

Analysis of *D-Dimer* Level and Prothombin Time (PT) Activated Prothombin Thromboplastin (APTT) on Heparin Administration to COVID-19 Patients

Dela Yorike¹, Muhammad Rizki Kurniawan¹, Mohamad Syafaat¹

¹Departement Medical Laboratory Technology, Faculty Science and Technology, Universitas Binawan, Jakarta

Correspondence:
Dela Yorike,
Gg. Sadar 1 No. 95 Bekasi, West
Java, Indonesia
Zip Code: 17431

Email: delayorike02@gmail.com

Received: September 18, 2021
Revised: February 22, 2022
Accepted: March 14, 2022
Published: April 28, 2022

DOI: 10.33086/ijmlst.v4i1.2487



Abstract

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). Coronavirus is a dangerous pathogen that affects both humans and animals. Symptoms and indicators of COVID-19 infection include fever, cough, and shortness of breath, which are common in respiratory illnesses. COVID-19 has spread globally with high mortality and morbidity rates. Prothrombin Time (PT), Activated Prothrombin Thromboplastin (APTT), and *D-Dimer* parameters are blood tests to evaluate the coagulation status of COVID-19 patients, all these parameters increased in COVID-19 patients. This study aims at determining the levels of *D-Dimer*, PT, and APTT in COVID-19 patients. Clinical and laboratory records were retrospectively reviewed from 100 cases of COVID-19 admitted to hospitals. This study used a cross-sectional, descriptive, secondary data analysis design. The sample included patients from the Bhayangkara TK. I R.Said Sukanto Hospital between April-July 2021. The sample is a COVID-19 patient who was treated in the Intensive Care Unit (ICU), worsened, and given heparin. An independent variable is the administration of intravenous heparin at prophylactic doses. Dependent variables are *D-Dimer*, PT, and APTT values. The collected data is processed using Microsoft Office Excel and then being analyzed. *D-Dimer*, PT, and APTT levels in COVID-19 patients were initially high or increased after heparin administration decreased or became normal. In conclusion, there was a decrease in *D-dimer* levels, PT values, and APTT after administration of intravenous heparin at prophylactic doses.

Keywords

Activated Prothrombin Thromboplastin, COVID-19, *D-Dimer*, Heparin, Prothrombin Time.



This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. ©2021 by author.

INTRODUCTION

Coronavirus is a dangerous pathogen that attacks humans and animals. Coronavirus comes from the subfamily *Orthocoronavirinae* in the family *Coronaviridae* and the order *Nidovirales*. This virus attacks the respiratory system in humans and causes several diseases such as *severe acute respiratory syndrome* (SARS), *Middle East Respiratory Syndrome* (MERS), and *Coronavirus Disease 2019* (COVID-19) (3). Symptoms and signs of COVID-19 infection include respiratory symptoms such as fever, cough, and shortness of breath (3). People who have a history of co-morbidities and are elderly are at high risk of contracting COVID-19 (4).

Coronavirus disease 2019 (COVID-19), the clinical syndrome associated with infection with *Severe Acute Respiratory Syndrome Coronavirus-2* (SARS-CoV-2), has been able to affect various worlds and scientific investigations have not occurred, previously there was a shortage of pharmacotherapy to fight the disease. The lack of treatment strategies with a variety of practice patterns already exists. Hypercoagulability in COVID-19 patients has sparked debate in clinical care regarding the use of heparin therapy (7).

The rapid spread of COVID-19 cases in various countries has put health status in a dangerous condition. The latest data from the World Health Organization reports that

confirmed COVID-19 sufferers in three days on 26 April 2020 in Europe (1,341,851 patients), Asia (43,846 patients) and Africa (20,316 patients) with a global death rate of 193,710, While in Indonesia, based on data from the National Disaster Management Agency on 26 April, 2020, COVID-19 sufferers numbered 8,882 and 743 people died. The most COVID-19 sufferers are in DKI Jakarta (3,798 patients), West Java (912 patients), East Java (785 patients), Central Java (649 people) and South Sulawesi (440 patients) (4).

