ANTICOAGULATION FOR COVID-19: ROLE OF ANTICOAGULATION THERAPY IN THROMBOTIC COMPLICATIONS IN COVID-19 PATIENTS

Walli Mohammed[1]*, Dr.Hemant Kumar Sharma[2]

[1] Research Scholar, Department of Pharmacy , Sri SatyaSai University of Technology and Medical Sciences, Sehore, Madhya Pradesh, India.

[2] Professor, Department of Pharmacy,Sri SatyaSai University of Technology and MedicalSciences, Sehore, Madhya Pradesh, India.

***Corresponding Author:**
Walli Mohammed
Research Scholar
Department of Pharmacy
Sri SatyaSai University of Technology and Medical Sciences, Sehore, Madhya Pradesh, India
Mail id: wallimohammedcare@gmail.com
Mobile:+91-9966241100

ABSTRACT:

Objective: COVID-19 patients are more likely to experience thrombotic issues, which has generated an intense debate on how to manage their anticoagulation.The objective of this study was to examine the clinical outcomes of anticoagulant medication in thrombotic events in patients hospitalized with COVID-19.

Method: The study was a cross sectional prospective study conducted on patients with confirmed COVID-19. The subjects were divided into 2 groups based on severity of COVID-19. All the parameters and outcomes were compared between the groups, effect and use of anticoagulation was studied.

Results: The results revealed increased D-dimer was reported in all the cases. The thrombotic events reported were pulmonary embolism in 33.3% subjects, deep vein thrombosis in 21.4% subjects, stroke in 32.1% subjects and myocardial infarction in 16.7% subjects. The anticoagulation management used was unfractionated heparin, low molecular weight heparin enoxaparin, direct oral anticoagulants and dalteparin during hospitalization whereas apixaban, clopidogrel and rivaroxaban was used as discharge medication for maintenance.

Conclusion: Anticoagulation appears to have a dose-dependent effect because there is a stepwise rise in the survival benefit seen with prophylactic regimens and a brief course of therapeutic anticoagulation compared to no anticoagulation. There is less evidence to support the empirical treatment of microthrombi than there is to support its use in the treatment of macrovascular events.

Keywords: COVID-19, Anticoagulation, therapeutic anticoagulation, prophylactic coagulation, thrombotic events, pulmonary embolism, deep vein thrombosis, apixaban.

DOI Number: 10.48047/nq.2021.19.12.NQ21265 NeuroQuantology 2021;19(12):652-661

INTRODUCTION:

In 188 nations around the world, the coronavirus disease 2019 (COVID-19) pandemic has impacted humans.[1] More than 900,000 individuals died from COVID-19, and more than 27 million patients tested positive for the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) globally.[1]The first case series was reported from the Wuhan (China) urban area.[2]Among other findings, it was discovered that older age, hypertension, diabetes, and cardiovascular comorbidities were risk factors for an unfavorable course of COVID-19.[2]However, a number of commonly used medications, including several antithrombotic therapies, may also be linked to outcomes,[3] as evidenced by autopsy investigations that found a higher than average prevalence of thromboembolic events in COVID-19 patients.[4,5,6]

The pathogenic process of the COVID-19 has been shown to involve hypercoagulability. A markedly abnormal coagulation profile on thromboelastography suggests hypercoagulability in the context of severe systemic inflammation, as have coagulation abnormalities such as elevated D-dimer and fibrinogen in combination with low anti-thrombin levels, evidence of endothelial dysfunction.[7,8,9]

Risk stratification on the admission of COVID-19 patients and management of a potentially developing coagulopathy are provided in the ISTH guidance guideline. It recommends that individuals with elevated D-dimers, which are arbitrarily defined as increases of three to four, be admitted to a hospital. Unless it is contraindicated, low-molecular-weight heparin should be taken into consideration for all patients who need to be hospitalized for COVID-19 infection.

Only case reports and case series have been used in studies evaluating coagulation methods, and estimates range from 1% in general wards to 69% in intensive care units employing screening ultrasound.[10]

MATERIALS AND METHODS:

Site of the study: The study was conducted in A.I.G tertiary care hospital, Hyderabad.

