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Pulmonary Embolism in Covid-19 Pandemic: A Threat to Recovery of the Infected Patients

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus 2 is a new type of coronavirus that can cause Coronavirus Disease 2019 (Covid-19) and is associated with an increased risk of thrombosis-related pulmonary embolism. Globally, doctors have revised their management strategies for

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suspected and confirmed PD in patients with Coronavirus disease (Covid-19) in 2019. Choosing the right drug and the right dose requires consideration of potential comorbidities, which can be explained by the direct and indirect pathological consequences of Covid-19, complement activation, cytokine release, endothelial dysfunction, and the interaction between different types of blood cells. Discuss the pathophysiological events, therapeutic mortality strategies, risk factors and clinical management of patients with Covid-19 pulmonary embolism.

Keywords:Pulmonary embolism; Covid 19 pandemic; haemostasis; threat to recovery.

1. INTRODUCTION

SARSCoV2 appears to use angiotensin-converting enzyme receptor 2 to enter lung cells [1]. These proteins are also expressed in endothelial cells, so this cell type may be a virus target [2]. In addition, a large number of severely ill patients with Covid-19 have hypoxia, which can lead to thrombosis by increasing blood viscosity and increasing systemic inflammation [3]. Patients with severe pneumonia caused by Covid-19 can cause sepsis and can induce the release of inflammatory cytokines (such as IL6, IL8, TNFα, etc.), which can promote the activation of hypercoagulable state [4]. Some patients even have more prominent inflammation, which is related to increase D-dimer levels [5]. Since the onset of Coronavirus Disease (Covid-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCoV2) infection in 2019, there have been several reports describing severe procoagulant events in these patients, including life-threatening pulmonary embolism [6,7]. Abnormalities in various coagulation parameters are often reported and are related to poor prognosis [8]. Unfortunately, due to the lack of large-scale prospective studies in this area, little is known about the epidemiology and pathophysiological mechanisms of Covid-19-related PD. Understanding these aspects is essential for the early diagnosis and proper management of this potentially fatal complication. Especially the optimal dose and the duration of preventive anticoagulation are the main problems. In fact, it is reported that despite thrombosis prevention, severely ill patients with Covid-19 still develop PD, questioning the possible effect of implementing higher thrombosis prevention doses than used in standard practice [9]. Pulmonary embolism (PE) is a blood clot that forms in a blood vessel in the body (usually in the legs). It then enters the pulmonary artery, where it suddenly blocks blood flow. The current literature on this topic defines the epidemiology, possible underlying pathophysiological mechanisms, mortality, risk factors, and therapeutic importance of Covid-19-related PD.

2. EPIDEMIOLOGY

The incidence of PE in hospitalized patients with Covid-19 is reported to be approximately 1.9% to 8.9% [10-13]. Interestingly, when the follow-up increased from 1 week to 2 weeks, the incidence of PE increased to 33.3%. At this time, increased awareness of the common occurrence of PD may lead to a higher index of suspicion and more diagnostic procedures to detect these types of complications [14]. Few cohort studies have reported the epidemiology of PD in Covid-19 patients, regardless of the severity of the disease and the need for hospitalization. The prevalence of pulmonary embolism is frequently reported in Covid-19 and is often seen in Covid-19 patients without other standard risk factors, indicating that it is an independent risk factor for VTE [7]. Data from previous experience in France show that the prevalence of PD in patients with severe Covid-19 infection is 23%. The requirement for mechanical ventilation is also closely related to the presence of PE on imaging [10]. There is currently no evidence to define the incidence of PE after rehabilitation [15].

High-level PE physiopathology observed in patients with Covid-19 observed in patients with Covid-19, not only continues to systemic inflammation but also reflects the true thrombotic diseases induced by cellular activation caused by viruses [16]. In addition, a split of 3.0 μg / ml for d-dimer had 76.9%, 94.9% and 92.5% sensitivity, specificity and negative predicted value to predict VTE. After receiving anticoagulation therapy, the D-dimer level decreases gradually, and D-dimer levels only predict thrombosis but also to monitor the effectiveness of the anticoagulant. Viral infections are predisposed to VTE and the systemic inflammatory response can be activated, which causes an imbalance between the influence of the accelerator and the influence of the anticoagulant. The coagulation pathway