Laboratory parameters to identify the blood coagulation disorders occurrence in COVID-19 patients are *D-Dimer*, *fibrin/fibrinogen*, *Prothrombin Time* (PT/time required for blood to form clots or blood platelets) (5). *D-Dimer* is a fibrin degeneration product that is useful for detecting abnormal clot formation or thrombotic events and assessing the presence of a clot breaking or fibrinolytic process. Quantification of *D-Dimer* levels plays an important role in guiding therapy. *D-Dimer* level is usually elevated in patients with COVID-19 (1). *Prothrombin Time* (PT) is the test of time length in blood clotting based on the extrinsic and common pathways. This test is performed to determine the presence of bleeding disorders and assess the treatment taken to prevent bleeding (1). *Activated Prothrombin Thromboplastin Time* (APTT) is the test of time length in blood clotting

based on the basic pathway (intrinsic pathway). The APTT test is usually paneled with the PT test to determine the presence of a bleeding disorder and the possibility of profuse bleeding during surgery (2).

COVID-19 patients have not been supported by sufficient research until now, so the treatment has not been established significantly. Heparin is a drug to treat and prevent blood clots caused by certain medical conditions or procedures. Heparin works by inhibiting the work of proteins that play a role in the blood clotting process, so the blood clots formation can be prevented. However, for the time being, the use of heparin and Low Molecular Weight Heparin (LMWH), can be used. The use of low-dose heparin was associated with a significant reduction in mortality within 28 days in patient with sepsis. Other studies have shown a reduction in the risk of death at days 7 to 28 and a significant increase in the $\text{PaO}_2/\text{FiO}_2$ ratio in *acute respiratory distress syndrome* (ARDS) patients receiving high-dose LMWH therapy (6).

In a previous retrospective study, 449 patients with severe COVID-19 in China, 99 of whom received heparin (mainly LMWH) for at least 7 days, found that prothrombin time was positively correlated with 28 days. Mortality and platelet count were negatively correlated. In general, no significant difference was found in mortality between heparin users and nonusers at 28 days (30.3%

vs 29.7%, $P = 0.910$), but the mortality of heparin users at 28 days was lower than that of nonusers in patients with *D-Dimer* levels were more than six times the upper limit of normal (32.8% vs 52.4%, $P = 0.017$) (18).

The primary purpose of this study was to give an analysis of *D-Dimer*, PT, and APTT in COVID-19 patients who were used heparin. The source of data used in this study is secondary data. The data that has been collected is processed using Microsoft Office Excel and made into a graph. Data analysis included testing the frequency data for respondent characteristics based on sex, age, *D-Dimer* level, PT level and APTT level.

MATERIALS AND METHODS

Source of patients Diagnosis criteria

This study was conducted in the laboratory of the Bhayangkara T.K.I Raden Said Sukanto Hospital, Jakarta-Indonesia used a descriptive research type and has been approved by Bhayangkara T.K.I Raden Said Sukanto Hospital Ethical Commission with the letter of Ethical Approval Number B/2245/VII/2021. The populations in this study were all patients who confirmed positive for COVID-19 in the ICU/HCU Bhayangkara T.K.I Raden Said Sukanto Hospital between April-July 2021. A total of 100 patients, all diagnosed with COVID-19 which had confirmed a positive result of the nucleic acid test of SARS-CoV-2 by real-time fluorescence RT-PCR.

Diagnosis criteria

The sampling technique in this study was purposive sampling, which uses the criteria that have been selected by the researcher in selecting the sample. The sample selection criteria are divided into inclusion and exclusion criteria. The inclusion criteria were above 30 years old, have comorbidities such as liver disease, kidney, heart, lung, digestive tract, urinary tract, brain, and others, and COVID-19 patients who deteriorated and need ICU. Meanwhile, the exclusion criteria are abortus, hypertension, and thrombocytopenia. The tools used in this study include equipment blood sampling (syringes, citrate vacuum tubes, alcohol swabs, plasters, tourniquet, label), coagulation analyzer (Sysmex® CA-600), centrifuge, and micropipette. The ingredients used in this study include plasma citrate blood, Dade Innovin reagents, Pathrombin SL reagents, CaCl₂ reagents, OVB reagents, and normal controls. The measurement method was used cross-sectional by looking at the decrease in the value of *D-Dimer*, PT, and APTT levels in the administration of heparin to COVID-19 patients.

