Critical Management of Haemodynamically Unstable Acute Pulmonary Embolism in COVID-19

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ABSTRACT

Thrombotic events occur in up to one-third of patients with COVID-19, predominantly manifesting as pulmonary emboli (PE), which are associated with higher morbidity and mortality. Acute PE should therefore be one of the main differential diagnoses of COVID-19 patients who develop hemodynamic instability. Early systemic thrombolysis remains the first line of treatment for hemodynamically unstable PE in those infected with COVID-19, particularly considering the risks of infection to other personnel during catheter-directed thrombolysis procedures. This report aims to describe a typical case of hemodynamically unstable acute PE with COVID-19 management in our center. A 66-year-old male presented to ER with shortness of breath and desaturation was suspected of having COVID-19. Despite unremarkable physical examination, he was later confirmed to be COVID-19 positive. While in the isolation ward, he experienced a cardiac arrest. 12-lead ECG showed sign of right ventricular strain and subsequently bedside echocardiography showed a fresh thrombus in the right atria with signs of acute right ventricular dysfunction. The diagnosis of acute PE with hemodynamic instability was made, and systemic thrombolysis was immediately initiated. Despite the bleeding complication, his symptoms and hemodynamic improved and he was discharged safely with oral anticoagulant. Our case demonstrates how early recognition and prompt treatment of acute PE especially in COVID-19 patients with hemodynamic instability, can be life saving. Recognizing the subtle signs of acute PE during emergency improves patients outcome considerably.

Keywords**:** *hemodynamic instability, acute pulmonary embolism, COVID-19.*

INTRODUCTION

COVID-19, the disease responsible for the devastating pandemic that began at the end of 2019, has been associated with a significantly increased risk of pulmonary thrombosis.[1] Thrombotic events, predominantly pulmonary embolism, occur in up to one-third of patients with COVID-19, and are associated with more severe disease and increased mortality.[2] The hypercoagulable state may be responsible for large-vessel thrombosis, while direct vascular and endothelial injury are more related to in-situ microvascular thrombosis.[1] Recent study suggested that venous thromboembolic events (VTEs) are more common among patients with COVID-19 hospitalized in the intensive care unit (ICU), reaching as high as 69%.[1] A meta-analysis also showed similar pattern with higher rates of thromboembolism among patients admitted to ICU, with venous thrombosis reaching 31% of

cases with 19% of cases presenting as pulmonary embolism (PE).[3] Arterial thrombotic events also occur, although with lesser frequency.

Importantly, the presence of thrombosis increases the odds of mortality among COVID-19 patients by 74% (odds ratio [OR], 1.74; 95% confidence interval [CI], 1.01 to 2.98; p=0.04). A study in Scotland found an increased risk of non-fatal thromboembolic events for hospitalized patients testing positive for SARS-CoV-2. The risk was particularly high for PE and deep vein thrombosis (DVT) within the first 7 days after a positive test result and remained significantly elevated up to 56 days after a positive test.[2]

Diagnosing acute PE requires high degree of suspicion, especially in hemodynamically unstable situation which should prompt more aggressive management. Bedside transthoracic echocardiography may play a pivotal role in in this circumstances, due to its quick and swift examination. Therefore, we report a case of hemodynamically unstable acute pulmonary embolism in a COVID-19 patient who presented with cardiac arrest which was successfully treated with systemic thrombolysis, signifying the role of early detection and prompt treatment in such cases.

CASE ILLUSTRATION

A 66-year-old male presented at the emergency department of the National Cardiovascular Centre Harapan Kita, chiefly complaining of shortness of breath for 2 days prior to admission. The symptoms occurred suddenly and worsened in the last 2 days. He denied any sort of chest pain, nausea, vomiting, or fever. However, he had a mild non-productive cough. He was recently discharged from hospital with a non-ST segment elevation myocardial infarction (NSTEMI) one month before admission. He had a history of chronic renal dysfunction, diabetes mellitus, and hypertension. He had not been infected with COVID-19 prior to admission and had had the COVID vaccination twice in 2020 with the COVID-19 vaccine AstraZeneca©. His last medication was Amlodipin 5 mg od, Bisoprolol 2.5 mg od, Candesartan 16 mg od, Aspirin 80 mg od, Clopidogrel 75 mg od, Furosemide 40 mg od, Metformin 500 mg bid, Nitroglycerin 5 mg bid, Simvastatin 20 mg od, Fenofibrate 300 mg od, Allopurinol 100 mg od, and Isosorbide dinitrate 5 mg (if needed). Coronary angiography performed during previous hospitalization due to NSTEMI one month prior showed non-significant coronary artery disease with mild myocardial bridging in distal left circumflex artery and thus conservatively treated.