Study Design: The study was a cross sectional prospective study.

Duration of the study: The duration of the study was six monthsOct 2020 to March 2021.

Source of data: The source of data was patient collection forms, medical records, case sheets and laboratory investigations.

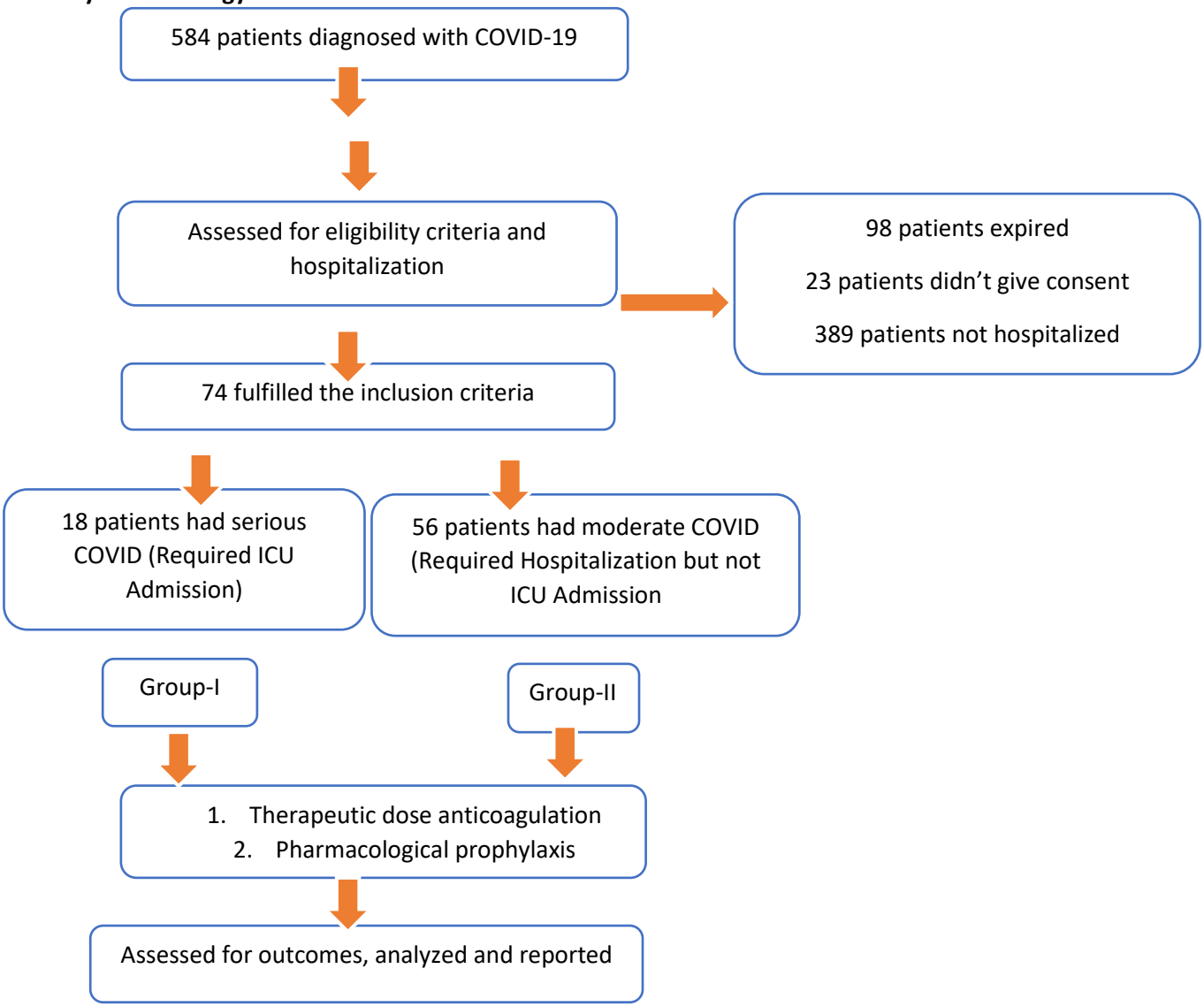
Inclusion criteria:

- Patients diagnosed with COVID-19 with positive PCR
- Patients hospitalized due to COVID-19 illness
- Patients willing to participate.