RESULTS

The distribution of respondent characteristics based on age when giving heparin to COVID-19 patients at Bhayangkara T.K.I Raden Said Sukanto Hospital obtained as shown in the Figure 1.

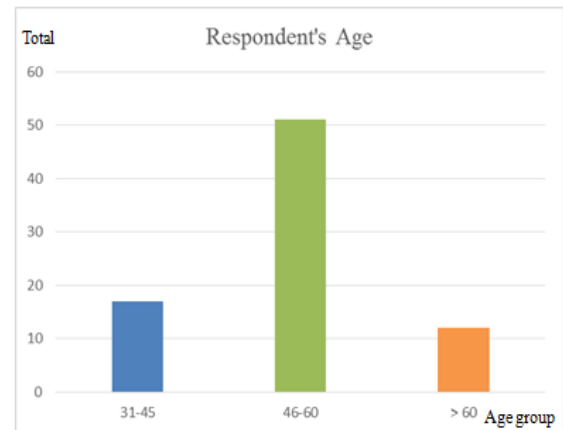


Figure 1. Frequency Distribution of Respondent's Age

Based on Figure 1, most of the respondents have an age category of 46-60 years (63.75%), followed by 31-45 years (21.25%), and > 60 years (15%). Moreover, the distribution of respondent characteristics based on gender when giving heparin to COVID-19 patients at Bhayangkara T.K.I Raden Said Sukanto Hospital is shown in Figure 2.

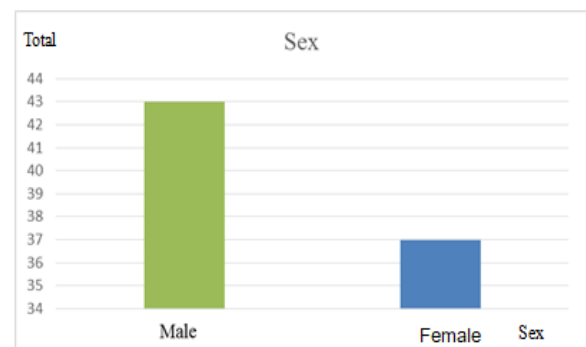


Figure 2. Frequency Distribution of Respondent's Sex

Based on Figure 2, most respondents were male (53.75%). Parameters of PT, APTT, and *D-Dimer* levels in the administration of heparin to patients with

Coronavirus Disease 2019 (COVID-19) at Bhayangkara T.K.I Raden Said Sukanto Hospital showed in Figure 3.

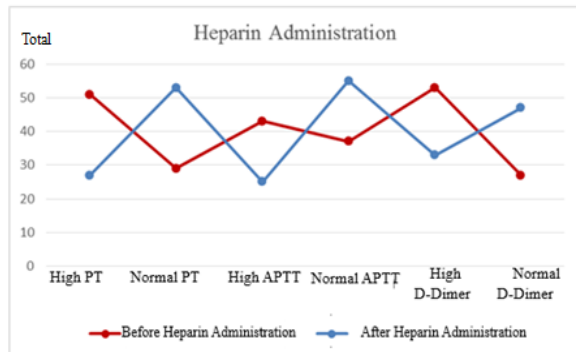


Figure 3 Parameters of PT, APTT and *D-Dimer* Levels on Heparin

Based on Figure 3, a decrease in PT and APTT levels as well as in *D-dimer* levels showed after heparin administration in COVID-19 patients. Most respondents with COVID-19 had a high PT value (63.75%) before heparin administration. Meanwhile, after heparin administration, there were 53 respondents with normal PT values (66.26%) and 27 respondents with high PT values (33.75%).

Before heparin administration, most respondents with COVID-19 had high APTT (long) values (53.75%). Meanwhile, after heparin administration, there were 55 respondents with normal APTT values (68.76%) and 25 respondents with high APTT values (31.25%). Before heparin administration, most respondents with COVID-19 had high (increase) *D-Dimer* levels (66.25%). After heparin administration, there were 47 respondents

with normal APTT values (58.75%) and 33 respondents with high APTT values (41.25%).