On admission, he looked mildly ill and was fully alert and conscious. His blood pressure was 130/90 mmHg with heart rate of 97 beats per minute and respiratory rate of 24 times per minute with room air oxygen saturation of 93%. His physical examination was unremarkable with minimal rales on both lung bases. Electrocardiography (ECG) showed sinus rhythm with Q wave and T inversion in III, which is similar to his previous ECG examination. Chest X-ray showed cardiomegaly, with infiltrate in the left lower lung. Bedside echocardiography showed normal ejection fraction with global normokinetic and good right ventricular systolic function.

Initial laboratory examination revealed leukocytosis (11280 cell/ml) with neutrophil to lymphocyte ratio (NLR) of 3.86, increased ureum and creatinine serum (creatinine 1.69 mg/dl, ureum 45.4 mg/dl) with eGFR 41 ml/min/1.73 m^2. Blood gas analysis on room air analysis showed oxygen saturation of 97% with compensated metabolic acidosis. NTproBNP level was also increased (1050 mg/dl). Random blood glucose were within normal range (150 mg/dl).

The patient was initially diagnosed with acute decompensated heart failure owing to heart failure with preserved ejection fraction (HFpEF), well-controlled type II DM, stage III chronic kidney disease (CKD), controlled hypertension, and compensated metabolic acidosis. Previous medication was continued, with Metformin changed to Gliquidone 30 mg bid, and Furosemide IV 40 mg bid was added in addition to initial suspected COVID-19 treatment regimen (i.e. IV Ceftriaxone 2 g daily and vitamin supplementation). However, routine screening of SARS-CoV2 nasal swab examination showed a positive result, and thus the patient was admitted to the isolation ward.

Approximately 37 hours after admission, the patient suddenly experienced loss of consciousness without pulse, thus cardiac arrest. CPR was performed and he had a return of spontaneous circulation (ROSC) after one cycle of CPR. He was fully conscious and able to follow commands. Upon recovery, the patient complained of chest pain with visual analog scale (VAS) of 5/10 and worsening dyspneu. ECG examination showed new right ventricular strain pattern, which prompted us to perform urgent bedside echocardiography that revealed a dilated right ventricle (RV) with right to left ventricle basal ratio >1. Mobile thrombus clearly visible in the right atrium along with positive Mc-Connel sign and right ventricular (RV) dysfunction (TAPSE was reduced to 12 mm from initially 24 mm) with distended inferior vena cava (IVC). Acute pulmonary embolism was highly suspected with hemodynamic instability and we decided to perform systemic thrombolysis with intravenous Alteplase 100 mg over 2 hours which was completed within six hours after the onset of cardiac arrest. Contraindication of thrombolysis was absent in this case. A vasoconstrictor (norepinephrine 0.05 mcg/kgBW/min) and inotropic agent (dobutamine 3 mcg/kgBW/min) was also initiated due to hypotension after ROSC. The D-dimer level increased to 20350 ng/ml, which supports the diagnosis of acute PE. A regimen for severe COVID-19 infection with intravenous Remdesivir and Dexamethasone was then given.

After the completion of thrombolysis, we initially continued anticoagulation with intravenous Unfractionated Heparin (UFH) infusion, since the patient had an acute kidney injury (AKI) with creatinine 3,92 mg/dl (eGFR 15 ml/min/1,73m^2) but was stopped temporarily due to major bleeding that involved deep hematoma in the right groin (8 cm x 15 cm), both arm (diameter 15 cm on right hand, 10 cm on left hand) and gastrointestinal bleeding. Blood transfusion of two units of packed red cells (PRC), cessation of antiplatelet and continuous infusion of protein pump inhibitor (PPI) was given for 48 hours. Anticoagulation was continued after bleeding stopped with adjusted dose of subcutaneous LMWH as renal function improve gradually and estimated glomerular filtration rate (eGFR) reach above 15 ml/min/1,73m^2. Duplex ultrasound showed normal arterial and venous blood flow with no sign of pseudoaneurysm on all extremities. Pulmonary CT angiography after fibrinolytic therapy showed thrombus in multiple left and right pulmonary artery segments, with crazy-paving signs in both lung parenchymal bases consistent with COVID-19 pneumonia.

