy transitioned to recovery (floor status/discharge) more quickly and more frequently. Correspondingly, use of tPA was associated with reduced mortality (47.6% [tTPA] vs. 71.0% [No tPA]) at the conclusion of the model.

A sensitivity analysis of initial (within 7 days) ARDS status (mild vs. moderate vs. compassionate use criteria ARDS) was performed (Figure 3). Utilization of tPA was estimated to significantly reduce 4-week mortality for initial mild (15.2% [tTPA] vs. 60.5% [No tPA]), moderate (26.4% [tTPA] vs. 62.0% [No tPA]) and compassionate use criteria (47.6% [tTPA] vs. 71.4% [No tPA]) ARDS.

##### *Population Based Mortality:*

Results of base case were extrapolated to Imperial College COVID-19 Response Team projections of COVID-19 temporal disease burdens. When only utilized in a compassionate use scenario peak mortality (deaths/100,000 patients) was reduced for optimal social distancing (70.5 [tPA] vs. 75.0 [No tPA]) and no social distancing (158.7 [tPA] vs. 168.8 [No tPA]) scenarios. However, when expanded to the entire COVID-19 mechanically ventilated population, mortality was drastically reduced, again for both optimal social distancing (39.1

[tPA] vs. 75.0 [No tPA]) and no social distancing (87.7 [tPA] vs. 168.8 [No tPA]) scenarios (Figure 4).

## DISCUSSION:

Current interest in utilizing tPA for ARDS patients represents a novel potential therapy to reduce mortality in the current COVID-19 pandemic. In our Markov model, compassionate use was estimated to have minimal impact on survival. However, the more aggressive use of tPA with all stages of ARDS was estimated to significantly improve ventilatory requirements for such patients, thereby improving survival. Furthermore, patients required critical care beds for reduced amounts of time compared to current estimates with utilization of standard methods of ARDS treatment. This model offers hope and support, globally, for the growing number of centers considering compassionate use of systemic tPA.

As Markov models rely on extrapolation, several weaknesses of the model should be addressed. Although the Hardaway et al demonstrated improvement in the P/F ratio with tPA administration in patients with severe ARDS P/F < 60%, it is not clear whether this effect would be sustained in COVID-19 patients, as tPA would theoretically reduce the sequelae of ARDS, but not lead to improved viral clearance. As such, long-term efficacy is not proven at the current time. Additionally, the model is based on data from the Wuhan experience, a population whose demographics approach but are not identical to those in the United States. Furthermore, in the No TPA arm, transition probabilities for ARDS progress/improvement and associated mortality was assumed to mirror non-COVID-19 diseases- an assumption for which insufficient data exists to validate.

## Conclusions

Despite the limitations of this Markov model the reality of the impending global disaster with the COVID-19 is coming true. Prior models of the overwhelming exponential growth of disease in Italy with saturation of the medical system have almost nightmarishly exceeded expectations[21]. Italy now has a mortality rate of >9% with more overall deaths than China[4]. Protocols for compassionate use of systemic tPA are in planning at several centers in the United States[10]. If compassionate use has efficacy in improving pulmonary function in ARDS related to COVID-19, a quick response to implement a clinical trial would be necessary to generate sufficient evidence for a validated treatment to effectively reduce ARDS related mortality. At the rate of growth of this pandemic, time is the enemy. Without effective social implementation to curtail the rapid spread of this virus, tPA may never have the opportunity to be used beyond compassionate use.

## Abbreviations

tPA: Tissue Plasminogen Activator

ARDS: Acute Respiratory Distress Syndrome

P/F: Ratio of Partial Pressure of Blood Oxygen Level to Percent of Oxygen Inhaled

## Declarations

- Ethical Approval: Not Applicable
- Consent for publication: Not Applicable
- Availability of Supporting Data: Not Applicable all data currently online
- Competing interests: Genentech provided 12 50mg vials of tPA for compassionate use, the company was not part of designing, drafting, or revising this manuscript and are donating medications for the initial cohort of patients being treated
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Data collection – All Authors  
Data analysis – RC  
Drafting Manuscript – RC, CB, HM, EM  
Critical Revisions - All Authors
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TABLE 1:

## State Transitions - Variable Table

Variable	Value	Reference
Severe to Moderate ARDS	45.0% in 7 days	Bellani et al, 2016[17]
Moderate to Severe ARDS	12.7% in 7 days	" "
Mild to Moderate ARDS	25.8% in 7 days	" "
Mild to Severe ARDS	4.5% in 7 days	" "
Mild ARDS to Floor/Recovery	60% in 28 days	" "
Severe ARDS Mortality	40.9% in 28 days	" "
Moderate ARDS Mortality	35.0% in 28 days	" "
Mild ARDS Mortality	29.6% in 28 days	" "
Mean Presenting PaO <sub>2</sub> /FiO <sub>2</sub> Ratio (mm Hg), ICU-COVID Patients	136 (IQR: 103-234)	Wang et al, 2020[6]
PaO <sub>2</sub> /FiO <sub>2</sub> Ratio (mm Hg), for Compassionate Use tPA	60	
Mean Improvement PaO <sub>2</sub> /FiO <sub>2</sub> Ratio (mm Hg), ICU-ARDS Patients	170 (IQR: 135-225)	Hardaway et al, 2001[18]
Death or non-fatal disabling stroke following systemic tPA	0.6%	GUSTO-I Trial[19]

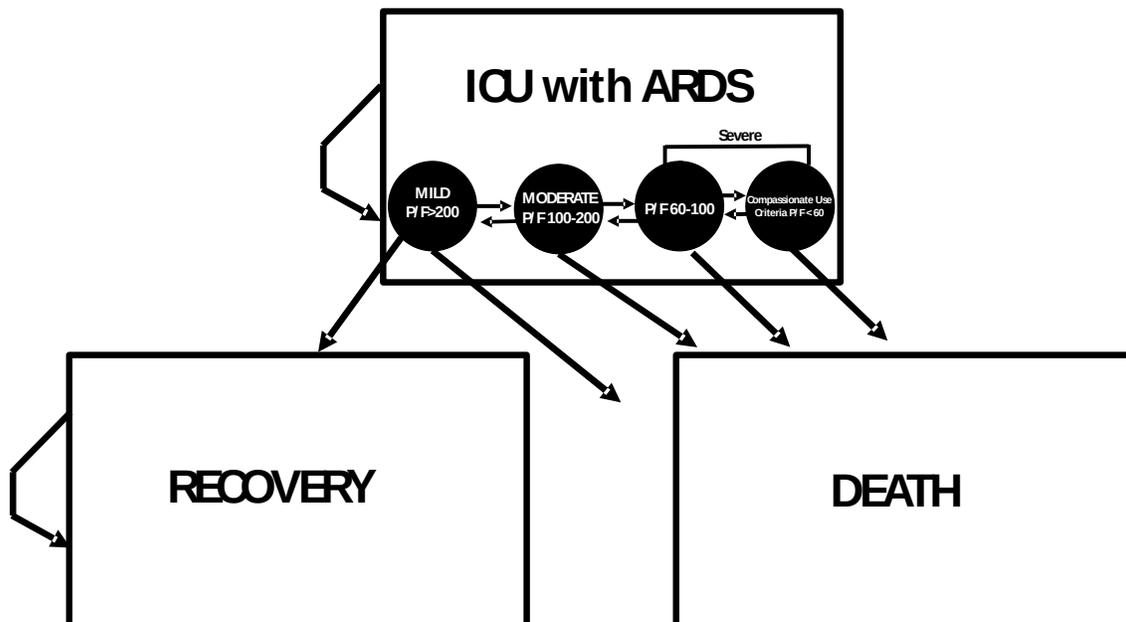
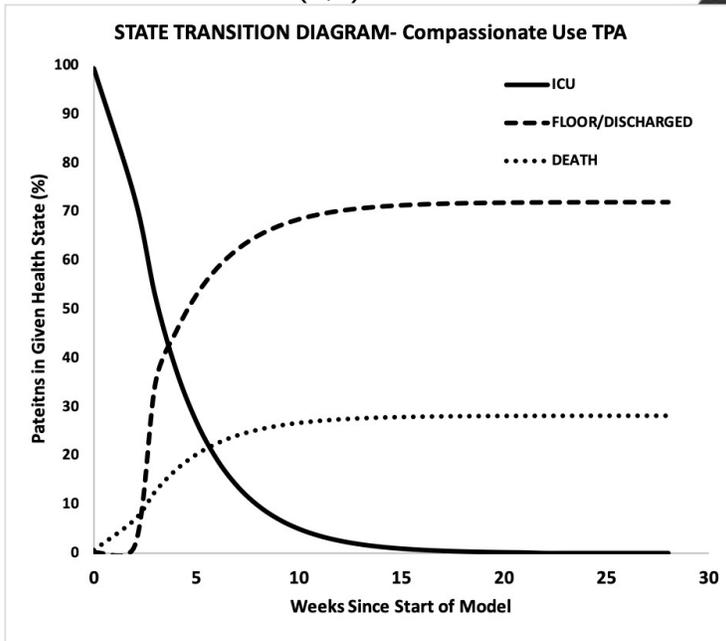