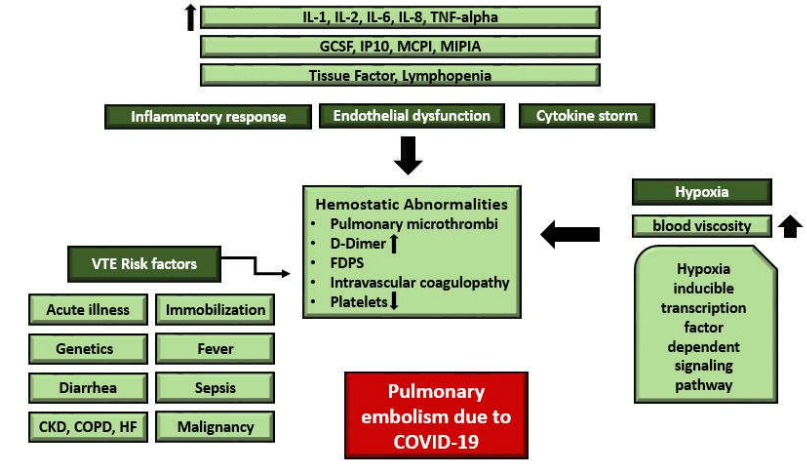

Fig. 1. Schematic diagram of the possible pathophysiological mechanism

and the Immune system are strictly connected. Thrombin and platelets play an important role in the relationship between the immune system and coagulation. On the one hand, thrombin directly links the coagulation path to the congenital immune response [17]. The infiltration of the virus causes inflammation of the lungs that induces the local activation of the haemostasis driven by the interaction between platelets and endothelia, which causes pulmonary inflammation to induce pulmonary vigorous inflammation [18]. It is presumed that the generation of Microslobe in Covid19 is associated with the dysfunction of endothelial cells [19,20]. Some mechanisms can contribute to the hyperacy state between Covid- 19 [21] and PMT (Fig. 1).

Fig. 1 Schematic diagram of the possible pathophysiological mechanism of pulmonary embolism (PE) in patients with coronavirus disease 2019 (Covid-19). CD: CD receptor, CKD: chronic renal failure, COPD: chronic obstructive pulmonary disease, FDP: fibrin degradation products, GCSF: granulocyte colony stimulating factor, HF: heart failure IFN: interferon, IL: interleukin, PI: Interferon-inducing protein, MCP: Monocyte chemotactic protein, MIP: Macrophage inflammatory protein, NK: Natural killer cell, PT: Prothrombin time, SARS CoV2: Coronavirus 2 Acute respiratory syndrome, TNF Alpha: Tumor Necrosis Factor Alpha [22].

2.1 Pathological Events of Pulmonary Embolism Caused by Covid-19

However, there is currently no strategy to understand pulmonary embolism, but by understanding the coagulation pathway and identifying its markers, we can diagnose PD early, and follow-up events can better understand pulmonary embolism and thrombosis formation leads to pulmonary embolism.

2.2 Crosstalk between Endothelial Dysfunction and Haemostasis

Covid-19 has worse clinical results in patients with endothelial dysfunction-related diseases (such as systemic hypertension, diabetes, and obesity), and there is evidence in the Covid-19 autopsy series that endothelial dysfunction [23,24]. The mechanism of endothelial dysfunction can be caused by SARS CoV2 directly invading endothelial cells or indirect inflammation [24]. The initiation of the host serine protease TMPRSS2 promotes the binding of the SARS CoV2 peak protein to the ACE2 receptor, followed by viral endocytosis and replication [25]. Subsequent endothelial damage and virus release will trigger a significant immune response, which can lead to further endothelial dysfunction.

2.3 Overview of Haemostasis

Endothelial injury and destruction of cell-to-cell connections in Covid-19 exposed the subendothelial matrix containing tissue factor (TF) and collagen [26]. This activates the clotting cascade and leads to the production of thrombin and the conversion of fibrinogen to fibrin, which together with the aggregates of platelets form a blood clot. Markers of endothelial activation (VWF, FVIII, Pselectin) are increased in Covid-19, and elevated soluble thrombomodulin (an

endoglin) and VWF are associated with poor clinical outcomes [27].

2.4 Plasminogen Activator Inhibitor 1 (PAI1)

Plasminogen Activator Inhibitor 1 (PAI1) Fibrinolysis inhibitors are increased in infections with COVID19, SARSCoV1, and other ARDS etiologies marked by insufficient fibrinolysis and fibrin deposition [28]. Inflammation promotes the release of PAI1 from endothelial cells, preventing urokinase-plasminogen activator and tissue plasminogen activator (tPA) from converting plasminogen into plasmin, which ultimately leads to reduced fibrin degradation [3,4] .