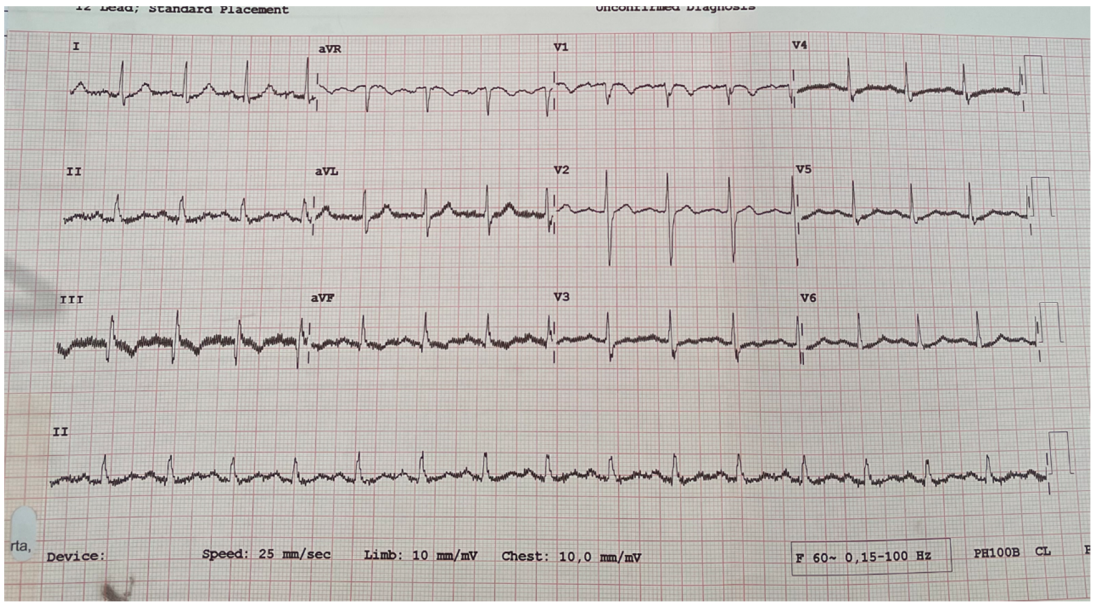

Figure 1. Electrocardiogram on admission in ER showed sinus rhythm with Q wave and T inversion in lead III and aVF on admission (upper), which did not differ from the patient's previous ECG at outpatient clinic one month before admission.

