

COVID-19 and Venous Thromboembolism

Murtuza Razi¹, Gu Jianping¹, He Xu¹, Mohammed Jameeluddin Ahmed¹

¹(Department of Interventional Radiology, Nanjing First Hospital Affiliated to Nanjing Medical University, China)

Abstract: Coronavirus disease 2019 or COVID-19 is a global health emergency declared by the WHO Emergency Committee. The clinical features exhibited of this pandemic disease consists of high grade fever, cough, fatigue, shortness of breath, flu like symptoms with loss of senses of taste and smell along with body aches which could proceed and evolve into severe respiratory disorders such as pneumonia, respiratory failure and may also result in other end-organ failure. Comorbidities that add to the severity or fatalities in COVID-19 include old age, hypertension, diabetes, hyperlipidaemia, pre-existing cardiovascular or respiratory diseases and organ and coagulation dysfunction. A number of coagulopathies such as Venous thromboembolism which is a very known and common disorder occurring in hospitalised patients is known to be a major factor which could contribute to high mortality rate. Venous thromboembolism is a vascular disease which comprises of deep vein thrombosis and pulmonary embolism. Prophylaxis with anticoagulation medications in COVID-19 patients with a no history of venous thromboembolism are known to have low fatality rates in severe COVID-19 pneumonia. This review article provides brief overview on COVID-19 its features, complications of venous thromboembolism in COVID-19 patients and its management in these infected patients

Date of Submission: 30-07-2020

Date of Acceptance: 15-08-2020

I. Introduction

Coronavirus disease 2019 is a very highly infectious disease due to infection with a virus called severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). This disease first detected in Wuhan, China now has evolved into an ongoing global health emergency [1]. Clinical features exhibited include high grade fever, cough, flu like symptoms, fatigue, body aches, shortness of breath and loss of sensation of smell and taste which may progress to become severe respiratory disorders like viral pneumonia, respiratory failure or end-organ failure [2][3][4]. Comorbidities like hypertension, hyperlipidaemia, diabetes, pre-existing cardiac and respiratory disorders results in high fatality or high mortality rates in COVID-19 patients alongside with lifestyle habits such as smoking and alcohol intake [5][6]. The disease mostly transmitted among people through close contact, primarily via droplet transmission by coughing and sneezing. Seldom, the infection could be acquired by touching the face with contaminated hands [6][7]. The incubation period of the disease varies from 3-14 days and in few cases symptoms have known to occur after 21 days as well, even though infection is possible before symptoms appear, and via asymptomatic patients as well [7]. The current gold standard for diagnosis is via real-time reverse transcription polymerase chain reaction (rRT-PCR) the sample for which is obtained via a nasopharyngeal swab [8]. High resolution Chest CT imaging has also proved to be key in diagnosis in individuals with high suspicions of infection is based on symptoms; however, it is recommended not to solely depend upon CT imaging as a routine screening modality [9][10][11]. Laboratory findings in COVID-19 patients include lymphocytopenia [12], mild thrombocytopenia, high CRP, prolonged Prothrombin time and increased D-dimer levels and fibrinogen in the early stages of the disease. Low levels of fibrinogen are seen to be complicated severe cases of COVID-19 [13] [14]. Venous thromboembolism (VTE), a common cardiovascular and respiratory complication seen among hospitalized patients, is one of the well-known sequelae of the illness. COVID-19 patients hospitalised are usually elderly, immobile, and display signs of coagulopathy [15]. Currently, the incidence rates of Venous thromboembolism are projected to be around 25% of patients admitted in the intensive care unit for COVID-19 even while undergoing prophylactic anticoagulant treatment [16] [17].

II. Venous Thromboembolism in COVID-19

Various ongoing studies suggest presence of hypercoagulable states in patients presenting with COVID-19 predominantly Venous thromboembolism. Venous Thromboembolism is a group of coagulation disorders, which comprises of two disorders namely deep vein thrombosis and pulmonary embolism. Deep vein thrombosis is a disorder in which the formation of blood clots occurs in the deep veins usually in the deep veins of the distal limbs, but then again it may also arise in other parts of the body as well [18] [19]. Venous thrombosis termed via the Virchow's triad which assumed three factors playing a key role in its formation and

