Journal of Research in Medical and Dental Science
2022, Volume 10, Issue 8, Page No: 186-191

Available Online at: www.jrmds.in
eISSN No.2347-2367: pISSN No.2347-2545

Pulmonary Embolism: Complication of COVID-19

Shalini Singh*, Swarupa Chakole, Guddi Leishram

Department of Community Medicine, Jawaharlal Nehru Medical College, Sawangi, Wardha, India

ABSTRACT

In COVID-19 patients, Pulmonary Embolism is one of the most dreaded complication causing prolonged hospitalisation and death, in which people who are infected are at high risk of thromboembolic events (DVT, PE, cerebrovascular accidents i.e. stroke). These events are related to the thrombo-inflammatory state within the pulmonary vessels, which is provoked by the infection, but some other risk factors like decreased movements, long term immobility and shock (as in case of dehydration or sepsis) also play an important role in disease progression. Increase in level of D-dimer (end product of fibrin degradation) which is a marker reflecting the activation of haemostatic and fibrinolytic system, and clinically presents as thrombocytopenia. Late presentation shows altered coagulation profile of patients including prolonged prothrombin time fibrinogens are also increased. Progression of disease can be monitored by testing various laboratory variables like d-dimer and fibrinogens. Radiological investigations include CTPA (more invasive); V/Q scan helps in diagnosis of the disease. Parenteral anticoagulants like heparin and LMWH are widely used in management of patients suffering from COVID-19. Patients with mild symptoms can now be treated in the outpatient setting and patient with more severe disease can be treated successfully with newly developed modalities, such as catheter-induced thrombolysis which is becoming available at various centres. IVC filters are used nowadays along with anticoagulation therapy. It benefits patients who are at more risk of pulmonary embolism during interventional therapy. Coagulopathy has got poor prognosis, hence various plan of action should be started for prior recognition of disease so that pulmonary embolism should be treated with various required treatment strategies.

Key words: COVID-19, Pulmonary embolism, ACE2 and TPS2, D-dimer, Anticoagulant, Catheter-induced thrombolysis, IVC filters

HOW TO CITE THIS ARTICLE: Shalini singh, Swarupa Chakole, Guddi Leishram, Pulmonary Embolism: Complication of COVID-19, J Res Med Dent Sci, 2022, 10 (8): 186-191.

Corresponding author: Shalini Singh
E-mail: drguddi2015@gmail.com
Received: 24-May-2022, Manuscript No. JRMDS-22-49385;
Editor assigned: 27-May-2022, Pre QC No. JRMDS-22-49385 (PQ);
Reviewed: 10-Jun-2022, QC No. JRMDS-22-49385;
Revised: 25-Jul-2022, Manuscript No. JRMDS-22-49385 (R);
Published: 03-Aug-2022

INTRODUCTION

Pulmonary embolism arises when there is an altered or disrupted blood flow in pulmonary vasculature mainly the pulmonary artery due to clots that has formed initially in some other part of the body. Platelets are important in formation of thrombi which are triggered by potent factor like Platelet Activating Factors (PAF).

PAF leads to stimulation of mast cells which leads to inflammation resulting into Severe Acute Respiratory Syndrome (SARS). Pulmonary embolism occurs when a part of this thrombus (different site of origination) tears off and enters the main pulmonary circulation. In deep vein thrombosis, a thrombus develops from the deep veins, most commonly in the lower extremities. PE and DVT combined known as venous thromboembolic phenomenon.

Pulmonary embolism can be classified into

High risk or catastrophic pulmonary embolism: Right heart function gets highly impaired causing severe fall in BP *i.e.* hypotension that requires aggressive vasopressor or ionotropic therapy and administration of high-flow oxygen. Intermediate risk PE: In addition to Right ventricular function impairment, altered levels of cardiac troponins and BNP *i.e.* brain natriuretic peptides level with mild decrease in blood pressure that can be treated with fluid administration. Low risk PE: Mild symptomatic or asymptomatic PE with absent right ventricular dysfunction and hypotension.

Clinical features of pulmonary embolism

- Breathlessness or dyspnoea (in majority of the patients)
- Increased respiratory rate *i.e.* tachypnoea>20 per minute
- Pleuritic chest pain (in case of pulmonary infarction)
- Increased heart rate *i.e.* tachycardia>100 bpm
- Cough (presence of comorbid condition)
- Haemoptysis (in case of pulmonary infarction)
- Apprehension (mostly in elderly patients)

- Pain in lower limbs
- Patients having clinically evident DVT
- Hypotension (less commonly)

On clinical examination of patient

A loud S2 is present because of loud pulmonary component (P2). Some adventitious sounds like crackles or wheezing may present due to some underlying diseases. In right ventricular failure, increase in Jugular Venous Pressure (JVP) and RV heave may be present.

It includes:

- Elderly people
- Immobility due to prolonged hospitalisation (surgeries or illnesses).
- Prior history of pulmonary embolism or deep vein thrombosis or certain other venous thromboembolic episodes.
- Chronic renal insufficiency
- Malignancy [1].