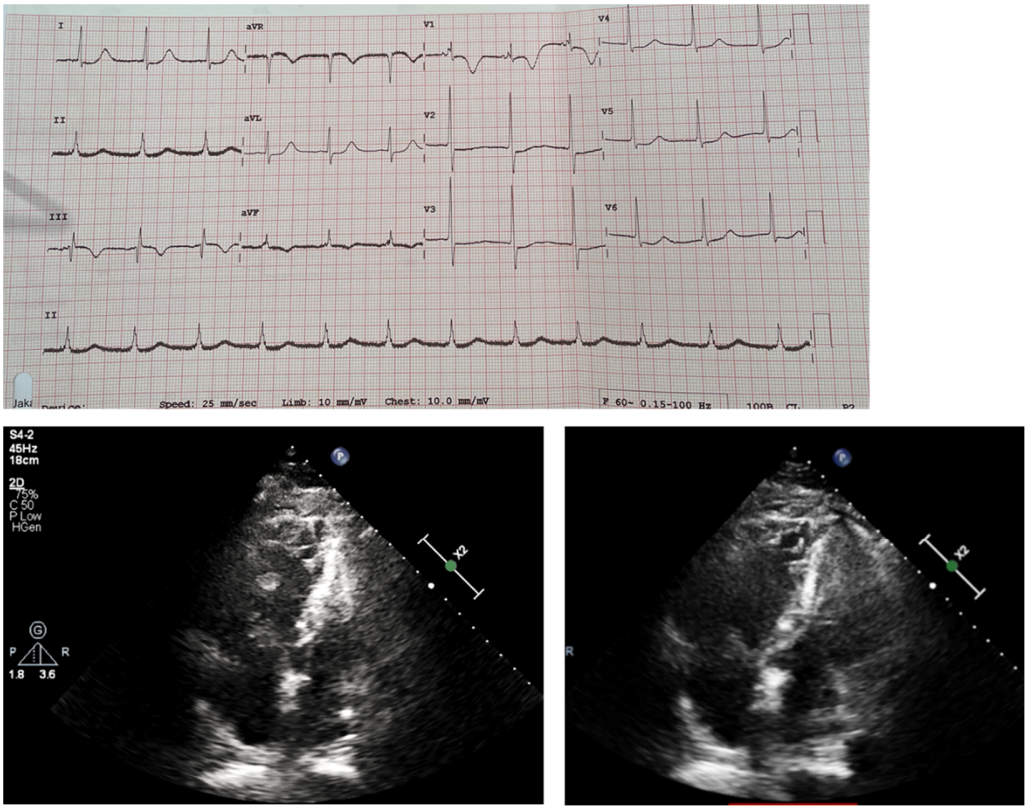

Figure 2. ECG examination after ROSC showed new right ventricular strain pattern in lead V1 (upper). Bedside echocardiography examination also revealed dilated RV with RV to LV basal ratio >1 (lower right), and mobile thrombus clearly visible in right atrial (lower left). McConnell's sign was positive. TAPSE was reduced to 12 mm with distended IVC. The right-side image showed disappearance of thrombus with smaller RV diameter in comparison to the previous examination.

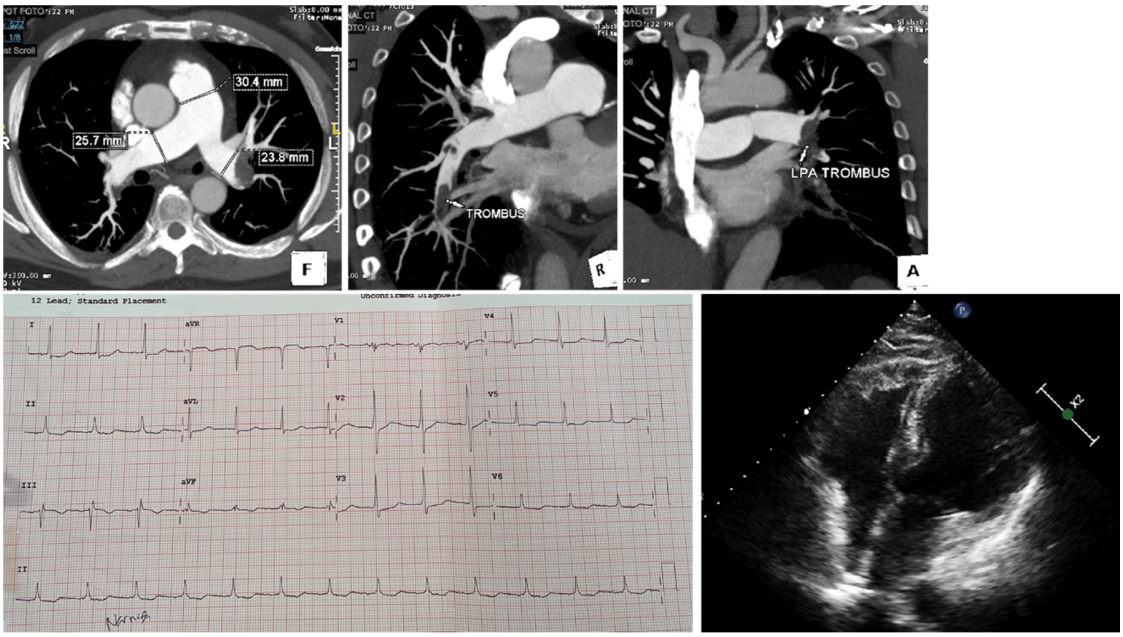

Figure 3. Pulmonar angiography computed tomography (CTPA) examination after completion of systemic fibrinolytic therapy showed evidence of thrombus in both main right and left pulmonary trunk and branches. Bedside echocardiography also showed the disappearance of mobile thrombus in the previous examination. ECG examination showed the resolution of RV strain pattern in lead V1.