propagation, the three factors include irregular blood flow, blood coagulation disorders and last of all the vessel wall abnormalities. The symptoms of venous thromboembolism include erythema, pain and edema [20] [21]. Patients infected with COVID-19 are reasonably often more inclined towards developing coagulation disorders more so in the ones that suffer the disease in its severe form. Coagulation disorders amongst COVID-19 patients is known to be associated with a high risk of death [22] [23]. In infections such as the corona virus, the human body through its innate immunity reaction induces a complex systemic inflammatory response. Commencement of this host defence mechanism results in consequent activation of coagulation pathway and generation of thrombin as an important communication factor between the humoral and cellular amplification pathways, an expression known as thromboinflammation or immunothrombosis [24] [25]. This results in release of enormous inflammation boosting cytokines which act on the liver thereby stimulating it into production of clotting factors [26] [2], for example fibrinogen levels in critically ill COVID-19 patients was found to be 10-14g/L [26]. In a study conducted among 16 COVID-19 infected patients with ARDS requiring mechanical ventilation by Ranucci confirmed and stated that elevated IL-6 levels were connected with elevated fibrinogen levels, thereby establishing and verifying the linkage between inflammation and procoagulant changes [27].

25% patients of the patients who do not receive any thromboprophylaxis have found to have developed venous thromboembolism [28] [29]. Elevated levels of D-dimers of $> 1.5\mu\text{g/ml}$ was seen in most of the patients thereby predicting its key role in Venous thromboembolism in COVID-19 patients [30] [31].

Pulmonary embolism is another noted thromboembolic event occurring in COVID-19 patients. The thrombi are formed in the pulmonary vasculature due to the local inflammatory processes instead of migrating from other parts of the body to the lungs [32]. It can be known that the activation of the coagulation pathway might perhaps take place through the contact system and kallikrein/kinin system (KKS) [33]. Even though it is thought to be a relatively late indication of severe COVID-19, it is important whether the apparent median period of 7 days to the onset of thrombotic event is rightly the median period after first onset of COVID-19 symptoms [34].

III. Thromboprophylaxis of Venous thromboembolism in COVID-19

In any acute and severe infections, there is a risk of incidence of venous thromboembolism (VTE) so hence thrombus prophylaxis at regular dosages is vital. Use of Low molecular weight heparins (LMWH), or unfractionated heparin (UFH) is ideally favoured over using direct oral anticoagulants (DOACs) which is due to occurrence of possible drug-drug interactions with associated antiviral drugs such as anti-HIV protease inhibitors like ritonavir or associated use of antibacterial medications such as azithromycin. Generally, without the necessity for alteration of the dosages of low molecular weight heparin (LMWH) on event of thrombocytopenia, though generally in few individuals needless to say at all times shall be well-adjusted against the risk of bleeding [35].

Infected patients at risk of developing thrombosis, it is crucial to not miss the occasional risk of Pulmonary embolism (PE) amongst patients with high risk probability, the treatment plan in stable patients is unlike the unstable patients. The treatment option preferred in unstable patients is reperfusion therapy which is done by thrombolysis and unfractionated heparin (UFH) [26]. Most of the COVID-19 patients have an out-and-out or a relative opposition to thrombolysis, which may be due to associated complications such as coagulation disorders, thrombocytopenia or a history of recent invasive procedure. [4, 14, 36].

The anticoagulation routine among the stable Pulmonary embolism (PE) patients generally involves using Low molecular weight heparin (LMWH) or direct oral anticoagulants (DOACs). Among patients associated with intermediate-/high-risk PE, Unfractionated heparin (UFH) can also be considered ideal owing to its short half-life and the advantage of administering the patients with protamine sulfate as an antidote in case of instances of need for performing an urgent procedure or bleeding. Inferior vena cava filters can be considered in certain patients with acute PE and complete contraindication to anticoagulation, or in case of recurrence in spite of proper anticoagulant treatment [37]. Regarding the initiation of treatment, the current European Society of Cardiology (ESC) PE guidelines [37] highlights the need of initiation of anticoagulation treatment in all suspected high or intermediate risk patients for PE without any holdup, while diagnostic workup to confirm the diagnosis is in progress.

