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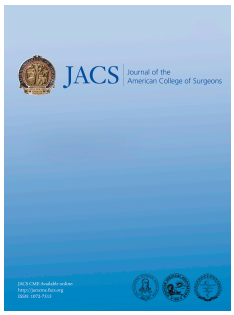

Fibrinolysis Shutdown Correlates to Thromboembolic Events in Severe COVID-19 Infection

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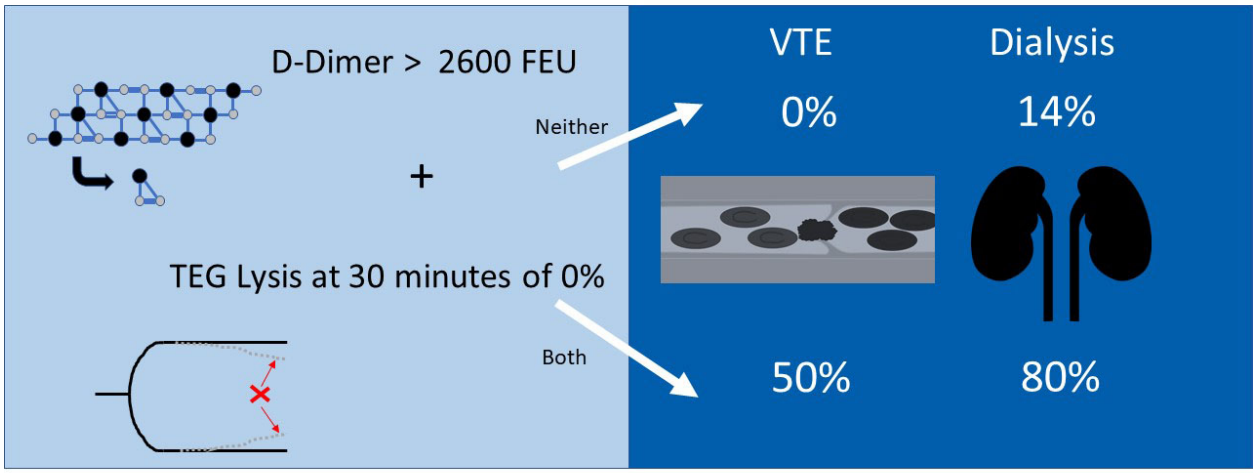

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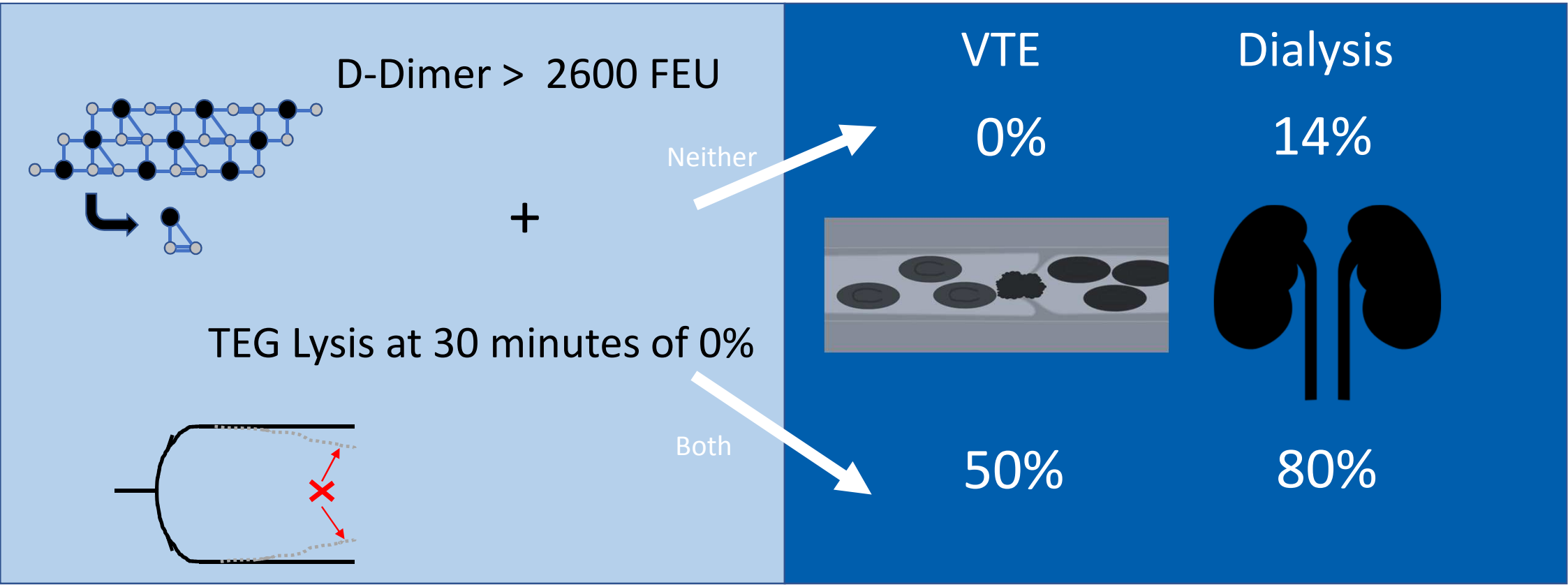
Fibrinolysis Shutdown Correlates to COVID-19 Associated Thromboembolic Events



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Fibrinolysis Shutdown Correlates to Thromboembolic Events in Severe COVID-19 Infection

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Acquisition of data – Vogler, PK Moore, Wright
Analysis and interpretation of data – HB Moore, Wright, EE Moore, McIntyre
Drafting of manuscript – Wright, HB Moore, Wohlauer, Urban
Critical revision – EE Moore, Wohlauer, Nydam, McIntyre

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Abstract:

Background

Coronavirus disease 2019 (COVID-19) predisposes patients to a prothrombotic state with demonstrated microvascular involvement. The degree of hypercoagulability appears to correlate with outcomes, however optimal criteria to assess for the highest risk patients for thrombotic events remain unclear; we hypothesized that deranged thromboelastography (TEG) measurements of coagulation would correlate with thromboembolic events.