Upon treatment, the patient clinical status was improving. Shortness of breath gradually subsided, and bleeding was controlled with no evidence of decreasing hemoglobin level on daily examination. Peripheral saturation was stable on 99–100% with nasal canulae. Both inotropic and vasopressor agent were stopped on the sixth day of hospitalization. Remdesivir was also stopped after 5 days of administration, and the anticoagulation treatment was switched to an oral agent with Rivaroxaban 10 mg once daily. Sildenafil 12.5 mg was also initiated three times daily as the echocardiography showed early signs of pulmonary hypertension based on pulmonary valve acceleration time (113 ms to 95 ms). A PCR evaluation of SARS-CoV2 PCR after 10 days of hospitalization showed a negative result, and the D-dimer level decreased to 4550. The patient was then discharged after 15 days of hospitalization with Rivaroxaban 10 mg daily and Sildenafil 12.5 mg tid in addition to his routine medication. Rivaroxaban was increased to 20 mg once daily one month after discharge. Two months after discharge the patient showed significant improvement and mainly complained of fatigue during moderate-intensity physical exercise. The D-dimer level has decreased to below the cut-off level three months after discharge.

DISCUSSION

Venous thromboembolism (VTE) is a common complication of COVID-19.[6] A few notable observations about COVID-19 were made early in the course of the pandemic: (1) many patients with COVID-19 demonstrate markedly abnormal coagulation parameters, particularly D-dimer, which correlate with mortality; (2) patients with COVID-19, especially those admitted into ICU, show a notably high incidence of thrombotic complications; (3) small autopsy series of patients with COVID-19 have demonstrated a high incidence of both pulmonary macrothrombi and microthrombi, despite the use of prophylactic anticoagulation; and (4) many COVID-19 patients with respiratory failure appeared to have hypoxemia that was much more severe in comparison to the evidence of lung compliance, which could be explained by the presence of pulmonary thrombosis.[1]

According to Fontana et al.[8], there are several hypotheses for this prothrombotic state. First, critically ill patients accumulate significant thromboembolism risk factors including profound immobility, a severe infectious and inflammatory state, hypoxia, and central venous lines. Second, COVID-19 appears to result in coagulopathy, with dramatically elevated fibrinolytic biomarkers without severe thrombocytopenia or hypofibrinogenemia. Whether this reflects a true prothrombotic intravascular state is unclear but likely. Third, endothelial lesions which enhance the prothrombotic state may also involved. The SARS-CoV-2 virus enters host cells through the ACE2 surface receptor, which can be found not only in lung alveolar cells but also in arterial and venous endothelial cells. Fourth, a high proportion of critically ill COVID-19 patients were found to have positive lupus circulating anticoagulant (88%), but the clinical significance of this finding remains unknown.[7,8]

The high incidence of thromboembolic events suggests COVID-19-induced coagulopathy. Accurate assessments of the true incidence of VTE in hospitalized patients with COVID-19 remain erratic, ranging from 4.8% to 85%.[1] The clinical signs and symptoms of acute PE, the most dangerous VTE event, are nonspecific. Some of the patients are asymptomatic, while others have nonspecific clinical manifestations, ranging from dyspnea, chest pain, hemoptysis, presyncope or syncope, to hemodynamic instability. They can overlap with the symptoms of COVID-19 infection or other complications such as acute respiratory distress syndrome (ARDS), or even myocarditis.[9]

The reported risk of VTE appears high among inpatients and very high among critically ill patients suffering from COVID-19.[8] Critically ill patients admitted to ICU are at very high risk of CTE because of ICU-specific risk factors (immobilization, sedation, vasopressors, or central venous catheters), in addition to individual patient-related risk factors (age, obesity, immobilization, history of personal or familial VTE, cancer, sepsis, respiratory or heart failure, pregnancy, stroke, trauma, or recent surgery). Thus, all hospitalized patients, and especially those in ICU, should be routinely assessed for VTE risk and given

thromboprophylaxis accordingly.[5,10,11] Risk scores such as the Wells score or the Geneva clinical prediction score may be useful in excluding unnecessary tests among those with low probability of VTE despite not validated for COVID-19 patients. Although not specific for PE, RV strain pattern on ECG and sinus tachycardia was present in our case and helped in the diagnosis of acute PE.[9]