FIGURE 2: State Transition Diagram, Compassionate Use TPA and No TPA for Patients with PF<60 (a,b)



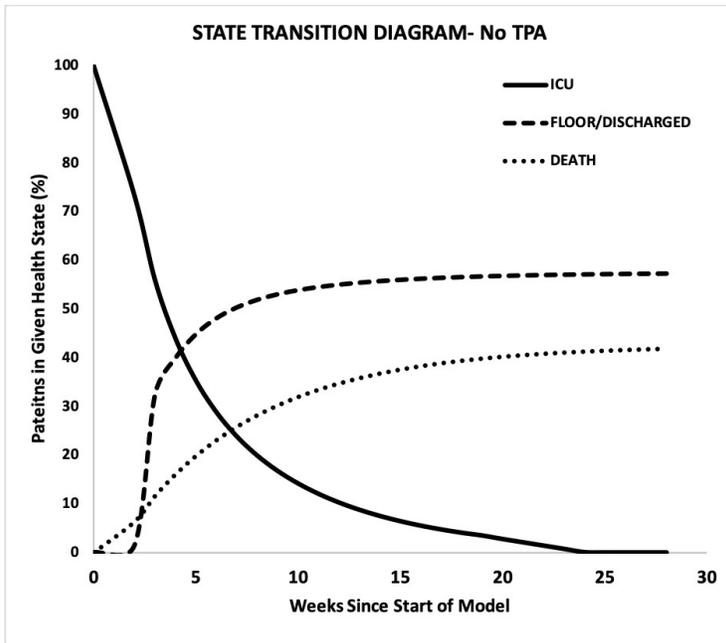


FIGURE 3: Survival by ARDS Severity

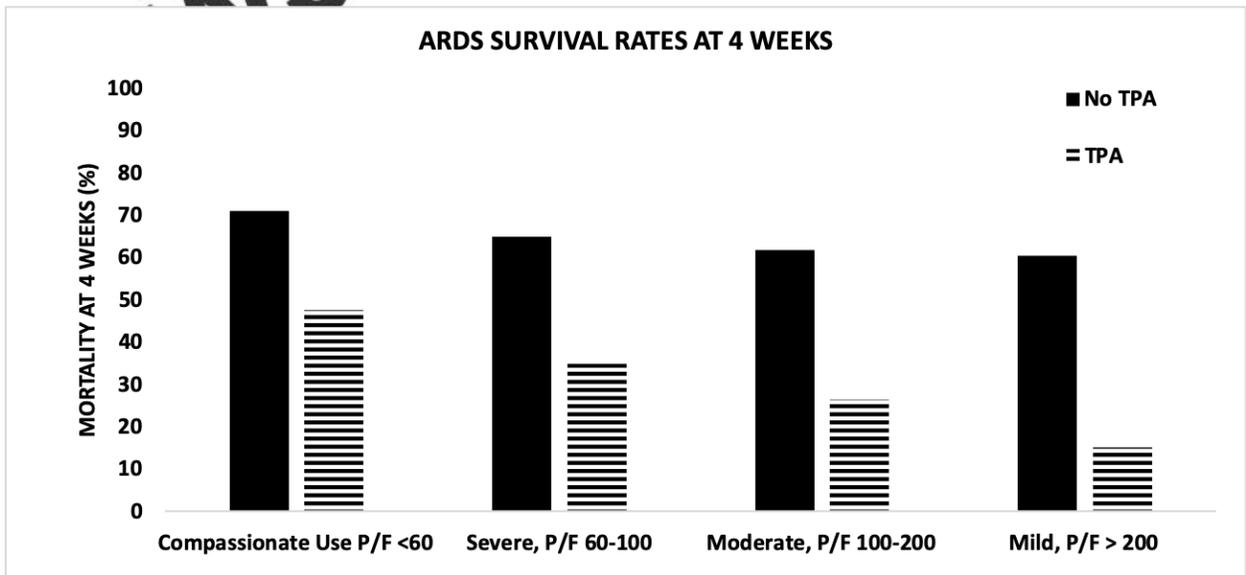