Methods

Patients admitted to an intensive care unit with COVID-19 diagnoses that had TEG analyses performed were studied. Conventional coagulation assays, D-dimer levels, and viscoelastic parameters were analyzed using a receiver operating characteristic curve to predict thromboembolic outcomes and new onset renal failure.

Results

Forty-four patients with COVID-19 were included in the analysis. Derangements in coagulation laboratory values including elevated D-Dimer, fibrinogen, PT, and PTT were confirmed; viscoelastic parameters showed an elevated maximum amplitude and low lysis at 30 minutes. A complete lack of lysis of clot at 30 minutes was seen in 57% of patients and predicted VTE with an AUROC of .742 (p=0.021). A D-Dimer cutoff of 2600 ng/ml predicted need for dialysis with an AUROC of .779 (p=0.005). Overall, patients with no lysis of clot at 30 minutes and a D-Dimer of greater than 2600 ng/ml had a rate of VTE of 50% compared to 0% for patients with neither risk factor (p=0.008) and had a hemodialysis rate of 80% compared to 14% (p=0.004).

Conclusions

Fibrinolysis shutdown, as evidenced by elevated D-Dimer and complete failure of clot lysis at 30 minutes on thromboelastography, predicts thromboembolic events and need for hemodialysis in critically ill patients with COVID-19. Further clinical trials are required to ascertain the need for early therapeutic anticoagulation or fibrinolytic therapy to address this state of fibrinolysis shutdown.

Keywords: COVID-19, SARS-CoV-2, thromboelastography, hypercoagulable, fibrinolysis shutdown, thromboembolism

Precis:

COVID-19 ICU patients are hypercoagulable. Fibrinolysis shutdown as demonstrated by complete lack of clot lysis at 30 minutes on thromboelastography combined with elevated D-Dimer levels predicts thromboembolic complications and new onset kidney failure.

Social Media Summary:

Patients with COVID-19 have frequent complications of venous thromboembolism, stroke, and kidney failure. A lack of any clot lysis on thromboelastogram combined with elevated D-dimer levels identifies a high-risk population potentially requiring more aggressive anticoagulation.

Introduction:

The novel coronavirus known as severe acute respiratory distress syndrome coronavirus2 (SARS-CoV-2), leading to Coronavirus disease 2019 (COVID-19), emerged in Wuhan, China in late 2019 and has become a worldwide pandemic. More than 2.7 million cases have been confirmed worldwide causing more than 190,000 deaths, with these numbers growing exponentially [1]. A subset of patients infected with COVID-19 progress to acute respiratory distress syndrome (ARDS), with 70% of critically ill patients requiring intubation and mechanical ventilation [2].

Viral infection associated inflammation clearly predisposes patients to prothrombotic states[3]. In particular, coronavirus infections with the coronaviruses SARS-CoV-1 and MERS-CoV cause intra-alveolar and systemic fibrin clots in animals and humans with severe respiratory disease[4].

Initial studies in Wuhan that utilized multivariate regression analyses suggested a higher mortality based on age, SOFA score, and D-Dimer levels [5]. Furthermore, previous work during the H1N1 viral pneumonia outbreak demonstrated that elevations in D-Dimer levels suggest an increased thrombosis risk [6]. Specific coagulation pathway product analysis demonstrated decreased survival in patients presenting with COVID-19 and elevations in the prothrombin time, D-dimer, and fibrin degradation products[7].

Broad evidence exists for using thromboelastography or the thromboelastogram (TEG) to predict thromboembolic rates in other disease processes. Across trauma, surgical, and mixed intensive care unit populations, hypercoagulability as demonstrated by TEG, especially an elevated maximum amplitude (MA), has reliably predicted thromboembolic events (see discussion for references). The initial study of TEG usage in 24 COVID-19 patients in Italy demonstrated that the TEG-MA and angle were elevated and

the TEG-R and K values were decreased, however these findings were not correlated with outcome measures such as rates of thrombotic events[8].

Based on prior data we hypothesize that abnormalities in TEG parameters would correlate with thromboembolic risk. The aim of this study was to develop an improved screening tool to suggest the highest risk of thromboembolic complications including renal failure.

Methods:

All patients admitted to the University of Colorado Hospital with documented COVID-19 infection were considered for inclusion beginning March 1st, 2020 through April 20th, 2020. Specially designed "Surge" COVID-19 ICU teams in physically isolated cohort units had been established and staffed by a multidisciplinary pool of pulmonary critical care, anesthesia critical care, and surgical critical care attendings. Any patient admitted to one of these Surge ICU teams who had TEG testing was included in this analysis; the first TEG drawn was used for analysis in an attempt to identify hypercoagulability early in the patients' course, thereby providing a potential window for therapeutic intervention.

IRB exemption was granted to this study by our institution (COMIRB Protocol 20-0947). Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the University of Colorado Anschutz Medical Campus.

Citrated Kaolin/Kaolin-heparinase TEG (Haemonetics, Braintree, MA) in vitro point of care testing was ordered at the discretion of the intensivist to guide clinical care and was more heavily used by the anesthesia and surgical critical care group who routinely use this tool intraoperatively and for critical care management of trauma and transplant patient populations. TEG indices recorded included r-time,

angle, maximum amplitude (MA), and lysis at 30 minutes (LY30). Additional coagulation measurements included a complete blood count for measurements of platelets, fibrinogen level, and D-Dimer. All coagulation assays were conducted by the clinical laboratory. Patients also had their P/F ratio and SOFA score calculated on the day of TEG assay, in addition to their International Society of Thrombosis and Hemostasis (ISTH) disseminated intravascular coagulation (DIC) score[9].