2.5 Platelets

The rupture of the endothelial layer exposes the subendothelial matrix containing collagen and leads to platelet activation and recruitment [29]. Subsequent platelet degranulation and aggregation will produce platelet plugs that serve as adhesion sites for clotting factors [30]. Platelet activation markers in COVID-19 (such as pselectin, soluble CD40L) are increased and pselectin can induce TF expression in monocytes, resulting in a procoagulant phenotype [31].

2.6 Hypoxia

Hypoxia occurs in moderate to severe COVID-19, which can lead to endothelial dysfunction and hypercoagulable state [32]. Upregulation of endothelial P-selectin and adhesion molecules (eg, Intercellular Adhesion Molecule 1 (ICAM1)) during hypoxia leads to the recruitment of platelets and leukocytes [33]. Monocytes bind to activated endothelial cells through P-selectin glycoprotein ligand 1, and also express TF and other pro-thrombotic factors [34].

2.7 Vascular Cell Adhesion Molecule 1 (VCAM1)

The expression of hypoxia-induced adhesion molecules, namely Pselectin, Eselectin, ICAM1, and vascular cell adhesion molecule 1 (VCAM1), destroys the endothelium. Subsequent increase in microvascular permeability exposes the subendothelial matrix and rapidly induces thrombosis [33]. Alveolar and tissue hypoxia in severe Covid-19 can initiate the cyclooxygenase (COX) pathway in endothelial cells; COX-induced combination of thromboxane A2 and B2 with prostaglandin thromboxane receptors triggers vascular smooth muscle cell contraction [30].

2.8 Other Mechanisms of Thrombosis

Other mechanisms are said to be related to thrombosis in Covid-19. The elevated levels of ferritin in Covid-19 may reflect cell damage and cause inflammation [35]. High levels of ferritin can adversely affect mitochondria, leading to the release of reactive oxygen species and cell death [30]. Mitochondrial platelet dysfunction can lead to inflammation and a pre-thrombotic state [36].

2.9 The Pulmonary Embolism Signal Molecule

First, the direct and indirect pathological consequences of Covid-19, such as severe hypoxia, pre-existing comorbidities, and related organ dysfunction, can lead to abnormal hemostasis, including disseminated intravascular coagulation (DIC) [37]. Hypoxia can induce thrombosis through increased blood viscosity and hypoxia-induced transcription factor-dependent signaling pathways [38]. Second, endothelial dysfunction, elevated von Willebrand factor (vWF), activation of the Toll-like receptor, and activation of the tissue factor pathway can induce pro-inflammatory and procoagulant effects through complement activation and cytokine release, which leads to disorders of the coagulation cascade. Subsequently, intraalveolar or systemic fibrin clots are formed [14,39]. 3. Elevated plasma levels of pro-inflammatory cytokines (IL2, IL6, IL7, IL8, granulocyte colony-stimulating factor, interferon-gamma-inducible protein 10 (IP10), monocyte chemoattractant protein 1 (MCP1), macrophage inflammation Protein release 1A (MIP1A)) and tumor necrosis factor (TNFα), the so-called "cytokine storm", is a common feature of sepsis. It is secondary to hemophagocytic lymphohistiocytosis and activates coagulation function and increases blood vessels. The risk of internal microthrombosis and secondary local wasting coagulopathy promotes the development of VTE [17]. Finally, the interaction between different types of blood cells (macrophages, monocytes, endothelial cells, platelets, and lymphocytes) can play an important role in the procoagulant effect of viral infections [22].

2.10 Pulmonary Embolism and Covid-19 Treatment Strategies

Anticoagulants, clot dissolving agents (thrombolytics), clot removers and venous filters

are all included in the treatment strategy. ISTH and the American Society of Hematology (ASH) recently recommended that all patients with suspected Covid19 or confirmed admission should start prophylactic doses of LMWH (40 mg per day) or subcutaneous injections of unfractionated heparin (5000 IU 3 times per day)[37,40,41]. For patients with known heparin-induced thrombocytopenia, fondaparinux sodium should be used. It has been found in animal models to effectively reduce sepsis-related coagulopathy. For patients with multiple risk factors for VTE and critically ill patients, medium-dose LMWH can be considered alone (for example, enoxaparin 4000 IU subcutaneously every 12 hours), because of the higher incidence of PE in this population [42-44]. In obese patients, higher doses may need to be increased based on body weight, 7500 IU UFH 3 times a day or 40 mg enoxaparin 2 times a day [45,46]. LMWH (for example, subcutaneous injection of enoxaparin 100 IU/kg twice daily or 150 IU/kg once daily, or nadroparin 86 IU/kg twice daily) is used as first-line treatment [47].