Exclusion criteria:

- Patients with negative PCR.
- Patients less than 16 years.
- Pregnant and lactating women.

Study Methodology:



Ethical approval:
The study was conducted after obtaining IEC approval (AIG/IECBH&R03/02.2020-05)

Data collection and analysis: A Case Report Form (CRF) was used to collect the necessary data, which was then analyzed. All the necessary and pertinent information from the patients' case sheets, treatment plans, laboratory findings, patient or patient caretaker interviews, and any other related sources. The information was entered into an MS Excel 2016 spreadsheet and exported to IBM SPSS Software Version 22 for further analysis of results.

RESULTS:

The study was conducted on 74 patients those were grouped as Group-I having serious COVID-19 and Group-II having moderate COVID-19. There were 18 patients in Group-I and 56 patients in Group-II. The results are stated below:

Table-1: Demographics

	Group-I	Group-II
Age (in years)		
18-44	10 (55.5%)	8 (14.3%)
45-74	4 (22.2%)	6 (10.7%)
>75	4 (22.2%)	42 (75%)
Gender		
Male	7 (38.9%)	35 (62.5%)
Female	11 (61.1%)	21 (37.5%)
Smoking Status	1 (5.6%)	5 (8.9%)
Race/Ethnicity		
Black	5 (27.8%)	12 (21.4%)
White	4 (22.2%)	3 (5.4%)
Asian	8 (44.4%)	36 (64.3%)
Others	1 (5.5%)	5 (8.9%)
Comorbidities		
HTN	10 (55.5%)	22 (39.3%)
DM	4 (22.2%)	16 (28.6%)
CKD	3 (16.7%)	9 (16%)
Chronic Respiratory Disease	2 (14.1%)	7 (12.5%)
Immunosuppressive Disease	1 (5.55%)	3 (5.4%)
Liver Disease	1 (5.55%)	1 (1.8%)
Cancer	1 (5.55%)	5 (8.9%)

Table-1 represents the data on demographics of subjects that included age, gender, smoking status, race/ethnicity and comorbidities.

Majority of patients were observed in age group of 18-44 years i.e. 10 (55.5%) subjects followed by 4 (22.2%) subjects in age group of 45-74 years and >75 years.

Female prevalence with 11 (61.1%) subjects was observed in Group-I followed by 7 (38.9%) male subjects. Male prevalence was observed in Group-II i.e. 35 (62.5%) subjects followed by 21 (37.5%) female subjects. Group-II subjects had the larger smoking status i.e.5 (8.9%) subjects and Group-I had 1 (5.6%) subjects.

In Group-I, based on the race and ethnicity, the Asians were higher i.e. 8(44.4%) followed by black i.e. 5(27.8%) subjects, white i.e. 4 (22.2%) subjects and others i.e. 1 (5.5%) subjects. IN Group-II, there were 36 (64.3%) Asian subjects, followed by 12 (21.4%) black subjects, 5 (8.9%) other subjects and 3 (5.4%) white subjects.

Table-2: Diagnostic parameters.

	Group-I	Group-II
Presenting symptom		
SOB	15 (83.3%)	41 (73.2%)
Fever	12 (66.7%)	28 (50%)
Palpitations	8 (44.4%)	15 (26.8%)