The primary outcomes were venous thromboembolic events (VTE) and new onset renal failure requiring dialysis. No routine VTE screening was performed, rather VTE were diagnosed by either ultrasound or CT imaging ordered based on clinical suspicion; empiric anticoagulation without radiographic evidence was not counted as a VTE. Only three CT pulmonary embolism studies were performed, and they were all negative. VTE was considered a macro-thrombotic event, whereas renal failure was considered a potential micro-thrombotic complication based on the recent histological reports of micro thrombosis in the kidneys of COVID-19 victims[10]. Arterial thrombotic events were also evaluated, which in our patient population consisted entirely of strokes. All patients received chemical VTE prophylaxis with at least enoxaparin between 40-60mg a day or unfractionated heparin between 10,000-15,000 units a day.

SPSS version 22 (IBM, Armonk, NY, USA) was used for statistical analysis. The first set of coagulation variables from thromboelastography were contrasted to fibrinogen and D-Dimer for performance using a received operating characteristic curve for predicting venous thrombotic events (VTE) and new onset need for dialysis. A Youden index was used for identification of the inflection point for highest sensitivity and specificity for each significant measurement of coagulation with the specific outcome. Patients were then dichotomized based on the Youden cut points for each associated outcome. Descriptive characteristics between cohorts are displayed as the median and 25^{th} -75^{th} percentile range or interquartile range (IQR). Variables contrasted between groups were tested with chi square and Fisher

exact for categorical data, and for continuous variables a Mann Whitney U test was performed. As both outcomes were predictors for micro- and macro-thrombosis, we performed an additional analysis of patients using both coagulation variables associated with the outcomes to stratify patients from thrombotic complications.

Results:

Demographics

A total of 44 patients infected with COVID-19 in the intensive care unit from March 22, 2020 to April 20, 2020 were eligible for the study; all patients had at least one TEG draw. Twenty-eight patients (64%) were male, the median age was 54 years (IQR 42-59, range 19-86), and the median BMI was 30 (IQR 27-37, range 18.6-85.6) (Table 1). The median time from symptom onset to hospital admission was 5 days (4-7). Forty-one (93%) of 44 patients required mechanical ventilation, 16 (36%) had acute renal failure requiring dialysis, 11 (25%) had a VTE, and 6 (14%) had a thrombotic stroke. The median SOFA score at the time of the first TEG draw was 8 (7-10) with a median P/F ratio of 163 (127-235) consistent with the majority of patients having moderate to severe ARDS. Using the WHO COVID-19 Ordinal Scale (8 point system) for clinical status at the nadir of illness, 36/44 (82%) of patients scored a 7 (ventilation + additional organ support), 5/44 (11%) of the patients scored an 8 (died during study period), 1 patient (2%) scored a 5 (high flow oxygen), and 2 patients (5%) scored a 4 (oxygen by mask). All patients with VTE had a score of 7 other than one patient who died; likewise, all patients with arterial thrombus had a score of 7 other than one patient who died.

Coagulation Parameters

The patients' conventional coagulation parameters are listed in table 2 (platelet counts, PT, PTT, D-Dimer and Fibrinogen). Pertinent abnormalities include an elevated D-dimer level, elevated fibrinogen, with normal platelet counts in the majority of patients and mildly elevated PT and aPTT with median values at or slightly above the upper limits of normal. The median ISTH DIC score was 0 (0-2), with no patients having a score higher that 4. TEG variables were consistent with a hypercoagulable state with an elevated MA and low LY30 (Table 2).

Coagulation Association with VTE

The receiver operating characteristic curve for VTE was only significant for TEG LY30 and VTE with an area under the curve of .742 (p=0.021 Figure 1a). The Youden Index for VTE was identified at 0. In this patient cohort, 57% had this extreme lack of fibrinolytic activity. These patients were categorized as fibrinolysis shutdown based on the presence of elevated D-Dimer and low fibrinolytic activity; fibrinolysis shutdown has previously been described as LY30 of less than 0.8% but the more complete shutdown seen in these patients results in an LY30 of 0% as a diagnostic cutoff based on the Youden Index for maximizing sensitivity and specificity. Descriptive variables of patient with fibrinolysis shutdown versus those without shutdown are listed in table 3. The only significant differences appreciated between groups were patients with fibrinolytic shutdown had a lower incidence of a history of hyperlipidemia and a lower TEG angle, even though fibrinogen levels were similar. Patients with fibrinolysis shutdown had a 40% rate of VTE compared to 5% in patients without shutdown (p=0.013). The time to VTE was significantly shorter in patients with fibrinolysis shutdown (Figure 2, Log Rank p=0.001). Overall, 24 of the 44 patients with severe COVID-19 infection in the ICU were placed on full therapeutic anticoagulation, despite only 14 of these patients having documented VTE or arterial

thrombotic events; 10 additional patients received therapeutic anticoagulation empirically based on physician concern for occult thrombotic events or bedside evidence of extreme hypercoagulability such as frequent clotting of central venous access or hemodialysis filters.

Coagulation Association with Need for Dialysis

The receiver operating characteristic curve for new onset need for dialysis was only significant for D-Dimer and TEG angle. The area under the curve for D-Dimer was .779 p=0.005 and TEG angle was .771 p=0.035. The remaining coagulation variables were not significant (Figure 1b). Due to the higher performance with D-Dimer, this coagulation measurement was used to find the inflection point for need for dialysis. The Youden index was found to be 2600 ng/ml. An elevated D-Dimer above this threshold was appreciated in 34% of the study population. Variables contrasting patients with high D-Dimers versus lower are listed in table 4. An elevated D-Dimer was associated with a 73% new onset need for dialysis versus 17% for lower D-Dimer levels (p=0.001 Figure 3). Need for dialysis occurred at a median of day 7 of hospitalization (IQR 4.5-9), with AKI occurring on day 3 (IQR 1-5), while VTE and thrombotic events did not occur until 12 (IQR 7-14.5) or 11.5 (IQR 9.5-21) days from hospital admission, respectively; all VTE or thrombotic events were noted after AKI or dialysis need had been established. In patients with VTE, all were either directly admitted to the ICU from the emergency department (n=9) or upgraded from ward status within 48 hours of hospital admission (n=2).