Despite the best anticoagulation therapy and the recurrence of clinically significant VTE in the case of absolute contraindications to anticoagulation therapy, PE is one of the few cases in which the application of inferior vena cava filters can be considered. Even in these cases, anticoagulation should be resumed as soon as possible [37,48].

2.11 Post-Discharge Strategy

Due to the procoagulant effect of Covid-19, apparently stable and asymptomatic patients may continue for several weeks after discharge. Therefore, among Covid-19 patients who are readmitted after initial hospitalization, PD is suspected to be prudent in clinical practice. After discharge from the hospital for acute medical conditions, the decision to extend preventive treatment for LMWH should be made by balancing the reduced risk of VTE with the increased risk of bleeding episodes (including major bleeding). In the absence of high-quality data, drug prophylaxis in this setting should be reserved for patients at higher risk, including those with mobility problems and a history of VTE or active malignancies [37]. According to the recommendations of the Italian Society of Thrombosis and Haemostasis (SISET), preventive anticoagulation therapy should be administered at home for 7 to 14 days after discharge or during the pre-hospital phase of self-isolation to prevent risk factors for VTE. Existing or persistent (ie, inconvenience, body mass index (BMI)> 30, previous VTE, active cancer, etc.) [22].

2.12 Risk Factors

Genetic diseases, genetic problems, such as Factor V Leiden, abnormal blood vessels such as varicose veins, certain diseases such as cancer or heart disease, pregnancy or within 6 weeks postpartum, smoking, obesity, prolonged bed rest, major surgery or trauma, Oral contraceptives/hormonal drugs, age factors (70 years or older), people with a history of thrombosis and not taking prescription blood thinners are at increased risk of pulmonary embolism. The coexistence of pneumonia and PE has been known for many years and remains a diagnostic challenge today [49]. Data from the international RIETE cohort show that patients with respiratory infections have a higher risk of PD than patients with other types of infections [50]. Other studies have shown that as many as 90% of patients admitted to the hospital for pneumonia have elevated procoagulant markers, and D-dimer is the most common one [51]. D-dimer is a very useful biomarker that can exclude PD in the general population when the clinical probability is low. However, it is usually not helpful in diagnosing the presence of PD, because other inflammatory conditions increase its value. In addition, this biomarker is not sufficient to exclude or confirm PD in patients with pneumonia who also have elevated D-dimer levels [52,53]. The same situation seems to occur in the Covid-19 disease [52].

There are many risk factors for thrombosis, but they are generally considered to be caused by three key mechanisms (Virchow's triad); endothelial injury, reduced blood flow/stasis, and hypercoagulable state [54]. Although there are many unknowns about this new disease, more and more experience shows that patients with severe Covid-19 infection have all three elements [15] [5]. After being discharged from the hospital for the first time, it was also observed that our patients had mobility problems, exercise difficulties, and fatigue easily. Obesity is a risk factor for VTE, which explains the risk of thromboembolism [15].

2.13PD Mortality Rate

With more and more reports of PD after Covid-19 infection, studies have shown that among the 1,835 Covid-19 patients, nearly two out of ten

patients develop PD. Fixation, inflammation, coagulation activation, and fibrinolysis have been proposed to explain the development of PD in Covid-19 patients; however, the incidence of PE in Covid-19 patients is higher than that of pandemic and seasonal influenza patients (3%) [55]. In addition, compared with general cases, the mortality rate of Covid-19 patients with PD can reach up to 45% (in-hospital mortality rate is 4%) [56]. Therefore, front-line health care professionals should be wary of severe and life-threatening complications of PD in patients with Covid-19 [57,58].

