Effect of Anticoagulant Therapy in COVID-19 Hospitalized Patients *COVID-19 Associated Coagulopathy*

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Abstract

INTRODUCTION: COVID-19 induces a prothrombotic state as evidenced by microvascular thrombi in the renal and pulmonary vasculature. However, limited data are available to guide the antithrombotic prophylaxis strategy OBJECTIVES: We sought to determine if empiric therapeutic anticoagulation (tAC) affected survival in COVID-19 patients compared to prophylactic anticoagulation (pAC) .

METHODS and MATERIALS: A retrospective cohort study was done to determine the impact of therapeutic AC in COVID-19 hospitalized patients between August 25-2020 and October 15-2020. Independent T_test was performed to calculate mean differences, and odds ratios were calculated to examine the relationship between AC dosing and clinical outcomes.

RESULTS: Among 106 patients 39 were treated with therapeutic AC and 67 were treated with prophylactic AC. When comparing clinical outcomes between the two arms; there was no statistically significant difference in in-hospital mortality (OR:1.23, 95%CI:0.5-3.1, P:0.6). As well as the upgrade to ICU/Intubation (OR:0.98, 95%CI:0.3-2.4, P:0.9), also the need to NIV (Non-invasive mechanical ventilation) was not statistically different (OR:1.06 ,95%CI:0.4-2.6, P:0.8). While major bleeding was significantly higher in the therapeutic group [(7.7%) versus (1.5%)] (OR:0.18 ,95%CI:0.01 -1.8, P:0.01). Thrombotic events occurred in 5 patients (4.7%), and was significantly higher in the prophylactic group [(6%) versus (2.6%)] (OR:2.4 ,95%CI:1.2-12.3, P:0.04).

CONCLUSION: Therapeutic AC compared to prophylactic AC did not result in a significant difference in the primary outcomes of in-hospital mortality, upgrade to ICU/Intubation, need to NIV. Our results do not support the empirical use of therapeutic dose in unselected patients. More studies are required to determine the optimal AC regimens.

KEY WORDS: , Anticoagulation , Bleeding ,Coagulopathy, COVID-19, Thrombosis,.

INTRODUCTION:

The SARS-CoV -2 pandemic is now challenging the world with COVID-19, after severe acute respiratory syndrome coronavirus SARS-CoV in 2002 ,H1N1 influenza in 2009 and Middle East respiratory syndrome coronavirus MERS-CoV in 2012 .

This three-year pandemic caused high morbidity and mortality. By August 2022 more than 600.000.000 cases and 6.000.000 deaths have been reported worldwide.

Special attention has been paid early to COVID-19 associated coagulopathy , with the emerging evidence indicating that patients with severe COVID-19 are at increased risk of developing thrombotic events,[1][2] As evidenced by microvascular thrombi in pulmonary vasculature on autopsy studies and clinical observations of the increased rate of venous thromboembolism in hospitalized patients .[3]

Although the pathophysiology is not fully defined , as this infection is recent , clinicians faced a lack of systemic information related to the pathophysiology of the virus and the associated coagulopathy .

Initial evaluation of the Wuhan data suggests that the coagulopathy associated with COVID-19 is a result of the inflammatory response to viral particles resulting in thrombo-inflammation and driving thrombosis.[4]With VTE being the most commonly reported thrombosis complication ,with higher incidence rates among critically ill patients.[5]

Later, huge efforts were made attempting to definite the pathophysiology of COVID-19 at the molecular level. Available evidence demonstrates that SARS-CoV-2 infection induces immune dysfunction, widespread endothelial injury, complement-associated coagulopathy and systemic microangiopathy and thromboembolism[6][7] . these complications may drive the clinical deterioration , ultimately lead to multi-organ failure and death.

these data suggested that anticoagulant drugs should be evaluated in the treatment of patients with COVID-19. Responding to these data many guidelines were published and the Approach to therapeutic anticoagulation in COVID-19 has evolved as data emerged with the course of pandemic. At present , most of the enterprises are following interm guidelines issued by the International Society on Thrombosis and Haemostasis [8][9] .