DISCUSSION

Parameters PT, APTT, and *D-Dimer* are blood tests to evaluate the patient's coagulation status. PT examination is to evaluate extrinsic coagulation factors, while PTT can detect the function of intrinsic coagulation factors and coagulation components. Both tests can help explain the cause of a bleeding or blood clotting disorder. APTT is part of PTT. The APTT panel is the endpoint of blood coagulation testing time that serves to assist in the diagnosis of coagulation factor deficiency in the intrinsic pathway. *D-Dimer* is a protein residue formed by the breakdown of blood clots. *D-Dimer* is a fibrin degradation product formed during the degradation of blood clots by fibrinolysis. Elevated *D-Dimer* in the blood is a marker of suspected thrombosis found in deep vein thrombosis, pulmonary embolism, arterial thrombosis, pregnancy, inflammation, chronic liver disease, cancer, surgery, vasculitis, and Disseminated Intravascular Coagulation (DIC) (19).

Prolonged PT, APTT, and increased *D-Dimer* values are often found in severe COVID-19 patients and are predictors *acute respiratory distress syndrome* (ARDS) occurrence, the need for care in the Intensive Care Unit (ICU), and death. Prolongation of

PT > 3 seconds or APTT > 5 seconds is a marker of coagulopathy (blood clotting disorder resulting in excessive bleeding) and a predictor of thrombotic complications in COVID-19 patients. COVID-19 patients with an increase in *D-Dimer* (3-4 times) need to be hospitalized even if there are no severe symptoms because it indicates there is an increase in thrombin generation and risk for thrombotic events. Efforts to prevent the occurrence of coagulopathy in these COVID-19 patients, it is necessary to provide prophylactic anticoagulants, namely Low Molecular Weight Heparin (LMWH) or Unfractionated Heparin (UFH) (20).

The results of this study are in line with coagulation parameter studies, namely *Prothrombin Time* (PT), *Activated Partial Thromboplastin Time* (APTT) and *D-Dimer*, which used a sample of 183 patients with 162 patients who survived. The study showed the average level of *D-Dimer* was 0.61 g/mL (normal: <0.5 g/mL), PT with a time of 13.6 seconds (normal: 11.5-14.5 seconds), and APTT with a time of 41.2 seconds (normal: 29-42 seconds). This study's results indicate an increase in coagulation levels among COVID-19 patients (21).

The results of this study are in line with study by Adie & Farina (21), that there is an increase in coagulation levels in COVID-19 patients, where the average *D-Dimer* level is 0.61 g/mL (normal: <0.5 g/mL), PT with a time of 13.6 seconds (normal: 11, 5-14.5

seconds), and APTT with a time of 41.2 seconds (normal: 29-42 seconds) (21).

The results of this study are in line with the study of Rusdiana & Akbar (22), which showed that the levels of *D-Dimer* in the five patients had varied patterns. In case 1, there was an increase in *D-Dimer* levels >2 mg/L in the middle of treatment, while cases 2 and 3 were stable with normal *D-Dimer* levels <2 mg/L, but at the time of the last examination, all patients' *D-Dimer* levels were normal < 2 mg/L after heparin administration and on discharge. In the group of patients who died, the *D-Dimer* levels were both > 7 mg/L. *D-Dimer* is derived from the lysis of cross-linked fibrin, where an increase in its level may indicate activation of coagulation and fibrinolysis (22).

Similar studies have also shown that an increase in *D-Dimer* >1.0 l/mL is the strongest predictor of mortality in COVID-19 patients (23). *D-Dimer* >1.5 l/mL was a predictor of venous thromboembolism in COVID-19 patients with a sensitivity of 85% and specificity of 88.5% (24).

The available evidence suggests that severe COVID-19 disease can lead to coagulopathy complications in the form of Disseminated Intravascular Coagulation (DIC), which is prothrombotic with a high risk of venous thromboembolism, where PT, APTT, and *D-Dimer* markers can be used as a parameter for blood coagulation disorders (24). Based on this, the experts recommend

anticoagulants, reflecting the recognition of clotting dysregulation in this situation (24) because of the effectiveness of heparin therapy (especially Low Molecular Weight Heparin / LMWH) for COVID-19 treatment therapy. Before heparin administration, most respondents had high or increased levels of *D-Dimer*, PT values, and APTT values. Therefore, after heparin administration, *D-Dimer* levels, PT values, and APTT values were decreased or became normal (25). The limitations of this research were the lack of monitoring of *D-Dimer*, PT, and APTT levels among COVID-19 patients with heparin administration. The recommendation for future research is to add parameters for evaluating the coagulation status of COVID-19 patients, such as C-Reactive Protein (CRP), ferritin, and Lactate Dehydrogenase (LDH) levels.