Combination Score

Patients were grouped into coagulation cohorts using both LY30 and D-Dimer inflection points. Patients with neither risk factor for hypercoagulability were present in 32% of the patient population, one

coagulation risk factor represented 45% of the patient population, and 23% of patients had both. The number of patients with VTE increased from 0 to 50% for patients with 0 to 2 coagulation risk factors respectively (p=0.008 Figure 4). Similarly, the need for dialysis increased from 14% to 80% (p=0.004 Figure 4). While not significant, thrombotic stroke rate was also increased from 7% to 30% (p=0.274 Figure 4). Patients with an LY30 of 0% and D-Dimer >2600 ng/ml demonstrated a significant decrease in D-Dimer levels over 24 hours compared to other cohorts (Supplemental Figure 1, p=0.009).

Discussion:

Coronavirus disease 2019 (COVID-19) patients in the intensive care unit undergoing viscoelastic testing have a hypercoagulable profile. This patient cohort had a high rate of renal failure which preceded VTE diagnosis. An elevated D-Dimer was associated with the need for dialysis, while a low LY30 was associated with VTE. Nearly a quarter of these critically ill patients had an LY30 of 0% and D-Dimer >2600 ng/mL and 80% of these patients required dialysis, 50% had a VTE, and 30% had a thrombotic stroke. These results demonstrate that fibrinolysis shutdown correlates with thrombotic complications. Of note, this cohort of critically ill COVID-19 patients was clearly hypercoagulable, despite high normal or frankly elevated PT and PTT levels, demonstrating the importance of using whole blood coagulation assays (which more closely approximate in vivo conditions including the presence of cells and platelets) such as the TEG for improved risk stratification. As a rapid test to demonstrate complete fibrinolysis shutdown, an LY30 of 0% in conjunction with D-Dimer levels over 2600 ng/ml may serve as a sensitive marker for the patients most at risk for VTE and other thrombotic complications.

Critically ill patients in ICU settings experience VTE rates of 13-30% without chemoprophylaxis and 5-15% with routine chemoprophylaxis[11]. An early series of 184 COVID-19 ICU status patients

demonstrated a VTE rate of 27% and arterial thrombosis rate of 3.7% supporting a particular predisposition to hypercoagulation in this new patient population[12]. Furthermore, an autopsy series in COVID-19 patients in the US has suggested a possible role for thrombotic microangiopathy in the lungs[13]. Low molecular weight heparin (LMWH) or unfractionated heparin (UFH) given at prophylactic doses in COVID-19 patients with elevated sepsis induced coagulopathy scores showed a mortality benefit in a retrospective study [14]. Interestingly, when comparing COVID-19 patients to a cohort with non-COVID-19 pneumonia, the non-COVID-19 patients had similar D-Dimer elevations but did not show mortality benefit with prophylactic LMWH/UFH[15].

In the trauma population, hypercoagulable TEG parameters predict venous thromboembolism (VTE) 2.4 – 6.7 fold higher based on higher maximum amplitude (MA) parameters despite appropriate prophylactic anticoagulation[16-19]. In a broad surgical patient population, patients with a TEG MA greater than 68 were 6 times more likely to have thrombotic events including VTE, myocardial infarction, and cerebrovascular accident[20]. In a mixed medical-surgical ICU population with baseline abnormal coagulation parameters, a TEG-MA of greater than 72 predicted thromboembolic events more effectively than conventional coagulation parameters such as INR, PTT, fibrinogen, or platelet count [21]. In a more recent study, a low LY30 suggestive of fibrinolysis shutdown was associated with an increased risk of thrombotic complications as early as 12 hours from injury[18]. Medical inhibition of fibrinolysis with tranexamic acid has also been associated with an increased risk of thrombotic complications in trauma patients[22]. TEG MA in this COVID-19 population was universally elevated regardless whether the patient developed thrombotic complications or not, but LY30 strongly differentiated those patients with and without VTE. The first publication to utilize TEG in the ICU with COVID-19 patients drew similar conclusions that viscoelastic testing demonstrated hypercoagulability in this patient population[8]; however, this study of 24 patients from Italy was descriptive and did not include any outcomes

associated with TEG indices. Our results suggest an that TEG LY30 serves as a prognostic marker that this patient population is at risk for thrombotic complications, and may have a better performance at identifying these at-risk patients than other coagulation measurements.

Elevated D-dimer levels were also associated with potential micro-thrombotic disease leading to renal failure. These results align with previous reports that patients with elevated D-Dimer levels have poor outcomes in the setting of COVID-19 infection[7]. Elevated D-Dimer and low LY30 have previously been defined as fibrinolysis shutdown in trauma[23]. This fibrinolytic phenotype has been associated with poor outcomes in trauma[24-28]. The cause of elevated D-Dimer levels in COVID-19 patients remains unclear but could be reflective of an excessive amount of intravascular polymerized fibrin. Fibrin acts as co-factor for its own destruction[30], therefore a high burden of fibrin will result in elevated D-Dimer levels with minimal systemic fibrinolytic activity. This occurs as there is more reagent that is more readily broken down due to an increase in binding opportunities for plasminogen activators and plasminogen to co-localize. Alternatively, it is possible that a high D-Dimer level could be representative of a viral activator of the fibrinolytic system with subsequent shutdown. Patients meeting this fibrinolysis shutdown laboratory definitions of low systemic fibrinolysis and elevated D-Dimers demonstrated marked drops in D-Dimer over 24-hour periods compared to the other patient cohorts that had mild increased in D-dimer during this time frame. This rise and fall of fibrinolytic activity has been demonstrated in animal models of endotoxin, in which plasminogen activation occurs within 2 hours of intravenous infusion but is followed by an abrupt inhibition of fibrinolysis[29]. In a study evaluating the addition of recombinant tissue plasminogen activator (rTPA) to viscoelastic blood analysis of septic patients without evidence of DIC, even low doses of rTPA did not correct the hypofibrinolytic state[31].