Although optimal dosing of antithrombosis drugs in patients with COVID-19 is still being studied during the management of our case.[4] The anticoagulation therapy of stable PE patients is usually low molecular weight heparin (LMWH) or direct oral anticoagulants. In patients with intermediate-risk/high-risk PE, UFH may be preferred due to its short half-life and the opportunity to give the patients protamine sulfate as an antidote in case of the need for an urgent procedure or in case of bleeding. On the other hand, UFH requires close monitoring, which we may want to avoid in such a contagious disease. Although LMWH is much more preferred in COVID-19 patients due to its convenience[9], acute kidney injury in our case hinder its usage before kidney function gradually improved thus allowing us to give subcutaneous LMWH.

Despite the nature of COVID-19 pandemic, ESC recommended that acute pulmonary embolism (PE) management should still be managed according to ESC guideline.[10] Regarding the timing of initiation of therapy, the European Society of Cardiology guidelines for PE emphasizes the importance of induction of anticoagulation therapy in all patients suspected of PE with high or intermediate clinical probability of PE without delay, while diagnostic workup is in progress.[11] For COVID-19 patients in whom PE is deemed as the cause of hemodynamic instability, options include catheter-directed thrombolysis (CDT) or systemic thrombolytic treatment. Given the lack of strong evidence and appropriate guidelines suggestive of the superiority of CDT for PE, many centers prefer intravenous systemic thrombolysis.[5]

In haemodynamically unstable or high risk acute PE, systemic fibrinolytic should administered as soon as possible, as it is most beneficial within the first 12 hours from onset.[11] The subtle clue of RV strain ECG pattern increased our suspicion of acute PE and prompt us to perform systemic thrombolytic therapy thus showing the importance of ECG pattern of acute PE despite being unspecific. Systemic thrombolysis leads to rapid improvement in pulmonary obstruction, pulmonary arterial pressure and resistance, and thus to an improvement in RV function and dimension. On these bases, systemic thrombolysis in high-risk PE demonstrated a significant reduction in mortality and VTE recurrence, albeit with an increased risk of severe extra- and intracranial bleedings.[12] In our case, the patient did not have any contraindication to fibrinolytic therapy, and was immediately started on Alteplase infusion which finished within 6 hours after ROSC. Haemodynamic was significantly improved, as we could completely weaned off both dobutamine and norepinephrine infusion within 48 hours after completion of systemic fibrinolytic therapy. Although significant GI bleeding and deep hematoma caused cessation of any antithrombotic therapy, it was well-managed and we resumed parenteral anticoagulation and eventually switched to oral long-term anticoagulant.

It has been well established that chronic thromboembolic pulmonary hypertension (CTEPH) is often a late complication of acute pulmonary embolism.[13] Studies show that 74,8% of patients with CTEPH have a history of acute pulmonary embolism, and 0.5–2% of patients with acute pulmonary embolism eventually progressed into CTEPH.[10,14,15] Therefore, anticoagulation should always be prescribed for at least three months after acute pulmonary embolism event, particularly in COVID-19 patients which pose higher thromboembolic risk.10 In addition to, in the absence of any indication for prophylactic anticoagulation, open label clinical trial showed that Rivaroxaban improved 30-days outcome among non-critically ill COVID-19 patients.[16] Diabetes and chronic kidney disease were also shown to be related with hypercoagulability other than COVID-19 and was also favor the prescribtion of oral anticoagulation after discharge.[17,18] Therefore, Rivaroxaban was prescribed at a prophylactic dose initially (10 mg daily) and was increased to a therapeutic dose one month after discharge

(20 mg daily) and was continued afterward in concordance with the national guideline of COVID-19.[19] Residual symptoms related to PE (i.e. fatigue) gradually improved during outpatient clinic visit, along with the declining D-dimer level below cut-off value that might signal the resolution of the thrombus.