2.14 Diagnosis of Pulmonary Embolism

Pulmonary embolism can be difficult to diagnose, especially in people with underlying heart or lung disease. For this reason, your doctor may review your medical history, perform a physical examination, and perform one or more of the following tests, including blood tests; Ddimer, a substance that dissolves clots, chest X-rays, magnetic resonance imaging, Computed tomography pulmonary angiography, ultrasound, ventilation-perfusion scan (V/Q scan) and pulmonary angiography.

2.15 Covid-19 Blood Markers of Coagulation, Fibrinolysis and Inflammation

Covid-19 patients may have mild thrombocytopenia, slightly prolonged prothrombin time, increased fibrinogen and increased D-dimer (Table 1), all of which are The blood pressure rises and becomes more pronounced [59]. It is a fibrin degradation product that is sensitive to fibrinolysis for detecting intravascular thrombus (ie VTE), but lacks specificity, and may increase in inflammation and other diseases [60]. Elevated D-dimer may be related to acute lung injury caused by covid-19, which is produced by the degradation of fibrin in the alveoli deposited in ARDS [24,61]. Other markers of clotting and inflammation in COVID19 can also be abnormal, such as ferritin, von Willebrand factor (VWF), C-reactive protein (CRP), complement, and cytokines (Table 1). This suggests that the complex interaction between the haemostatic system and the immune system can lead to a thrombotic phenotype.

2.16 Clinical Management of Pulmonary Embolism

Once PD has been diagnosed, it is recommended to use composite materials that include clinical manifestations, systolic blood pressure, heart rate, respiratory rate, oxygen demand, PD severity index or PD severity index simplified, RV dysfunction imaging (CTA) Perform standard risk stratification or echocardiography) and / or biomarkers (troponin, brain natriuretic peptide, or NTprobrain natriuretic

Table 1. **Blood markers of coagulation, fibrinolysis and inflammation in Covid-19**

Blood Test	Direction of change	Reference
aPTT	→	[35]
Complement ↑	↑	[62]
Factor VIII ↑	↑	[27]
PAI-1 ↑	↑	[28]
VWF	↑	[27]
Soluble P-selectin	↑	[27]
Leucocytes	↑	[63]
Lymphocytes	↓	[63]
CRP	↑	[63]
Ferritin	↑	[35]
Platelets	→ / ↓	[64]
Neutrophils	↑	[63]
PT	→ / ↑	[63]
Procalcitonin	↑	[35]
D-Dimer	↑	[59]
Fibrinogen	↑	[59]
Antithrombin	→ / ↑	[27]

peptide). Elevated troponin can be seen in COVID19 infection, which can confuse its clinical utility. Similarly, Covid-19-associated cardiomyopathy may be another cause of RV dysfunction. However, the presence of cardiomyopathy does not rule out concurrent PE and, in fact, it may be an independent risk factor for PE based on low cardiac output. Risk stratification should consider the relative contribution of lower respiratory tract infection by Covid-19 and PE as causes of respiratory failure [23,64-66].

3. CONCLUSIONS AND FUTURE PERSPECTIVES

Most of the Covid-19 studies are cross-sectional studies of patients with more serious diseases. To fully understand the crosstalk of immune hemostasis leading to pulmonary embolism, longitudinal measurements are needed in different cohorts, which will guide the best time and cohort when intervention will be beneficial. A greater understanding of the complex pathobiological interactions between the immune system and haemostasis in Covid-19 will help develop new treatments and reduce the effects of off-target regulation.

CONSENT

It is not approval.