Recently, acute fibrinolysis shutdown has been demonstrated in early sepsis and found to correlate to increased morbidity and mortality[32]. Fibrinolysis shutdown and organ failure has historically been associated with DIC[33], however the ISTH score of 4 or greater to define overt DIC[9] was not present in a single patient in our study despite the majority of patients having respiratory and renal failure with laboratory evidence of a hypercoagulable state. COVID-19 autopsies have clearly demonstrated diffuse micro thrombi including the kidney and lungs and are believed to be the cause of organ failure in this patient population[10,13]. Microthrombi have been demonstrated in animal models of shock[34] and these can be reversed with pre-treatment using heparin[35] or post-treatment with a fibrinolytic agent[36]. Despite evidence of a DIC-type picture in lungs and kidneys supported by COVID-19 autopsy studies, platelet counts remain relatively normal and fibrinogen levels are elevated in these patients, suggesting that the conventional ISTH DIC score fails to capture the prothrombotic coagulopathy seen in this patient population.

Surprisingly in our patient population of COVID-19 infected patients, marked D-dimer elevation and TEG LY30 levels of 0% were seen in patient samples drawn more than 2 weeks into their ICU course and the ISTH score for DIC remained low. These findings suggest the possibility of a prolonged imbalance between native tPA and plasminogen activator inhibitor 1 (PAI1), a strong inhibitor of the fibrinolytic system. The use of fibrinolytic agents in phase I clinical trials to treat ARDS in critically ill patients have also demonstrated promising results in improving oxygenation[37,38]. The use of fibrinolytics to treat ARDS in COVID-19 have been proposed[39], utilized as salvage therapy in New York City[40], and projected to have a large impact on patient outcomes[41], if efficacy is as promising as early use of fibrinolytic therapy to treat ARDS in prior Phase I trials.

The need for more aggressive anticoagulation or fibrinolytic therapy remains unclear, and there exist scant data to guide more aggressive therapies to mitigate the hypercoagulable state. Microvascular thrombosis may contribute to acute respiratory distress syndrome, acute renal failure, and liver function test elevations frequently observed in these patients. It is unclear but biologically plausible that treatment of the hyperthrombotic state of these patients with COVID-19 could prevent or decrease the extent of renal injury seen.

There are inherent limitations to this retrospective descriptive study. First there was variability in the laboratory testing patterns based on intensivist preference. In addition, the TEG and other coagulation parameters were drawn at variable times of the patient disease processes. Studies done to evaluate for thromboembolic events were performed for clinical suspicion rather than routine screening and therefore some VTE or arterial emboli were likely not captured or had delays in diagnosis. Clotting of central lines and iHD/CRRT circuits was commonly noted in these critically ill patients with COVID-19 but was not reliably captured in our data set, again potentially leading to an underestimation of hypercoagulable outcomes. Due to the sudden influx of patients with a COVID-19 diagnosis, outcome data are inherently limited since many patients still remain hospitalized and there are logistical hurdles to effective diagnosis of VTE. In addition, less common outcomes such as stroke and mortality would require a large cohort of patients to obtain adequate power to determine if the coagulation parameters we identified that were associated with VTE and renal failure are also associated with these adverse events.

Conclusion:

COVID-19 causes not only hypercoagulability but also fibrinolysis shutdown which is associated with VTE, stroke, and renal failure. Defining the optimum predictive test for micro- or macro-thromboses

requires further study, however the TEG in conjunction with the D-dimer appear to be a sensitive marker for severity of disease which will need to be studied in a prospective fashion. A TEG LY30 of 0% and a D-dimer of greater than 2600 ng/ml together suggest complete fibrinolysis shutdown and markedly elevated risk of renal failure, VTE, and thrombotic events. The optimum medical therapy to address this hypercoagulable and fibrinolytic state is still unknown, however these results suggest the need to consider therapeutic anticoagulation and potentially tPA therapy to directly addresses the failure in the coagulation cascade of this high-risk group of patients.

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Table 1 – Demographics	
Patients	44
Age	54 (42-59)
Gender	
Male	28 (63.6%)
Female	16 (36.6%)
Ethnicity	
Asian	7 (15.9%)
Caucasian	4 (9.1%)
African American	10 (22.7%)
Hispanic/Latino	20 (45.5%)
Other	2 (4.5%)
Unknown	1 (2.3%)
Body Mass Index (BMI)	30 (27-37)
Co-Morbidities	
Cardiac Arrhythmias	3 (6.8%)
Hypertension	21 (47.7%)
Diabetes Mellitus	18 (40.9%)
Hyperlipidemia	11 (25%)
COPD	2 (4.5%)
Asthma	4 (9.1%)
Smoking/Vaping	2 (4.5%)
EtOH/Substance Use Disorder	0
Immunosuppression	1 (2.3%)
None of the above	8 (18.2%)

Table 2 – Coagulation Parameters (PT=Prothrombin Time, PTT=activated partial thromboplastin time, MA=maximum amplitude, LY30=clot lysis at 30 minutes, FEU=fibrinogen equivalent units)

Conventional Coagulation Measurement	Median (IQR)	Reference Range
Platelet Count	232 (186-298)	150-400 10^9/L
PT	14.5 (13.5-15.9)	12-14.5 seconds
PTT	37 (31-49)	22.6-34.1 seconds
Fibrinogen	656 (560-779)	150-400 mg/dL
D-Dimer	1,840 (935-4,085)	< 500 ng/mL FEU
Viscoelastic Indices		
R-time	5.8 (4.8-8.6)	2-8 minutes
Angle	71 (66-74)	55-78 degrees
MA	73 (67-77)	50-70 mm
LY30	0 (0-0.4)	0.8-3%