CONCLUSIONS

Heparin are widely used anticoagulants by inhibitit coagulation. In COVID-19

patients, *D-Dimer*, PT, and APTT values before heparin administration were high or increased. Meanwhile, after heparin administration, *D-Dimer*, PT, and APTT values levels were decreased or became normal.

AUTHOR CONTRIBUTIONS

Dela Yorike: validation, visualization, formal analysis. Muhammad Rizki Kurniawan: conceptualization, writing - review and editing, supervision. M. Syafaat: methodology, software.

ACKNOWLEDGEMENT

We would like to express special thanks of gratitude to Bhayangkara T.K.I Raden Said Sukanto Hospital for supporting this research.

CONFLICT OF INTEREST

All authors reported no conflict of interest.

REFERENCES

1. Indranila KS, Imam BW, Widjaja. Diagnostic tests for examination of plasma D-Dimer levels in the diagnosis of ischemic stroke. [Uji diagnostik pemeriksaan kadar D-Dimer plasma pada diagnosis stroke iskemik], Fakultas Kedokteran Universitas Diponegoro Semarang; 2010.
2. Burhanuddin B, Mansyur A, Agus A, Misnah. Examination of Prothrombin Time and Activated Partial Thromboplastin Time with Humaclot VA and Sysmex CA 500. [Pemeriksaan Prothrombin Time dan Activated Partial Thromboplastin Time dengan Humaclot VA serta Sysmex CA 500]. Fakultas Kesehatan Masyarakat UNHAS; 2012.
3. M Fariz Al-Hakim. Comparison of hemostatic parameters in COVID-19 and Non-COVID-19 Patients. [Perbandingan parameter hemostatis pada pasien COVID-19 dan Non COVID-19]. Fakultas kedokteran Universitas Sriwijaya; 2020.
4. Maria KRK, Nur F, Halbina FH. COVID-19 diagnostic examination. [Pemeriksaan diagnostik COVID-19]. Jurnal Keperawatan Muhammadiyah; 2020.
5. Rizki A, Taofik R. Recent developments in anticoagulant therapy in COVID-19 patients with severe symptoms. [Perkembangan terkini terapi antikoagulan pada pasien COVID-19 dengan gejala berat]. Jurnal Sains, Farmasi, dan Klinis; 2020.