ISTH ,ASH and major societal guidelines recommended that all hospitalized patients with COVID-19 should receive pharmacological thrombo-prophylaxis. However, the rising incidence of the thrombotic complication has led most hospitals to adopt the strategy of increasing the dose of AC for prophylaxis.[10]

This approach to counterbalance the risk of VTE was based on empirical approach and clinical judgment. However, the observational studies and randomised trials suggest potential benefit of the therapeutic AC during hospitalization, but the treatment remain controversial.[11][12]

The purpose of this study is to evaluate the overall clinical effects of therapeutic AC in our hospital. We hypothesized that the therapeutic AC would be associated with a reduction in the endpoints of in-hospital mortality, upgrade to ICU /IMV ,need to NIV.

1)METHODS AND MATERIALS:

2.1.DATA SOURCES: Data were retrieved from the medical records of patients. Variables collected included; demographic, laboratory measurements at the time of admission, comorbidities, procedures and outcomes (Death, intubation ,NIV, hospital discharge, major bleeding, thrombotic complications).

2.2. STUDY DESIGN AND PARTICIPANTS: This retrospective cohort study included all patients >18 years old admitted with laboratory confirmed SARS-COV-2 infection between August-25-2020 and October-15-2020 to Tishreen University Hospital. Critically ill patients or patients who need ICU care within first 24 hours of admission were excluded, as well as patients treated with therapeutic AC for a confirmed thrombotic event or previous indication for antithrombotic therapy. patients who had a contraindication for anticoagulation therapy were also excluded.

2.3. EXPOSURE: The primary exposure of interest was therapeutic AC compared with prophylactic AC. All Types of AC were included; Unfractionated heparin UFH, Low Molecular weight Heparin LMWH, Direct Oral Anticoagulation DOACs and Fondaparinux.

2.4. OUTCOMES: The primary endpoint was in-hospital mortality, secondary endpoints were ICU admission, intubation, NIV non-invasive mechanical ventilation, major bleeding and thrombotic complication. Consistency checks were performed to properly align these data tables and minimize missing data.

2.5. STATISTICAL ANALYSIS:

Categorical data were analyzed using the Chi-square and fisher exact test. Continuous variables were reported as mean and standard deviation SD and were analyzed using T-test analysis. An unadjusted odds ratio OR was calculated to measure effects of exposure with a value >=2 was considered statistically significant. A P value of less than 0.05 was considered statistically significant and all values were reported with a 95% confidence interval CI.

Statistical analysis was performed using the SPSS software (version 29, Windows) .

2) RESULTS:

3.1.Demographic and baseline characteristics:

Our study population consisted of 106 patients which were divided into two groups: therapeutic AC versus prophylactic AC (n=39 vs n=67) respectively.

The mean age was 63 years old in the therapeutic arm, and 58 years old in the prophylactic arm.

There was a uniform distribution of underlying comorbidities in both arms of the study with no statistically significant difference except for chronic heart disease which was more common in the therapeutic arm (n=3(4.5%) vs n=12(30.8%) ,P:0.0001).Other commodities as follows : Diabetes(n=21(31%) vs n=12(30.8%) ,P:0.9),HTN (n=33(49%)vs n=17(43%) ,P:0.05). Chronic lung disease (n=4(6%) vs n=2(5.1%),P:0.8).Table 1.

Table 1:Baseline characteristic of patients admitted with COVID-19 by anticoagulation therapy (prophylactic versus therapeutic):

	Prophylactic AC	Therapeutic AC	P-value
Demographic variables:			
Men Women	43(64.2%) 24(35.8%)	25(64.1%) 14(35.9%)	0.9
Age	58.77-+14.08	63.07+9.4	0.09
Smoking	0(0%)	3(7.7%)	0.3
Comorbidities:			
Diabetes	21(31.3%)	12(30.8%)	0.9
HTN	33(49.3%)	17(43.6%)	0.5
Chronic heart disease	3(4.5%)	12(30.8%)	0.0001
Chronic pulmonary disease	4(6%)	2(5.1%)	0.8
Severity of cases:			
Moderate Severe	36(53.7%) 31(46.3%)	4(10.3%) 35(89.7%)	0.0001

However, the use of steroids, antibiotics ,Hydroxychloroquine HCQ ,antiviral was similar in the therapeutic and prophylactic groups , according to the adopted protocol in our hospital during the period of the study.