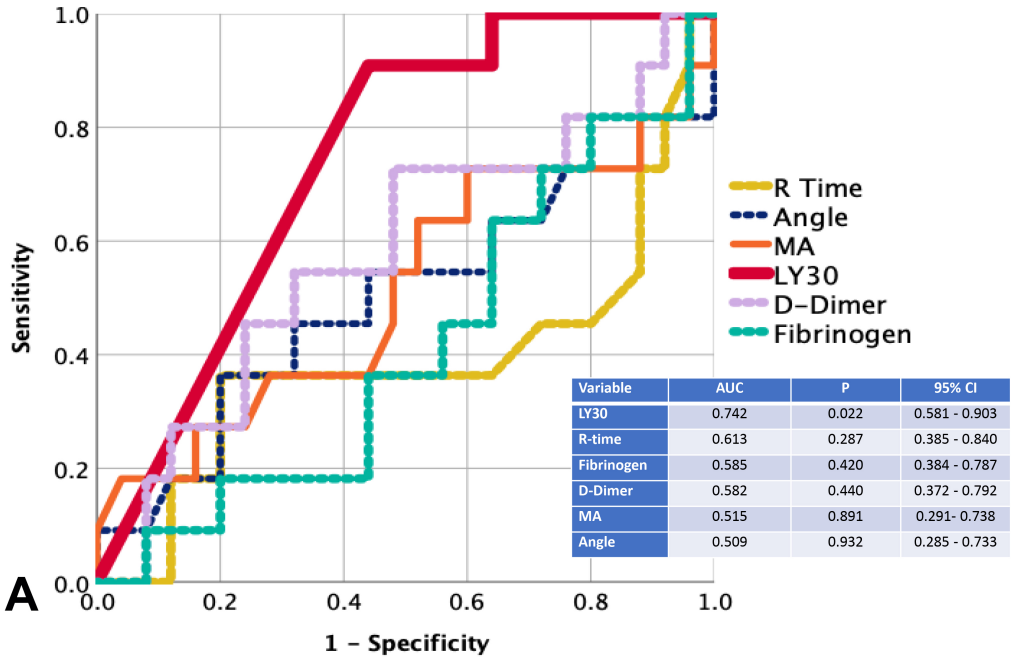
Table 3 – Comparison between patients with and without complete fibrinolysis shutdown (Median (IQR), BMI=Body Mass Index, EtOH/Substance=Alcohol or substance use disorder, PT=Prothrombin Time, PTT=activated partial thromboplastin time, CRP=C-Reactive Protein)

Variable	**No Fibrinolysis Shutdown**	**Fibrinolysis Shutdown**	P Value
Age	56 (46-58)	53 (45-62)	0.859
BMI	30 (27-38)	30 (28-33)	0.760
Cardiac Arrhythmias	10%	4%	0.570
Hypertension	53%	44%	0.761
Diabetes Mellitus	37%	44%	0.760
Hyperlipidemia	42%	12%	**0.035**
COPD	5%	4%	0.999
Asthma	0	16%	0.122
Smoking/Vaping	0	8%	0.498
EtOH/Substance	0	0	0.999
Immunosuppression	0	4%	0.999
None of the above	43%	57%	0.999
Platelet Count	243 (198-341)	226 (184-280)	0.343
PT	14 (13-15)	16 (14-16)	0.117
PTT	31 (30-40)	37 (34-49)	0.146
Fibrinogen	728 (563-944)	649 (556-773)	0.360
D-Dimer	2,685 (1,850-8,740)	2,720 (1,595-17,270)	0.355
CRP	181 (73-271)	127 (87-250)	0.485
R-Time	7.1 (4.5-7.8)	6 (4.5-10.2)	0.537
Angle	74 (72-75)	67(63-72)	**0.019**
MA	77 (72-78)	73 (66-78)	0.999

Table 4 - Comparison between patients with and without D-Dimer elevation (Median (IQR), BMI=Body Mass Index, EtOH/Substance=Alcohol or substance use disorder, PT=Prothrombin Time, PTT=activated partial thromboplastin time, CRP=C-Reactive Protein, MA=maximum amplitude, LY30=clot lysis at 30 minutes)

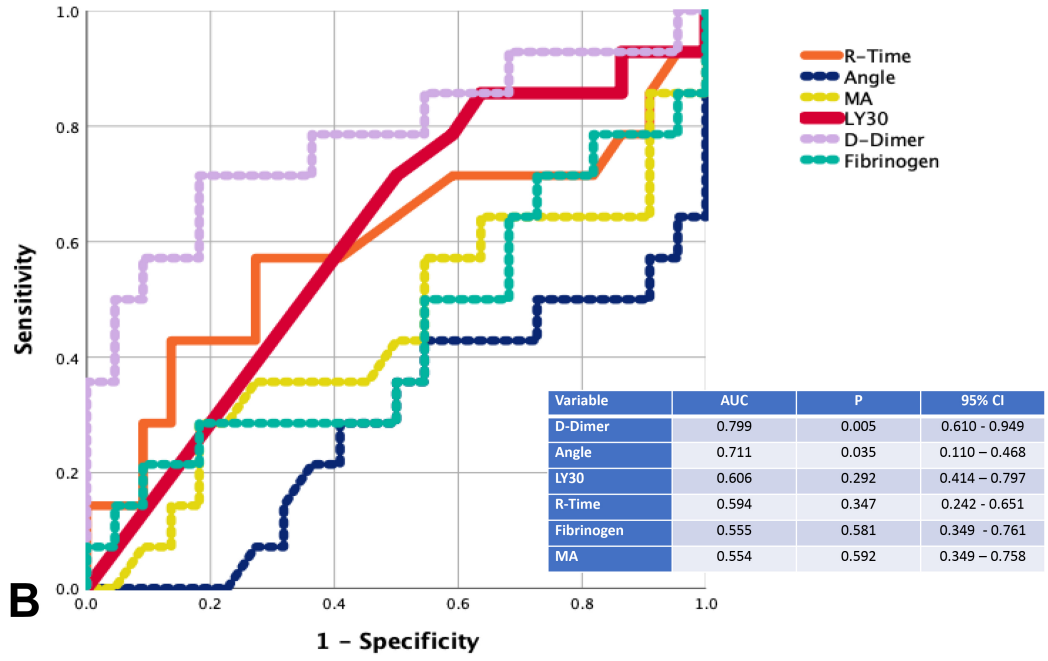
Variable	D-Dimer <2600 ng/ml	D-Dimer >2600 ng/ml	P Value
Age	48 (37-56)	58 (53-59)	0.147
BMI	30 (28-32)	30 (28-33)	0.516
Cardiac Arrhythmias	6%	7%	0.999
Hypertension	55%	53%	0.752
Diabetes Mellitus	41%	40%	0.999
Hyperlipidemia	24%	27%	0.999
COPD	7%	0%	0.540
Asthma	7%	13%	0.596
Smoking/Vaping	0	13%	0.111
EtOH/Substance	0	0	0.999
Immunosuppression	3%	0	0.999
None of the above	45%	52%	0.999
Platelet Count	262 (167-409)	229 (198-254)	0.820
PT	14 (13-16)	15 (14-16)	0.278
PTT	38 (30-42)	35 (30-50)	0.820
Fibrinogen	675 (544-759)	686 (568-862)	0.455
CRP	112 (67-218)	186 (120-271)	0.240
R-Time	6.3 (4.8-7.5)	7.6 (4.1-10.6)	0.577
Angle	71 (64-76)	68 (64-75)	0.528
MA	75 (68-77)	75 (68-77)	0.999
LY30	0 (0-0.6)	0 (0-0.2)	0.366