6. Mochamat, Taufik EN, Famila. Use of High-dose Heparin in COVID-19 Patients with ARDS and hypertension in the Intensive Care Unit (ICU). [Penggunaan heparin dosis tinggi pada pasien COVID-19 dengan ARDS dan hipertensi di Unit Perawatan Intensif (ICU)]. *Jurnal Anestesiologi Indonesia*. Fakultas Kedokteran Universitas Diponegoro; 2020.
7. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood*. 2020; 135(23), 2033-2040.
8. Rangga V, Soesilowati D. Comparison of subcutaneous and intravenous heparin on D-Dimer Levels in the prevention of Deep Vein Thrombosis. [Perbandingan pemberian heparin subkutan dan intravena terhadap kadar D-Dimer pada pencegahan Deep Vein Thrombosis]. Semarang: Universitas Diponegoro: 2012
9. Yao Y, Cao J, Wang Q, Shi Q, Liu K, Luo Z, Chen X, Chen S, Yu K, Huang Z, Hu B. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. *Journal of intensive care*. 2020; 8 (1), 1-11.
10. Djoerban Z. Provision of Prophylactic Anticoagulants in Hospitalized Covid-19 patients. [Pemberian antikoagulan profilaksis pada pasien Covid-19 yang dirawat di Rumah Sakit]. Rekomendasi IDI. Jakarta, 2020.
11. Maharani C. Coronavirus Disease 2019/Covid-19. Program Karya Tugas Ilmiah Universitas Negeri Jakarta; 2020.
12. Siska M, Aldo DP, Yelvi L. Corona Disease 2019 (Covid-19) pathogenesis, clinical manifestations, and treatment options. [Corona Disease 2019 (Covid-19) Patogenesis], manifestasi klinis, dan pilihan terapi. *Jurnal Kedokteran dan Kesehatan*. Fakultas Kedokteran Universitas Surabaya; 2021.
13. Misnah M. The Role of Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) parameters. [Peran parameter Prothrombin Time (PT) dan Activated Partial Thromboplastin Time (APTT)]. *Jurnal Klinik Patologi*. 2020.
14. Sri T, Wahdaniah. The Role of Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) parameters. [Hubungan jumlah trombosit dengan Nilai Prothrombin Time (PT) dan Activated Partial Thromboplastin Time (APTT) Pada Persiapan Tindakan Operasi Caesar]. *Jurnal Laboratorium Khatulistiwa* 1. 2017;(1),8-12.
15. Himawan S, Danu S, Sigit K. Comparison of subcutaneous and intravenous heparin in coagulation and D-Dimer studies in patients at risk for venous thrombosis. [Perbandingan pemberian heparin subkutan dan intravena terhadap studi koagulasi dan D-dimer pasien dengan risiko trombosis vena]. *JAI (Jurnal Anestesiologi Indonesia)*. 2012; 4 (3), 164-170.
16. John WE, James CF, Jeffrey IW. A Test in Context: D-Dimer. *Journal American College Of Cardiology*. 2017; 70 (19), 2411-2420.
17. Ery L, Jati LP, Satrio AW. The Effect of deep vein thrombosis prophylaxis with subcutaneous and intravenous heparin on APTT and platelet count in critical patients in the ICU Dr. Kariadi Semarang. [Pengaruh profilaksis trombosis vena dalam dengan heparin subkutan dan intravena terhadap APTT dan jumlah trombosit pada pasien kritis di ICU RSUP Dr. Kariadi Semarang]. *JAI (Jurnal Anestesiologi Indonesia)*. 2012; 4 (3), 171-182.
18. Wael AM, Saad IM, Bassam A. Anticoagulation in COVID-19. *Eur Heart J Cardiovasc Pharmacother*. 2020; 6 (4), 260-261.
19. Gunawan ACV, Novita BD. Hyper-coagulation and the used of anticoagulant for patient with COVID-19. *Jurnal Widya Medika*, 2020; 6(2), 103-110.
20. Purba RT, Adhi MP, Kusumawardhani E, Hardian R, Tobing AL. Potential for giving Tocilizumab to COVID-19g in the ICU of Ulin Hospital Banjarmasin. [Potensi pemberian Tocilizumab pada pasien COVID-19 di ICU RSUD Ulin Banjarmasin]. *JAI (Jurnal Anestesiologi Indonesia)*. 2020; 12(3), 17-33.
21. Adie SK, Farina N. Impact of COVID-19 on monitoring of therapeutic unfractionated heparin. *Journal of Thrombosis and Thrombolysis*. 2021; 51(3), 827-829.
22. Rusdiana T, Akbar R. Recent developments in anticoagulant therapy in severely symptomatic Covid-19 Patients. [Perkembangan terkini terapi antikoagulan pada pasien Covid-19 Bergejala Berat]. *Jurnal Sains Farmasi & Klinis*. 2020; 7(3), 244-250.
23. Willim HA, Hardigaloe AT, Supit AI, Handriyani H. Coagulopathy in Coronavirus Disease-2019 (COVID-19). [Koagulopati pada Coronavirus Disease-2019 (COVID-19)]. *Intisari Sains Medis*. 2020; 11 (3): 749-756
24. Vlot EA, Van den Dool EJ, Hackeng CM, Sohne M, Noordzij PG, Van Dongen EPA. Anti Xa activity after high dose LMWH thrombosis prophylaxis in Covid-19 patients at the Intensive Care Unit. *Thrombosis Research*. 2020; 196, 1-3.
25. Van der Wal LI, Kroft LJM, Van Dam LF, Cobbaert CM, Eikenboom J, Huisman MV, de Jonge E. Early effects of unfractionated heparin on clinical and radiological signs and d-dimer levels in patients with COVID-19 associated pulmonary embolism: An observational cohort study. *Thrombosis Research*. 2021; 200, 130-132.