In terms of disease severity, there was a significant difference between the two arms with severe cases were more common in the therapeutic arm(n=31(46.3%) vs n=33(89.7%),P:0.0001)

Inflammation and coagulopathy markers:
The D-Dimer level at the time of admission was significantly higher in the therapeutic arm compared to prophylactic arm (mean=673.4 ng /ml vs 1466 ng/ml, P:0.0001). Similarly, CRP level at the time of admission was significantly higher in the therapeutic arm compared to prophylactic (mean 97 mg/l vs 130 mg/l, P:0.001). Laboratory measurements at the time of admission in both arms in Table 2.

Table 2: Initial labs and inflammatory markers of COVID-19 patients by anticoagulation therapy; prophylactic versus therapeutic:

	Prophylactic AC	Therapeutic AC	P-value
CRP (mg/l)	97.10± 51.9	130.87± 43.5	0.001
WBC(per microliter)	5980 ±3794	6056 ± 3447	0.9
PLT(10^9/l)	213.86 ±76.6	232.97 ±125.2	0.3
HGB (g/dl)	12.33 ±1.5	11.65± 1.2	0.02
LYM(per microliter)	752.9 ±434.9	583.84± 348.9	0.04
INR	1.11 ±0.2	1.24± 0.2	0.005
D-dimer (ng/ml)	673 ±458	1460± 1070	0.0001

3.2.Odds Ratios of outcomes:
All-cause mortality was lower in the therapeutic arm compared to prophylactic arm with a non significant statistical unadjusted odd ratio (29.9%vs 25.6%),(OR:1.23 ,95%CI:0.5-3.1), P:0.6).
The unadjusted odds for patients requiring an upgrade to ICU/intubation were higher in patients in the therapeutic arm as compared to patients in the prophylactic arm (25.4%vs 25.6%) (OR:0.98,95%CI:0.3 -2.4, P:0.9).
Also patients who received therapeutic AC showed no significant reduction in the need of NIV compared to the control group (26.9% vs 25.6%), (OR:1.06 ,95%CI:0.42.6 ,P:0.8).Table 3.

Table 3: Odds ratio of outcomes with p value of difference of COVID-19 patients by anticoagulation therapy (prophylactic versus therapeutic):

Clinical outcomes:	Prophylactic AC	Therapeutic AC	P-value	Odds ratio (95%CI)
Death **Discharge**	20(29.9%) 47(70.1%)	10(25.6%) 29(25.6%)	0.6	1.23[0.5-3.1]
Upgrade to ICU/IMV	17(25.4%)	10(25.6%)	0.9	0.97[0.3-2.4]
Need for NIV	18(26.9%)	10(25.6%)	0.8	1.06[0.4-2.6]
Thrombotic event	4(6%)	1(2.6%)	0.04	2.4[1.2-12.3]
Major bleeding	1(1.5%)	3(7.7%)	0.01	0.18[0.01-1.8]

3.3.Safety outcomes:

There were 3(7.7%) major bleeding events in the therapeutic arm and 1(1.5%) in the prophylactic arm (OR:0.18 ,95%CI:0.01-1.8 ,P:0.01).there were one case of intracranial haemorrhage ,two cases of gastrointestinal bleeding and one case of massive hemoptysis. In the other hand, there were 4(6%) thrombotic events in the prophylactic arm compared to 1(2,6%) in the therapeutic arm (OR:2.4,95%CI:1.2-12,3 ,P:0.04).there were one case of acute coronary syndrome ,one case of CVA (stroke),two cases of pulmonary embolism and one case of radial artery thrombosis.