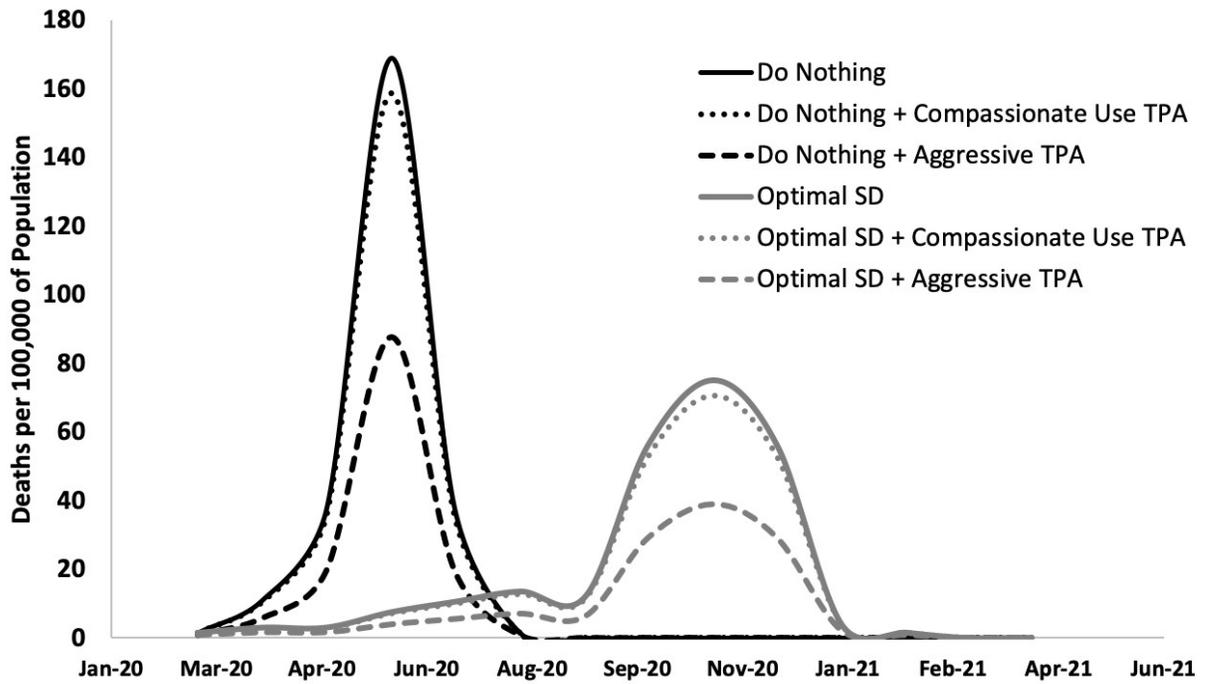


FIGURE 4: Population Based Mortality Over Time

Deaths per 100,000 of Population Over Time



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