Productive cough	14 (77.8%)	32 (57.1%)
Malaise	17 (94.4%)	48 (85.7%)
Laboratory values		
WBC (cells/mm^3)	16.2 (10.6-20.4)	7.6 (6.9-11.5)
Platelets (cells/mm^3)	218 (172-290)	221 (171-290)
D-Dimer (ng/mL)	3.8 (0.85-12.2)	1.78 (1.0-8.62)
Creatinine (mg/dL)	3.2 (1.0-5.6)	0.9 (0.7-1.1)
PT (s)	25 (17-30)	14.3 (12.0-18.3)
aPTT (s)	28.5 (15.3-40.7)	17.6 (13.8-31.3)
Fibrinogen		
Ferritin (ng/ml)	1215 (540-2106)	703 (412-1600)
LDH (U/L)	864 (453-1675)	314 (211-548)
CRP (mg/L)	319 (128-540)	148(43-180)
Procalcitonin (ng/ml)	1.4 (0.5-2.0)	0.9 (0.6-2.5)
Requirement of respiratory support		
Low-flow nasal cannula/face mask	10 (55.5%)	43 (76.8%)
High-flow nasal cannula	1 (5.5%)	25 (44.6%)
Non-invasive mechanical ventilation	1 (5.5%)	14 (25%)
Invasive mechanical ventilation	14 (77.8%)	5 (8.9%)
Extracorporeal membrane oxygenation	1 (5.5%)	0 (0%)

Table-2 represents the data on diagnostic parameters that included presenting symptoms, laboratory values and the requirement of respiratory support.

In Group-I there were 17 (94.4%) subjects who presented with malaise, followed by 15 (83.3%) subjects with SOB, 14 (77.8%) subjects with productive cough, 12 (66.7%) subjects with fever and 8 (44.4%) subjects with palpitations. In Group-II,, there were48 (85.7%) subjects with malaise, followed by 41 (73.2%) subjects with SOB, 32 (57.1%) subjects with productive cough, 28 (50%) subjects with fever and 15 (26.8%) subjects with palpitations.

Based on the COVID severity in Group-I, invasive ventilation was required by most of the patients i.e.14 (77.8%) subjects, followed by 10 (55.5%) subjects requiring face mask, 1 (5.5%) subjects requiring high-flow nasal cannula, noninvasive mechanical ventilation and extracorporeal membrane oxygenation. Whereas in Group-II, 43 (76.8%) subjects required face mask, followed by 25 (44.6%) subjects requiring high-flow nasal cannula, 14 (25%) subjects requiring non-invasive mechanical ventilation and 5 (8.9%) subjects requiring noninvasive mechanical ventilation.

Table-3: Anticoagulation profile

	Group-I	Group-II
Number of events		
PE	6 (33.3%)	8 (14.3%)
DVT	3 (16.7%)	12 (21.4%)
Stroke	5 (27.8%)	18 (32.1%)
MI	3 (16.7%)	9 (16%)

Other thrombotic events	1 (5.6%)	0 (0%)
D-Dimer Values(ng/mL)		
<230	1 (5.6%)	15 (26.8%)
231-499	8 (44.4%)	34 (60.7%)
500-1999	5 (27.7%)	8 (14.3%)
2000-5000	7 (38.8%)	5 (8.9%)
Anticoagulation management given		
UFH	14 (77.8%)	34 (60.7%)
LMWH	12 (66.7%)	47 (83.9%)
Enoxaparin	9 (50%)	29 (51.8%)
Dalteparin	3 (16.7)	18 (32.1%)
DOACs	8 (44.4)	42 (75%)

Based on the number of events reported in Group-I, Pulmonary Embolism had the highest prevalence with 6 (33.3%) subjects followed by 5 (27.8%) subjects who had stroke, 3 (16.7%) subjects who had deep vein thrombosis and myocardial infarction and 1 (5.6%) subject with other thrombotic events. In Group-II, Stroke was reported in 18 (32.1%) subjects, followed by deep vein thrombosis reported in 12 (21.4%) subjects, pulmonary embolism in 8 (14.3%) subjects, and myocardial infarction in 9 (18%) subjects.

In Group-I, D-dimer values of <230ng/mL were reported in 1 (5.6%) subjects, 231-499ng/mL was reported in 8 (44.4%) subjects, 500-1999ng/mL were reported in 5 (27.7%) subjects, 2000-5000ng/mL were reported in 7 (38.8%) subjects. In Group-II, D-dimer values of <230ng/mL were reported in 15 (26.8%) subjects, 231-499ng/mL was reported in 34 (60.7%) subjects, 500-1999ng/mL was reported in 8 (14.3%) subjects, 2000-5000ng/mL was reported in 5 (8.9%) subjects.