3.4.risk factor for in-hospital mortality:

To better understand what factors were associated with poor survival among patients (prophylactic and therapeutic AC users),we conducted follow up analysis comparing survivors)n=67) and non-survivors (n=30).

Non survivors were characterized by significantly older age (p:0.0001) ,higher prevalence of diabetes (p:0.03) ,HTN (p:0.03) ,chronic heart disease (p:0.02),chronic respiratory disease (p:0.03), lower lymphocyte count (p:0.04), higher CRP level (p:0.0001), higher D-dimer level (p:0.0001) with higher incidence of Thrombotic events (p:0.002) ,of note all patients that developed Thrombotic events have died.The majority of non-survivors were male)p:0.5).

Table 4: Characteristics of survivors and non-survivors of COVD-19 hospitalized patients with P value of difference:

	Non-Survivors n =30	*Survivors n =76*	*P-value*
Men Women	*18 (60%) 12(40%)*	*50(65%) 26(34.2%)*	*0.5*
Smoking	*2(6.7%)*	*15(19.7%)*	*0.09*
Diabetes	*14(46.7%)*	*19(25%)*	*0.03*
HTN	*18(60%)*	*32(42.1%)*	*0.03*
Age	*68.16 ±10.9*	*57.27± 12.04*	*0.0001*
Chronic heart disease	*8(26.7%)*	*7(9.2%)*	*0.02*
Chronic pulmonary disease	*4(13.3%)*	*2(2.6%)*	*0.03*
Upgrade to ICU/IMV	*25(83.3%)*	*2(2.6%)*	*0.0001*
Need for NIV	*5(16.7%)*	*23(30.3%)*	*0.1*
Thrombotic events	*5(16.7%)*	_____	*0.002*
Major bleeding	*1(3.3%)*	*3(3.9%)*	*0.8*
CRP	*137.4 ±50.6*	*98.52± 47.7*	*0.0001*
WBC	*5713.3 ±4576*	*6125± 3247*	*0.6*
PlT	*243.9± 111.09*	*211.8± 90.4*	*0.1*
HGB	*11.89± 1.3*	*12.15± 1.5*	*0.4*
LYM	*569 ±415*	*738 ±403*	*0.04*
D.dimer	*1467.8± 1003.9*	*766.82 ±664.5*	*0.0001*
INR	*1,27± 0.2*	*1.11± 0.2*	*0.001*

3)DISCUSSION:

The uncertainty in optimal AC regimen has been translated into variability in hospital policies and clinician decisions to use a variety of types and doses of antithrombotic drugs,[13][14] and reports from different observational studies and randomized clinical trials evaluating modified regimens of thromboprophylaxis have yielded conflicting results.

In this observational study, our analysis identified no evidence that therapeutic anticoagulation tAC emperically perscribed to patients with moderate to severe COVID-19 improve the efficacy outcomes _including all-cause mortality, upgrade to ICU/intubation, the need for Non-Invasive Mechanical Ventilation NIV_ compared with standard prophylactic anticoagulation pAc.

In line of our results, Nadkarni et al. Found that any form of AC (prophylactic or therapeutic) was associated with lower mortality and rates of intubation; However, they could not demonstrate improvements in mortality when using higher doses of AC. [11]

Also in their study Al Samkari et al._a multicenter study of 3239_ were unable to find improved mortality with early tAC.[15] Conversely, Jonmarker et al. reported lower death and VTE risk with high dose prophylaxis dose in critically ill patients .[16] While Motta et al. reported that tAC was associated with increased risk in in-hospital mortality ,and increased risk of bleeding .[17]

Conflicting results are likely due to variable inclusion criteria, severity of illness, timing of AC, selection bias, type of the study with various uncontrolled confounding factors.