CONCLUSION

We reported a case of a 66-year-old male presenting with dyspneu and desaturation which turned out to be COVID-19 with hemodynamically unstable acute pulmonary embolism. Early detection and prompt treatment of PE especially in COVID-19 patients is pivotal as it might improve clinical outcomes. Early treatment with systemic thrombolysis remains the first-line option in acute PE with unstable hemodynamic profile, especially in patients with COVID-19, which hinders implementation of invasive intervention due to health personnel infection risk.

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REFERENCES

1. Poor HD. Pulmonary Thrombosis and Thromboembolism in COVID-19. Chest [Internet]. 2021;160(4):1471–80.
2. Loo J, Spittle DA, Newnham M. COVID-19, immunothrombosis and venous thromboembolism: biological mechanisms. Thorax [Internet]. 2021;76(4):412–20.
3. Tan BK, Mainbourg S, Friggeri A, et al. Arterial and venous thromboembolism in COVID-19: a study-level meta-analysis. Thorax [Internet]. 2021;76(10):970–9.
4. Malas MB, Naazie IN, Elsayed N, Mathlouthi A, Marmor R, Clary B. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis. E Clinical Medicine [Internet]. 2020;29–30:100639.
5. Kyriakoulis KG, Kokkinidis DG, Kyprianou IA, et al. Venous thromboembolism in the era of COVID-19. Phlebol J Venous Dis [Internet]. 2021;36(2):91–9.
6. Vaughn VM, Yost M, Abshire C, et al. Trends in Venous Thromboembolism Anticoagulation in Patients Hospitalized With COVID-19. JAMA Netw Open [Internet]. 2021;4(6):e2111788.
7. Wichmann D, Sperhake J-P, Lütgehetmann M, et al. Autopsy findings and venous thromboembolism in patients with COVID-19. Ann Intern Med [Internet]. 2020;173(4):268–77.
8. Fontana P, Casini A, Robert-Ebadi H, Glauser F, Righini M, Blondon M. Venous thromboembolism in COVID-19: systematic review of reported risks and current guidelines. Swiss Med Wkly [Internet]. 2020;150:25–6.
9. Tal S, Spectre G, Kornowski R, Perl L. Venous thromboembolism complicated with COVID-19: What do we know so far? Acta Haematol [Internet]. 2020;143(5):417–24.
10. The Task Force for the management of COVID-19 of the European Society of Cardiology. ESC guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic: part 2—care pathways, treatment, and follow-up. European Heart Journal. 2022;43:1059–103.
11. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). European Heart Journal. 2020;41:543-603.
12. Kollias A, Kyriakoulis KG, Lagou S, Kontopantelis E, Stergiou GS, Syrigos K. Venous thromboembolism in COVID-19: A systematic review and meta-analysis. Vasc Med [Internet]. 2021;26(4):415–25.
13. Gong X, Yuan B, Yuan Y. Incidence and prognostic value of pulmonary embolism in COVID-19: A systematic review and meta-analysis. Lazzeri C, editor. PLoS One [Internet]. 2022;17(3):e0263580.
14. Scudiero F, Pitì A, Keim R, Parodi G. Acute pulmonary embolism in COVID-19 patient: a case report of free-floating right heart thrombus successfully treated with fibrinolysis. In: Mukherjee R, Timothy C T, Nisha M, Elena S, Ross T, editors. Eur Hear J - Case Reports [Internet]. 2021;5(1):0–4.
15. Zhu Y-J, Zhou Y-P, Wei Y-P, et al. Association between anticoagulation outcomes and venous thromboembolism history in chronic thromboembolic pulmonary hypertension. Front Cardiovasc Med [Internet]. 2021;8:1–8.
16. Gavilanes-Oleas F, Alves-Jr J, Fernandes C, et al. Use of direct oral anticoagulants for chronic thromboembolic pulmonary hypertension. Clinics [Internet]. 2018;73:10–2.
17. Ramacciotti E, Agati LB, Calderaro D, et al. Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised, controlled trial. Lancet. 2022;399:50–9.
18. Pretorius L, AThomson GJA, Adams RCM, et al. Platelet activity and hypercoagulation in type 2 diabetes. Cardiovasc Diabetol. 2018;17:141.
19. Nunns GR, Moore EE, Chapman MP, et al. The hypercoagulability paradox of chronic kidney disease: The role of fibrinogen. Am J Surg. 2017;214(6): 1215–8.