IV. Conclusion

In COVID-19 patients, venous thromboembolism presents a unique challenge to an already unique illness. After the diagnosis is confirmed, one needs to plan out starting full-dose anticoagulation and the risk associated by the diagnostic workup. At present only two studies are available describing an incidence of 27% for VTE in COVID-19 patients hospitalized in the ICU receiving prophylactic case reports. Further data and evidence regarding the disease will surely be available in the immediate future. COVID-19 as of now still stands as a major, lengthy, complex, and at times fatal threat. Sometimes in the cases with VTE, mostly due to the risk of underdiagnoses and under treatment and possible progression to PE may occur. Hence, it is important

to understand the significance and the perceptible burden of VTE in these patients, and the need to formulate an appropriate treatment strategy in these extraordinary situations, cannot be underplayed. A proper treatment protocol for COVID-19 isn't available as of now, but VTE is a well-established clinical disorder, with avertable and curable consequences. Further studies are required to be conducted to obtain a stronger insight into their efficacy and a model needs to be formulated to ensure their implementation and achieve better results in management of VTE in COVID-19 patients.

Conflict of Interest

The authors have no conflict of interest.

References

- [1]. TanuSinghal. A Review of Coronavirus Disease-2019 (COVID-19). The Indian Journal of Pediatrics (April 2020) 87(4):281–286. <https://doi.org/10.1007/s12098-020-03263-6>
- [2]. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395(10223):497–506.
- [3]. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020.
- [4]. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020.
- [5]. Xu XW, Wu XX, Jiang XG, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. *BMJ*. 2020;368:m606.
- [6]. CelestinoSardu, Jessica Gambardella, Marco Bruno Morelli, Xujun Wang, Raffaele Marfella and Gaetano Santulli. Hypertension, Thrombosis, Kidney Failure, and Diabetes: Is COVID-19 an Endothelial Disease? A Comprehensive Evaluation of Clinical and Basic Evidence. *J. Clin. Med.* 2020, 9, 1417
- [7]. "Q&A on coronaviruses (COVID-19)". World Health Organization. 17 April 2020. Archived from the original on 14 May 2020. Retrieved 14 May2020.
- [8]. "Interim Guidelines for Collecting, Handling, and Testing Clinical Specimens from Persons for Coronavirus Disease 2019 (COVID-19)". U.S. Centers for Disease Control and Prevention (CDC). 11 February 2020. Archived from the original on 4 March 2020. Retrieved 26 March 2020.
- [9]. Chan JF-W, Yuan S, Kok K-H, To KK-W, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* 2020.
- [10]. Lei J, Li J, Li X, Qi X. CT imaging of the 2019 novel coronavirus (2019-nCoV) pneumonia. *Radiology* 2020:200236.
- [11]. Huang P, Liu T, Huang L, et al. Use of chest CT in combination with negative RT-PCR assay for the 2019 novel coronavirus but high clinical suspicion. *Radiology*. 2020.
- [12]. Lippi G, Plebani M, Michael Henry B. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. *Clin ChimActa* 2020.
- [13]. Lippi G, Favaloro EJ. D-dimer is associated with severity of coronavirus disease 2019 (COVID-19): a pooled analysis. *ThrombHaemostIn press*.
- [14]. P. Demelo-Rodríguez, E. Cervilla-Muñoz, L. Ordieres-Ortega, et al., Incidence of asymptomatic deep vein thrombosis in patients with COVID-19 pneumonia and elevated D-dimer levels, *Thrombosis Research* (2020), <https://doi.org/10.1016/j.thromres.2020.05.018>
- [15]. Zhou F, Yu T, Du R et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020.
- [16]. Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. *J ThrombHaemost*2020;(May).10.1111/jth.14888. 32369666
- [17]. Karen R. Bruni-FitzgeraldMSN, RN, NP, CVN. Venous thromboembolism: An overview. *Journal of Vascular Nursing*, Volume 33, Issue 3, September 2015, Pages 95-99.
- [18]. Bevis PM, Smith FCT. Deep Vein Thrombosis. *Surgery (Oxford)* 2016; 34(4):159-64.
- [19]. Min S-K, Kim YH, Joh JH, Kang JM, Park UJ, Kim HK, et al. Diagnosis and Treatment of Lower Extremity Deep Vein Thrombosis: Korean Practice Guidelines. *Vasc Specialist Int*. 2016;32(3):77-104.
- [20]. Mark O, Robert C. Deep Venous Thrombosis. *Emergency Medicine Clinics of North America* 2017; Vol 35(4): 743-70.
- [21]. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020 Mar 13. doi: 10.1001/jamainternmed.2020.0994.
- [22]. Guan W-J, Ni Z-Y, Hu Y et al (2020) Clinical characteristics of Coronavirus disease 2019 in China. *N Engl J Med*. <https://doi.org/10.1056/NEJMoa2002032>
- [23]. Jean M. Connors, MD; Jerrold H. Levy, M.D., FAHA, FCCM. COVID-19 and its implications for thrombosis and anticoagulation. *Blood*. 2020 Jun 4;135(23):2033-2040. doi: 10.1182/blood.2020006000.
- [24]. Jackson SP, Darbousset R, Schoenwaelder SM. Thromboinflammation: challenges of therapeutically targeting coagulation and other host defense mechanisms. *Blood* 2019;133:906-18.
- [25]. Jacqui Wise. Covid-19 and thrombosis: what do we know about the risks and treatment? *BMJ* 2020;369:m2058 doi: 10.1136/bmj.m2058 (Published 21 May 2020)
- [26]. Ranucci M, Ballotta A, Di Dedda U, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. *J ThrombHaemost* 2020.
- [27]. Tal S, Spectre G, Kornowski R, Perl L. Venous Thromboembolism Complicated with COVID-19: What Do We Know So Far? [published online ahead of print, 2020 May 12]. *Acta Haematol*. 2020;1-8. doi:10.1159/000508233
- [28]. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J ThrombHaemost*. 2020. <https://doi.org/10.1111/jth.14830>.
- [29]. AnastasiosKollias, Konstantinos G. Kyriakoulis, Evangelos Dimakakos, GaryphalliaPoulakou, George S. Stergiou and Konstantinos Syrigos, Thromboembolic risk and anticoagulant therapy in COVID-19 patients: emerging evidence and call for action. *BJ Haem Volume*189, Issue5,June 2020,Pages 846-847. <https://doi.org/10.1111/bjh.16727>