It is possible that tAC is an ineffective treatment for this syndrome and higher rates of occlusive events among patients receiving tAC may support this.[17]

When assessing causes of death in patients who expired in our study, we found that most patients expired due to refractory acute respiratory failure, shock, multi-organ failure. Although thrombosis may have a role, mortality may be associated with reasons unrelated to thrombosis _direct end organ damage or the systemic inflammatory response syndrome SIRS.

In terms of safety outcomes, the incidence of VTE was significantly lower with the tAC than with pAC, but at a cost of a significantly increased risk of major bleeding.

Interestingly, our rates of VTE were much lower than reported in literature with an overall incidence rate 4,7%. For example, in their study Jimenez et al. reported pooled rates of VTE to be 17% [18], in another meta-analysis the overall rate of VTE was 14,1% and 20.7% in critically ill patients. [19] In contrast our rates are comparable to the study of Cohen et al. Who also reported an overall rate of 2.9%. [20]

Higher reported rates may be explained by selection bias which may lead to overrepresentation of VTE, also rates of VTE are likely dependent on severity of the disease in included patients and frequency of screening; routine periodic screening will increase the likelihood of discovering VTE, including clinically insignificant one.

In our study we screened for DVT only if clinically indicated, moreover some patients especially severe cases could not undergo diagnostic procedure. This may explain the lower rates in our study.

Our study showed an overall bleeding rate of 3.7%, and those treated with therapeutic dose had a higher rate (7.7% vs 1.5%) . In general our results are comparable to those of Nadkarni et al.[12] Who had an overall low bleeding rate 2% , 3% in the therapeutic group and 1.7% in the prophylactic group , while Motta et al.[18] reported a bleeding rate of 0.3% in the prophylactic group and 2.7% in the therapeutic group. The high rate reported in the therapeutic group in our study may be due to a selecting bias (older age ,sever disease...)

In our subanalysis comparing characteristic of survivors and non-survivors we found that: older age ,chronic heart disease , chronic pulmonary disease ,high levels of CRP and D-dimer ,low lymphocyte count were all associated with poor outcome. Taking into consideration these results ,we suggest that all patients must be risk-stratified at admission according to; clinical manifestations , comorbidities and laboratory tests, trying to select the group of patients that may require an aggressive therapeutic approach.

However, many questions need to be addressed; first, Anticoagulants may reduce propagation or additional formation of thrombus, but alternative strategy may be required to prevent or target the desregulated immunothrombsis. Given the extensive cross-talk between haemostasis and the immune system as a persumed mechanism of COVID-19 associated coagulopathy CAC., treatments that target their pathways may mitigate the adverse Macrovascular and Microvascular effect of COVID-19 infection; Antiplatelets, Fibrinolyric, immunmodulators, ..etc.[21] Second , whether coagulation is driving the underlying pathophysiology of COVID-19 or it is a result of the SARS-CoV-2 infection is still unclear. Third , the balance between thrombotic and hemorrhagic complications in patients with COVID-19 appears extremely complex and patients must be risk stratified at presentation for individual risk for the risk of thromboembolism and the risk of bleeding.

Thus, it is incumbent on the clinicians to remain updated on emerging literature in this area in order to optimize the care of covidn19 patients .

We acknowledge important limitations in our study. First, its single center, observational and retrospective nature makes it susceptible to selection bias and prevents us from assigning causation. Second, the decision to administer prophylactic or therapeutic anticoagulation to each patient was based more on Individual physician preference with no uniform protocol. Third, many of the sicker patients could not undergo CT angiogram for evaluation of PE, thus it is possible that VTE in our study are underrepresented. Forth, mortality after the patients left the hospital was not captured in this study this could lead to some misclassification bias in the outcome.

4)CONCLUSION:

Among patients hospitalized with COVID-19 ,prophylactic versus therapeutic anticoagulation showed similar in-hospital mortality ,upgrade to ICU/IMV and need for NIV. These findings don't support the routine use of therapeutic anticoagulation in unselected patients. However, to reach a more reliable AC strategy in COVID-19 patients further studies need to be done and more data are required.

Conflicts of interest ;

there is no conflict of interest regarding the publication of this paper.

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