ETHICAL APPROVAL

It is not approval.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Kumar V et al. COVID-19 pandemic: mechanism, diagnosis, and treatment. 2021;96(2):299-308.
2. Yesudhas D, SrivastavaA, GromihaMMJI, COVID-19 outbreak: history, mechanism, transmission, structural studies and therapeutics. 2020:1-15.
3. Guo T, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). 2020;5(7):811-818.
4. de Lucena TMC et al. Mechanism of inflammatory response in associated comorbidities in COVID-19. 2020;14(4):597-600.
5. Blokhin IO, LentzSRJCoih. Mechanisms of thrombosis in obesity. 2013;20(5):437.
6. Chen Q, et al. Clinical characteristics of 145 patients with corona virus disease 2019 (COVID-19) in Taizhou, Zhejiang, China. 2020;48(4):543-551.
7. Danzi, G.B., et al., Acute pulmonary embolism and COVID-19 pneumonia: a random association? 2020;41(19):1858-1858.
8. Cui, S., et al., Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. 2020;18(6):1421-1424.
9. Helms J, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. 2020;46(6):1089-1098.
10. Grillet F, et al., Acute pulmonary embolism associated with COVID-19 pneumonia detected with pulmonary CT angiography. 2020;296(3):E186-E188.
11. Lodigiani C, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. 2020;191:9-14.
12. Galeano-Valle F et al. Antiphospholipid antibodies are not elevated in patients with severe COVID-19 pneumonia and venous thromboembolism. 2020;192:113-115.
13. Stoneham SM et al. Thrombotic risk in COVID-19: a case series and case–control study. 2020;20(4):e76.
14. Klok F et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. 2020;191:145-147.
15. Vadukul P, SharmaDS, VincentPJBcrC, Massive pulmonary embolism following recovery from COVID-19 infection: inflammation, thrombosis and the role of extended thromboprophylaxis. 2020 ;13(9):e238168.
16. Oudkerk M et al. Diagnosis, prevention, and treatment of thromboembolic complications in COVID-19: report of the National Institute for Public Health of the Netherlands. 2020;297(1):E216-E222.
17. Maas C, RennéTJB. The Journal of the American Society of Hematology, Coagulation factor XII in thrombosis and inflammation. 2018;131(17):1903-1909.
18. Thachil J, SrivastavaA. Maintaining Hemostasis and Preventing Thrombosis in

COVID-19—Part I: SARS-2 Coronavirus–Associated Hemostatic Lung Abnormality in COVID-19: Is It Pulmonary Thrombosis or Pulmonary Embolism? in Seminars in Thrombosis and Hemostasis.. Thieme Medical Publishers; 2020.
19. Varatharajah N, RajahSJFP. Microthrombotic complications of COVID-19 are likely due to embolism of circulating endothelial derived ultralarge von willebrand factor (eULVWF) decorated-platelet strings. 2020;37(6):258.
20. Mosleh W et al. Endotheliitis and endothelial dysfunction in patients with COVID-19: its role in thrombosis and adverse outcomes. Multidisciplinary Digital Publishing Institute; 2020.
21. Rouhezamin MR, HaseliSJAr. Diagnosing pulmonary thromboembolism in COVID-19: a stepwise clinical and imaging approach. 2020;27(6):896.
22. Sakr Y et al. Pulmonary embolism in patients with coronavirus disease-2019 (COVID-19) pneumonia: a narrative review. 2020;10(1):1-13.
23. Rosovsky, R.P., et al., Diagnosis and treatment of pulmonary embolism during the COVID-19 Pandemic: a position paper from the National PERT Consortium; 2020.
24. Ackermann M et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. 2020;383(2):120-128.
25. Djomkam ALZ, et al. Commentary: SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. 2020:10.
26. Shubha C. Citation metadata; 2020.
27. Goshua G. et al. Endotheliopathy in COVID-19-associatedcoagulopathy: evidence from a single-centre, cross-sectional study. 2020;7(8):e575-e582.
28. Whyte CS, et al. Fibrinolytic abnormalities in acute respiratory distress syndrome (ARDS) and versatility of thrombolytic drugs to treat COVID-19. 2020;18(7):1548-1555.
29. Golebiewska EM, PooleAWJBr. Platelet secretion: From haemostasis to wound healing and beyond. 2015;29(3):153-162.
30. Loo J, SpittleDA, NewnhamMJT, COVID-19, immunothrombosis and venous thromboembolism: biological mechanisms. 2021;76(4):412-420.
31. Hottz ED et al. Platelet activation and platelet-monocyte aggregate formation trigger tissue factor expression in patients with severe COVID-19. 2020;136(11):1330-1341.
32. Price LC et al. Thrombosis and COVID-19 pneumonia: the clot thickens! Eur Respiratory Soc; 2020.
33. Chan CK, VanhouttePMJAPSB, Hypoxia, vascular smooth muscles and endothelium. 2013;3(1):1-7.
34. Swystun LL, LiawPCJB. The Journal of the American Society of Hematology, The role of leukocytes in thrombosis. 2016;128(6):753-762.
35. Henry BM et al. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. 2020;58(7):1021-1028.
36. Saleh J et al. Mitochondria and microbiota dysfunction in COVID-19 pathogenesis. 2020;54:1-7.
37. Bikdeli B. et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. 2020;75(23):2950-2973.
38. Gupta N, WishJBJAJoKD. Hypoxia-inducible factor prolyl hydroxylase inhibitors: a potential new treatment for anemia in patients with CKD. 2017;69(6):815-826.
39. Giannis D, ZiogasIA, GianniPJJoCV. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. 2020;127:104362.
40. Obi AT, et al. Practical diagnosis and treatment of suspected venous thromboembolism during COVID-19 pandemic. 2020;8(4):526-534.
41. Spyropoulos AC et al. Scientific and standardization committee communication: Clinical guidance on the diagnosis, prevention and treatment of venous thromboembolism in hospitalized patients with COVID-19; 2020.
42. Schünemann HJ et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. 2018;2(22):3198-3225.
43. Keshari RS et al. Fondaparinux pentasaccharide reduces sepsis coagulopathy and promotes survival in the baboon model of Escherichia coli sepsis. 2020;18(1):180-190.