Figure 1a – AUROC for VTE Prediction
Figure 1b – AUROC for Acute Renal Failure Prediction
Figure 2 – LY30 of any value greater than 0% predicts less VTE
Figure 3 – D-Dimer Levels and Timing of Dialysis
Figure 4 – Combination score predicts VTE and dialysis risk
Supplemental Figure 1 – D-Dimer decreases in fibrinolysis shutdown



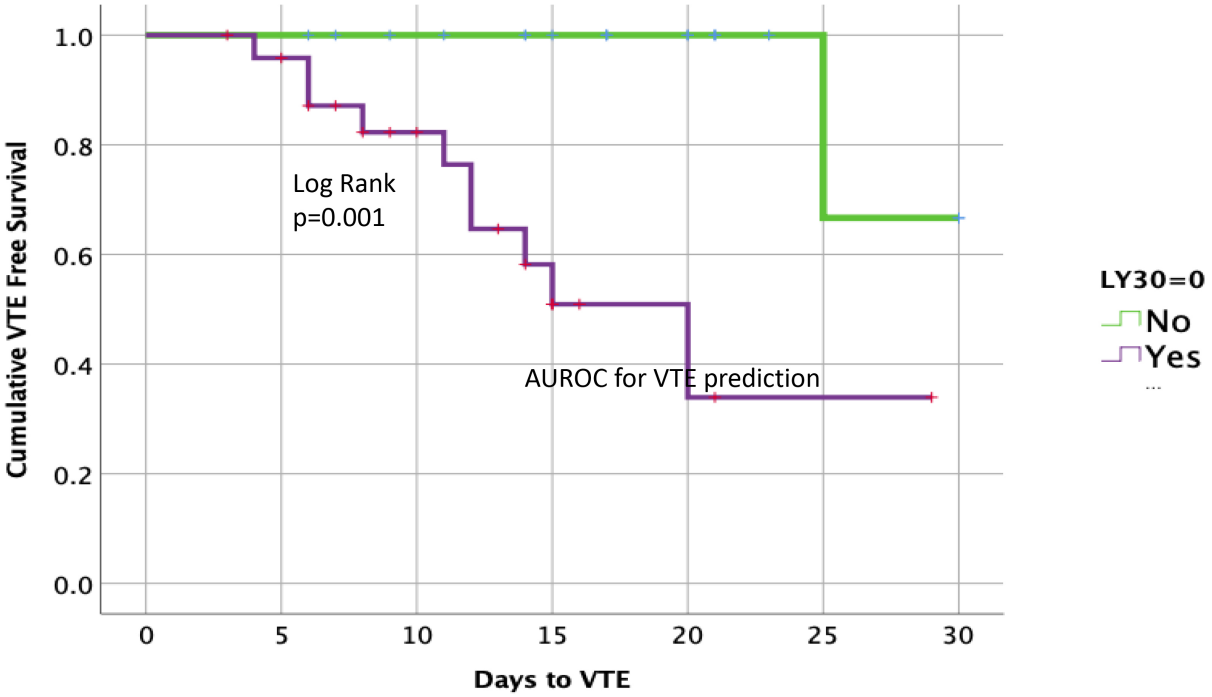
A

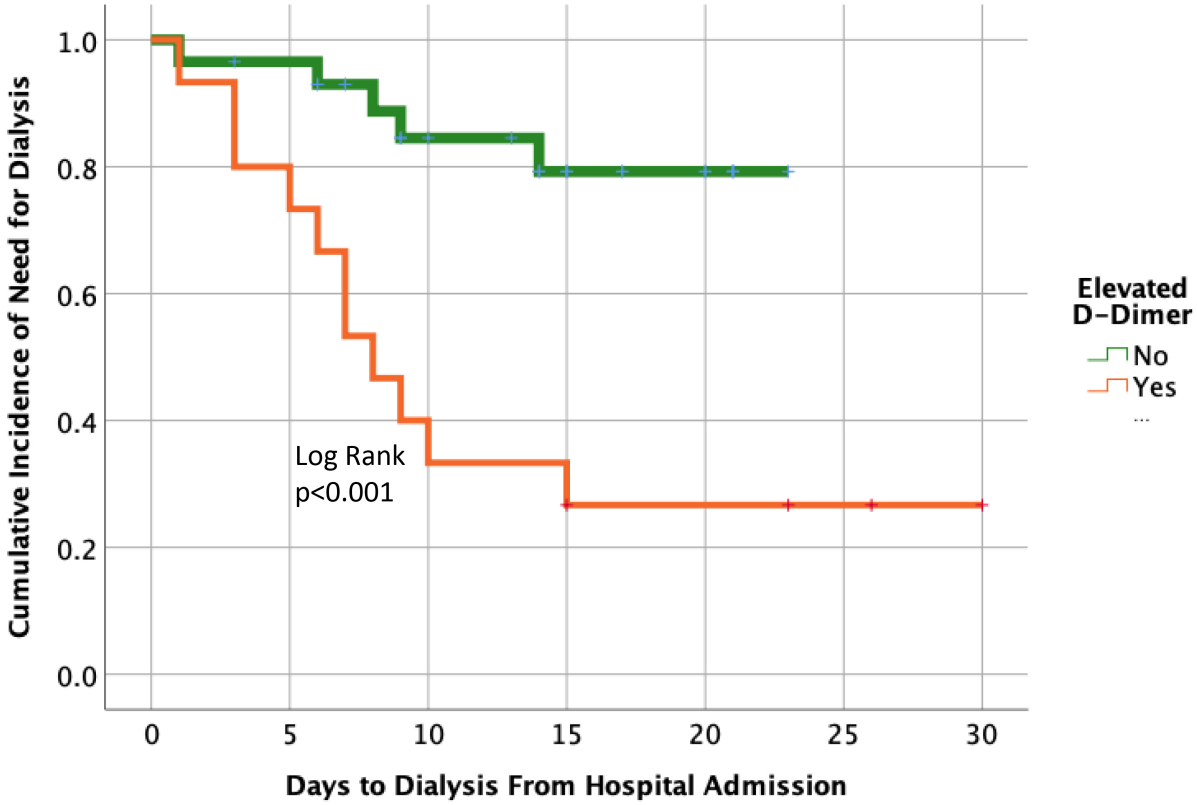
Variable	AUC	P	95% CI
LY30	0.742	0.022	0.581 - 0.903
R-time	0.613	0.287	0.385 - 0.840
Fibrinogen	0.585	0.420	0.384 - 0.787