The management given in Group-I included unfractionated heparin in 14 (77.8%) subjects, low molecular weight heparin in 12 (66.7%) subjects, enoxaparin in 9 (50%) subjects, dalteparin in 3 (16.7%) subjects and direct oral anticoagulation in 8 (44.4%) subjects. In Group-II, unfractionated heparin was given to 34 (60.7%) subjects, low molecular weight heparin was given to 47 (83.9%) subjects, enoxaparin was given to 29 (51.8%) subjects, dalteparin was given to 18 (32.1%) subjects and direct oral anticoagulation was given to 42 (75%) subjects.

Table-4: Discharge Medications

	Group-I	Group-II
Apixaban	2	42
Rivaroxaban	1	6
Clopidogrel	7	10

Table-4 gives information about the discharge medications. In Group-I, clopidogrel was prescribed in most of the patients i.e. 7 subjects, followed by apixaban in 2 subjects and rivaroxaban in 1 subject. In Group-II, apixaban was prescribed to 42 subjects followed by clopidogrel in 10 subjects and rivaroxaban in 6 subjects.

DISCUSSIONS:

It has recently been observed that 15% of individuals acquire the severe form of coronavirus disease 2019 (COVID-19).[11] Because the lungs are the organs most frequently affected, clinical deterioration can happen within a few days after symptom start, progressing to hypoxemic respiratory failure and acute respiratory distress syndrome (ARDS).[12]A high shunt fraction and the presence

of thrombi in the microcirculation, which have been identified in autopsy studies, may indicate a vascular component of the disease, explaining the discrepancy between changes in gas exchange, radiological findings, and findings regarding respiratory mechanics.[13] Up to one-third of patients in this situation have been described as having hematological alterations and a hypercoagulable state, with an increase in D-dimer levels being a key indicator of unfavourable outcomes.[14]

A minimum 3-day course of either (a) intravenous unfractionated heparin (UFH) with at least one documented activated partial thromboplastin time in the anticoagulation range (45 seconds); (b) subcutaneous enoxaparin at doses of 1 mg/kg twice daily or 1.5 mg/kg once daily (while allowing for dose adjustment based on creatinine clearance); (c) intravenous argatroban infusion; (d) subcutaneous fondaparinux at doses of 5–10 mg once daily (weight-based dosing); or (e) oral anticoagulants (warfarin, apixaban, rivaroxaban, dabigatran) prescribed before and continuing throughout hospitalization was considered therapeutic anticoagulation.

One of the following administrations was considered prophylactic anticoagulation (pAC) on the majority of hospitalization days: 1) Subcutaneous injection of UFH in doses of 5000 units twice or three times per day; 2) Subcutaneous injection of enoxaparin in doses of 30–40 mg once day; or 3) Subcutaneous injection of fondaparinux in doses of 2.5 mg once daily.

16.0% of COVID-19 patients hospitalized in a significant New York City health system experienced a thrombotic episode. Independently, thrombotic events and D-dimer level at presentation were related. This is consistent with an early coagulopathy.[4,15]

Although earlier investigations had different estimates of the incidence of thrombosis, they all seemed to point to patients with COVID-19 as having a higher risk. This investigation discovered variance depending on the clinical environment and thrombosis event type. The thrombotic risk in COVID-19 appears to be higher even if thrombosis is seen in other acute infections5 (for example, 5.9% prevalence during the 2009 influenza pandemic). Patients with COVID-19 may develop thrombosis for a variety of reasons, including a cytokine storm, hypoxic damage, endothelial dysfunction, hypercoagulability, and/or elevated platelet activity.