44. Marietta M et al. COVID-19 and haemostasis: a position paper from Italian Society on Thrombosis and Haemostasis (SISET). 2020;18(3):167.
45. Pannucci CJ et al. Enoxaparin 40 mg per day is inadequate for venous thromboembolism prophylaxis after thoracic surgical procedure. 2018 ;106(2):404-411.
46. Wang TF et al. Efficacy and safety of high-dose thromboprophylaxis in morbidly obese inpatients. 2014;111(01): 88-93.
47. Zhai Z et al. Prevention and treatment of venous thromboembolism associated with coronavirus disease 2019 infection: a consensus statement before guidelines. 2020;120(06):937-948.
48. Kearon C et al., Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. 2016;149(2):315-352.
49. Zhang Y. et al. Risk factors for pulmonary embolism in patients preliminarily diagnosed with community-acquired pneumonia: a prospective cohort study. 2016;41(4):619-627.
50. Frasson S. et al. Infection as cause of immobility and occurrence of venous thromboembolism: analysis of 1635 medical cases from the RIETE registry. 2016;41(3):404-412.
51. Milbrandt, E.B., et al., Prevalence and significance of coagulation abnormalities in community-acquired pneumonia. 2009 ;15(11):438-445.
52. Alonso-Fernández A, et al. Prevalence of pulmonary embolism in patients with COVID-19 pneumonia and high D-dimer values: A prospective study. 2020;15(8):e0238216.
53. Castro DJ et al. Diagnostic value of D dimer in pulmonary embolism and pneumonia. 2001;68(4):371-375.
54. OBE BH et al. Practical guidance for the prevention of thrombosis and management of coagulopathy and disseminated intravascular coagulation of patients infected with COVID-19; 2020.
55. Rothberg MB, HaesslerSDJCcm. Complications of seasonal and pandemic influenza. 2010;38:e91-e97.
56. Bikdeli B et al. Pulmonary embolism hospitalization, readmission, and mortality rates in US older adults. 1999-2015. 2019;322(6):574-576.
57. Mojoli F. et al. Our recommendations for acute management of COVID-19. BioMed Central; 2020.
58. Liao SC et al. Incidence and mortality of pulmonary embolism in COVID-19: a systematic review and meta-analysis. 2020;24(1):1-5.
59. Wright FL et al. Fibrinolysis shutdown correlation with thromboembolic events in severe COVID-19 infection. 2020;231(2):193-203. e1.
60. Olson JDJAicc, D-dimer: an overview of hemostasis and fibrinolysis, assays, and clinical applications. 2015;69:1-46.
61. Hunt BJ, LeviMJBJoH. Re The source of elevated plasma D-dimer levels in COVID-19 infection; 2020.
62. Magro C. et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. 2020;220:1-13.
63. Bao J. et al. Comparative analysis of laboratory indexes of severe and non-severe patients infected with COVID-19. 2020;509:180-194.
64. Ifeanyi OE .Emerging Clinical & Medical Challenges and Appropriate Solutions during Covid-19 Pandemic Times. Med Clin Rev.2020; 6 (5): 108. DOI: 10.36648/2471-299X.6.5.108
65. Obeagu EI. (Mental Health Care during the COVID-19 Pandemic. Journal of Public Health and Nutrition.2020; 3: 5
66. Obeagu EI, Okorie HM, Nnokam NP, Okpoli HC. Cytokines, coagulation profile and haematological changes in covid 19 patients as indicators of their health staus: A review. European Journal of Biomedical and Pharmaceutical sciences. 7(7): 724-729.

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