- [30]. Tomasz J. Guzik, Saidi A. Mohiddin, Anthony Dimarco, Vimal Patel, Kostas Savvatis, Federica M. Marelli-Berg, Meena S. Madhur, Maciej Tomaszewski, Pasquale Maffia, Fulvio D'Acquisto, Stuart A. Nicklin, Ali J. Marian, Ryszard Nosalski, Eleanor C. Murray, Bartłomiej Guzik, Colin Berry, Rhian M. Touyz, Reinhold Kreutz, Dao Wen Wang, David Bhella, Orlando Sagliocco, Filippo Crea, Emma C. Thomson, Iain B. McInnes. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. *Cardiovasc Res.* 2020 Apr 30; cvaa106. doi: 10.1093/cvr/cvaa106
- [31]. F. Ciceri, L. Beretta, A.M. Scandroglio, S. Colombo, G. Landoni, A. Ruggeri, J. Peccatori, A. D'Angelo, F. De Cobelli, P. Rovere-Querini, M. Tresoldi, L. Dagna, A. Zangrillo, Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): an atypical acute respiratory distress syndrome working hypothesis, *Crit. Care Resusc.* (2020)
- [32]. A.H. Schmaier, The contact activation and kallikrein/kinin systems: pathophysiologic and physiologic activities, *J. Thromb. Haemost.* 14 (1) (2016) 28–39.
- [33]. F.A. Klok, M. Kruip, N.J.M. van der Meer, M.S. Arbous, D. Gommers, K.M. Kant, F.H.J. Kaptein, J. van Paassen, M.A.M. Stals, M.V. Huisman, H. Endeman, Incidence of thrombotic complications in critically ill ICU patients with COVID-19, *Thromb. Res.* (2020). <https://doi.org/10.1016/j.thromres.2020.04.013>
- [34]. Marco Cattaneo, Elena M. Bertinato, Simone Bircocchi, Carolina Brizio, Daniele Malavolta, Marco Manzoni, Gesualdo Muscarella, Michela Orlandi. Pulmonary Embolism or Pulmonary Thrombosis in COVID-19? Is the Recommendation to Use High-Dose Heparin for Thromboprophylaxis Justified? *Thromb Haemost.* 2020 Apr 29. doi: 10.1055/s-0040-1712097.
- [35]. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease: CHEST Guideline and Expert Panel Report. *Chest.* 2016 Feb; 149(2): 315–52.
- [36]. Phend C. Anticoagulation Guidance Emerging for Severe COVID-19 [cited 2020 Apr 9]. *Infect Dis.* 2020. Available from: <https://www.medpagetoday.com/infectiousdisease/covid19/85865>.
- [37]. European Society of Cardiology. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC) [cited 2020 Apr 7]. Available from: <https://academic.oup.com/eurheartj/article/41/4/543/5556136>.

Murtuza Razi, et. al. "COVID-19 and Venous Thromboembolism." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 19(8), 2020, pp. 45-48.