Poorer outcomes have been associated with substantial increases in D-dimer levels and markers of endothelial dysfunction (soluble thrombomodulin, von Willebrand factor antigen).[16,17,18]A high incidence of thrombotic complications (31%) was described in one case series of critically ill COVID-19 patients[4]A large number of autopsy case series have described pulmonary and other visceral microthromboses, indicating that coagulation anomalies are likely key pathogenic components rather than merely epiphenomena.[13,19,20,21]

In a 198-patient single-center cohort analysis, an elevated D-dimer was linked to a 50% higher risk of developing VTE.[22] In addition, laboratory results for COVID-19 patients may be predictive. In COVID-19, higher D-dimer levels have been linked to a higher risk of mortality.[10]In a 343 patient trial, those with a D-dimer of less than 2.0 g/mL had a 51.5-fold higher chance of dying in the hospital than those with a D-dimer of 2.0 g/mL or more.[18] In a comprehensive study with 1099 COVID-positive patients from 552 hospitals in China, it was discovered that 46.4% of the patients had D-dimer concentrations over the threshold of 0.5 mg/L, and 60% of them had severe symptoms. D-dimer levels in these patients were 2.12 mg/mL (0.77-5.27) which was four times higher than the values in non-severely affected patients (0.61 mg/mL, 0.35-1.29). So, in addition to the patient's age, D-dimer concentration and SOFA score offer crucial information about the prognosis of COVID-19 disease. Lymphopenia, leukocytosis, and elevated laboratory values of alanine aminotransferase, LDH, extremely sensitive troponin I, creatine kinase, serum ferritin, IL-6, PT, creatinine, and procalcitonin were additional risk factors for a serious result.[11,23]

A study discovered a dose- and duration-dependent delay in death in a cohort of 127 deceased patients with severe COVID-19. A small number of retrospective studies have found that thromboprophylactic-dose anticoagulation is associated with improved outcomes in patients with COVID-19.[24]Numerous studies have also found a link between laboratory results and the severity of the condition.

99 out of 449 individuals in a study with severe COVID-19 symptoms received heparin (mostly LMWH) for seven days or longer. Comparisons were done regarding the various risks of coagulopathy stratified by the sepsis-induced coagulopathy score (SIC) and D-dimer value, as well as the 28-day mortality between heparin users and nonusers. In a multivariate study, D-dimer, PT, and age were positively connected with 28-day mortality, but platelet count was negatively correlated. Heparin users and nonusers experienced the same 28-day mortality (30.3% vs 29.7%, P 14.910). However, in patients with SIC score 4 (40.0% vs 64.2%, P 14.029) or D-dimer >6 times the upper limit of normal value (32.8% vs 52.4%, P 14.017), the 28-day mortality of heparin users was lower than that of nonusers.Additionally, after receiving LMWH medication, originally high levels of D-dimer and fibrinogen degradation products considerably dropped, suggesting that the hypercoagulable status of COVID-19 patients had improved. The therapeutic benefit of LMWH may be attributable to its ability to reduce IL-6 release and boost lymphocytes that can slow down or stop the inflammatory cytokine storm.[25,26]

The unique SARS-CoV-2 infection clinical spectrum includes asymptomatic infection to deadly septic shock. Patients with COVID-19 may have cytokine storms and increased hypercoagulability as their condition progresses from mild to severe. Similar to all coagulopathies, the underlying condition must be treated. To avoid thrombotic events and organ damage in COVID-19, preventive anticoagulation with LMWH should be administered as soon as possible. The preliminary International Society on Thrombosis and Hemostasis (ISTH) guidance on the identification and treatment of coagulopathy in COVID-19 recently published recently endorsed this.

CONCLUSIONS:

An important complication among COVID-19 hospitalized patients is thromboembolic diseases. There is growing evidence that thrombotic events play a significant role in the pathogenicity of COVID-19, and that anticoagulation has a positive impact on survival.Patients with critical illnesses primarily experience the most substantial benefits, while hospitalized non-ICU patients also recovered. With a stepwise increase in the survival benefit observed with the use of prophylactic regimens and a few days course of therapeutic anticoagulation compared to no anticoagulation, the effect of anticoagulation appears to be dose-dependent.

REFERENCES:

1. University JH (2020) John Hopkins University. https://coronavirus.jhu.edu/map.html.
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet. 2020 Feb 15;395(10223):497-506.
3. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, Nigoghossian CD, Ageno W, Madjid M, Guo Y, Tang LV. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. Journal of the American college of cardiology. 2020 Jun 16;75(23):2950-73.
4. Klok FA, Kruip MJ, Van der Meer NJ, Arbous MS, Gommers DA, Kant KM, Kaptein FH, van Paassen J, Stals MA, Huisman MV, Endeman H. Incidence of thrombotic complications in critically ill ICU patients with COVID-19.