D-Dimer	0.582	0.440	0.372 - 0.792
MA	0.515	0.891	0.291- 0.738
Angle	0.509	0.932	0.285 - 0.733

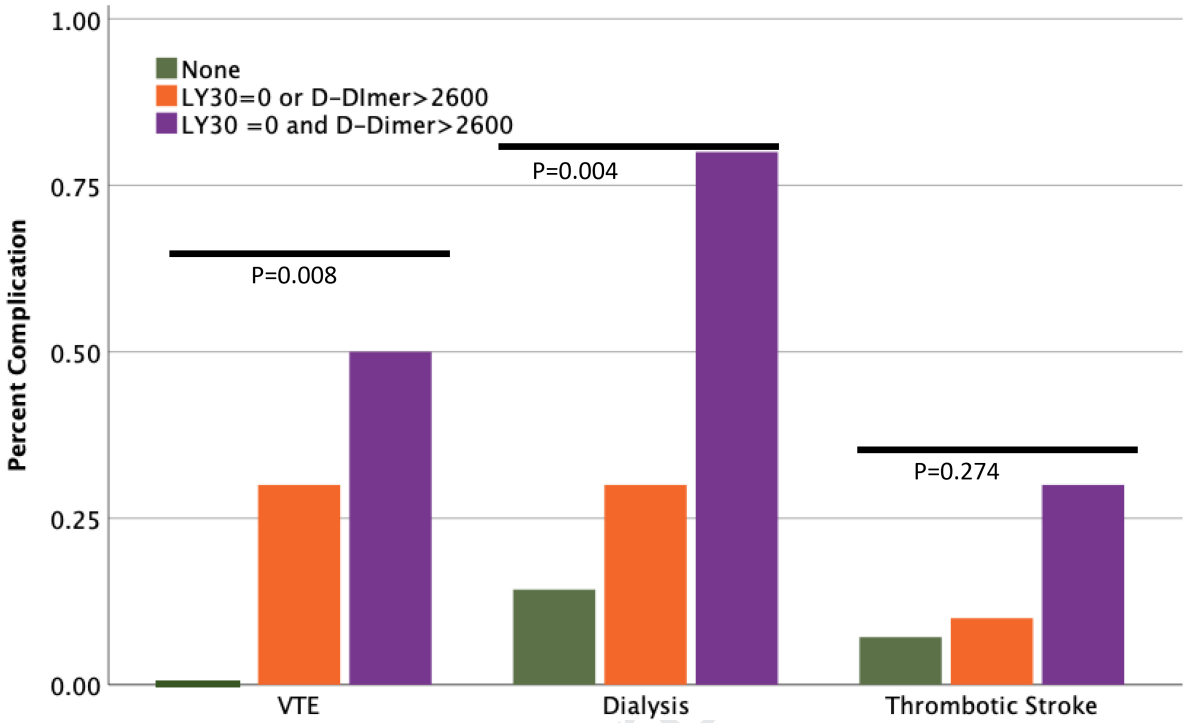


B

Variable	AUC	P	95% CI
D-Dimer	0.799	0.005	0.610 - 0.949
Angle	0.711	0.035	0.110 – 0.468
LY30	0.606	0.292	0.414 – 0.797
R-Time	0.594	0.347	0.242 - 0.651
Fibrinogen	0.555	0.581	0.349 - 0.761
MA	0.554	0.592	0.349 – 0.758






1.00
0.75
0.50
0.25
0.00
Percent Complication
None
LY30=0 or D-DImer>2600
LY30 =0 and D-Dimer>2600
P=0.008
P=0.004
P=0.274
VTE
Dialysis
Thrombotic Stroke