Thrombosis research. 2020 Jul 1;191:145-7.

5. Wichmann D, Sperhake JP, Lütgehetmann M, Steurer S, Edler C, Heinemann A, Heinrich F, Mushumba H, Kniep I, Schröder AS, Burdelski C. Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. Annals of internal medicine. 2020 Aug 18;173(4):268-77.
6. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, Li WW. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. New England Journal of Medicine. 2020 Jul 9;383(2):120-8.
7. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. Am J Hematol. 2020;95(7):834-847.
8. Panigada M, Bottino N, Tagliabue P, et al. Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelas-tography findings and other parameters of hemostasis. J ThrombHaemost JTH. 2020;18(7):1738-1742.
9. Ranucci M, Ballotta A, Di Dedda U, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. J ThrombHaemost JTH. 2020;18(7):1747-1751.
10. Rosovsky RP, Sanfilippo KM, Wang TF, Rajan SK, Shah S, Martin KA, Ainle FN, Huisman M, Hunt BJ, Kahn SR, Kevane B. Anticoagulation practice patterns in COVID-19: a global survey. Research and practice in thrombosis and haemostasis. 2020 Aug 1;4(6):e12414.
11. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DS, Du B. Clinical characteristics of coronavirus disease 2019 in China. New England journal of medicine. 2020 Apr 30;382(18):1708-20.
12. Gattinoni L, Chiumello D, Rossi S. COVID-19 pneumonia: ARDS or not?.Crit Care. 2020;24(1):154. https://doi.org/10.1186/s13054-020-02880-z
13. Dolhnikoff M, Duarte-Neto AN, de Almeida Monteiro RA, da Silva LFF, de Oliveira EP, Saldiva PHN, et al. Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19. J ThrombHaemost. 2020;18(6):1517-1519. https://doi.org/10.1111/jth.14844
14. Wynants L, Van Calster B, Collins GS, Riley RD, Heinze G, Schuit E, et al. Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal [published correction appears in BMJ. 2020 Jun 3;369:m2204]. BMJ. 2020;369:m1328. https://doi.org/10.1101/2020.03.24.20041020
15. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia.JThrombHaemost. 2020;18 (6):1421-1424.
16. Goshua G, Pine AB, Meizlish ML, et al. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study. Lancet Haematol. 2020;7(8):e575-e582.
17. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortal-ity of adult inpatients with COVID-19 in Wuhan, China: a retrospec-tive cohort study. Lancet. 2020;395(10229):1054-1062.
18. Zhang L, Yan X, Fan Q, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J ThrombHaemost. 2020;18(6):1324-1329

19. Fox SE, Akmatbekov A, Harbert JL, Li G, Brown JQ, Heide RSV. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. Lancet Respir Med. 2020;8(7): 681-686.
20. Magro C, Mulvey JJ, Berlin D, et al. Complement associated micro-vascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. Transl Res. 2020;220:1-13.
21. Nadkarni GN, Lala A, Bagiella E, et al. Anticoagulation, mor-tality, bleeding and pathology among patients hospitalized with COVID-19: a single health system study. J Am CollCardiol. 2020;76(16):1815-1826.
22. Middeldorp S, Coppens M, van Haaps TF, Foppen M, Vlaar AP, Muller MCA, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J ThrombHaemost. 2020. https://doi.org/10.1111/jth.14888
23. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Yu T. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The lancet. 2020 Feb 15;395(10223):507-13.
24. Ionescu F, Grasso-Knight G, Castillo E, et al. Therapeutic anticoag-ulation delays death in COVID-19 patients: cross-sectional analysis of a prospective cohort. TH Open. 2020;04(3):e263-e270.
25. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. Journal of thrombosis and haemostasis. 2020 May 1;18(5):1094-9.
26. Miesbach W, Makris M. COVID-19: coagulopathy, risk of thrombosis, and the rationale for anticoagulation. Clinical and applied thrombosis/hemostasis. 2020 Jul 16;26:1076029620938149.