Literature Review

Pathogenesis

Initiation of inflammation leads to activation of coagulation cascade activation. The primary site of origin is assumed to be in pulmonary system and is caused by diffuse bilateral inflammation and also known as pulmonary intravascular coagulation [2,3]. Inflammation of pneumocystis (type 2) with SARS-CoV-2 leads to aggregation of lung macrophages or dust cells and polymorphonuclear lymphocytes which triggers diffuse pulmonary inflammation and immunothrombosis [4]. Formation of small thrombi in pulmonary vasculature activates local fibrinolytic activity in the lung. Thus, ultimately, the local immune thrombosis caused by COVID-19 could result in pulmonary infarction and haemorrhage, with resultant PIC-induced pulmonary hypertension. A recent small study compared the lungs from patients who had died of COVID-19 and patients who had died of influenza A (H_1N_1) infection [5]. It leads to overproduction of some pro-inflammatory cytokines known as cytokines storm or Macrophage Activation Syndrome (MAS) [6,7]. MAS cause injuries to diverse body organs after being infected with SARS-CoV-2. Cytokines like IL-2, IL-6, IL-7 and IL-8 activates platelets and modifies the endothelial nature from an anti-coagulant to a pro-coagulant state by interfering with the glycocalyx. It also activates the clotting factors like VWB factor [8,9]. After which the neutrophils release various tissue factor, triggering and initiating the extrinsic pathway of coagulation and releasing various thrombotic factors like Neutrophil Extracellular Traps (NETs) that helps in activation of platelets [10,11]. The overall effect of all this results into disseminated intravascular coagulation or DIC and It is characterised by decreased platelet count or thrombocytopenia, decreased coagulation factors and increased levels of fibrin degradation factor D-dimer [12,13].

Pathophysiology

When there is formation of DVT, thrombus from the primary site dislodges and passes across the venous system and hence to heart (right side) to settle in the lung vessels. In pulmonary arteries, thrombus occludes or blocks the vessels partially or completely. The outcome of disease depends on various factors like:

- Number and size of emboli
- Overall condition of lungs
- Right ventricle functioning
- Body's ability to dissolve the clot with the help of its own thrombotic system.

When major pulmonary artery is blocked by a large or several small emboli, there is an increase in right ventricle pressure leading to acute right ventricle failure causing sudden death of the patient. However, the cardiopulmonary status of the patient and rate of increase in right ventricle pressure determines the risk of death of the patient. Patients having pre-existing cardiac problems are at high risk.

Diagnosis

A diagnostic algorithm includes clinical assessment, pulmonary scan, and non-invasive tests respectively:

- **Plasma D-dimer assessment with the help of ELISA:** D-dimer concentration>500 microgram/L gives the diagnosis of pulmonary embolism. When ELISA is negative for D-dimer test reduces the need for helical spiral CT to some extent. Plasma D-dimer level is an important prognostic marker for mortality in COVID-19 patients [14-16].
- **Chest X-ray finding**: Focal loss of vascular markings is the classical finding also known as Wester mark Sign. CXR also shows wedge-shaped opacity which arises from pleura, and enlarged right descending branch of pulmonary artery are indicative of pulmonary embolism however it is less common.
- **B-mode venous compression ultrasonography of lower limb:** highly specific for DVT and suggests anticoagulant treatment without having pulmonary angiography. Doppler ultrasonography shows poor compressibility of the vein because of thrombus and hence reducing blood flow. This test has >95% sensitivity and specificity.
- **CTPA (being an invasive test):** It is mainly used for segmental pulmonary embolism and has been frequently used in diagnosis of pulmonary embolism. CTPA results are rapid and having high sensitivity and specificity. However, CT angiography has got low sensitivity for emboli present in sub-segmental vessels. It shows presence of defect in filling of pulmonary vessels.
- **Helical or spiral Computed Tomography (CT):** it can replace the need for doing pulmonary angiography.
- **V/Q scanning:** it detects areas of lungs which are ventilated but are not perfused. It has got very low specificity as it takes much more time than CT

angiography. Its sensitivity is very high when there is no significant findings present in chest x-ray and when underlying lung condition is normal. Results are reported as low probability (15% chances of pulmonary embolism), medium possibility (30%-40% chances of pulmonary embolism), and highest possibility (80%-90% chances of pulmonary embolism).

- **Echocardiography:** It can be used in high risk patients and may show thrombus in right atria or ventricle.

There are certain Clinical Prediction scores like wells score or the Pulmonary Embolism Rule-Out Criteria (PERC) may help physicians in diagnosing it. Following parameters are included in pulmonary embolism rule-out score (this test basically lowers the need for further testing for PE).

Criteria are as following:

- Patient age>50 years
- Heart rate<100 bpm
- spo2>95%
- No history of previous thromboembolic phenomenon (DVT or PE)
- Absence of swelling of unilateral lower limb
- No history of prior oestrogen uses
- No history of surgery or trauma within 4 weeks
- No complaints of haemoptysis.

For screening purposes as in case of outpatients, plasma D-dimer and ultrasonography of lower limbs are the most cost effective strategy.

Prognosis of pulmonary embolism in COVID-19 patients

Pulmonary embolism has got poor prognosis as almost 10% patients dies within first few hours after their presentation. Hence the best way to reduce mortality due to PE in these patients is:

- Early detection and rapid diagnosis of PE specially in patients who presents with nonspecific symptoms
- Risk stratification and appropriate prophylaxis in high risk patients
- Rapid initiation of anticoagulation therapy

Treatment of pulmonary embolism

Supportive therapy: Patient should be rapidly assessed for any need of supportive therapy. Patients with low blood oxygen should be administered high flow oxygen as soon as possible.

In hypotensive patient (in massive PE), fluid administration in the form of 9% normal saline can be cautiously given IV. Vasopressors can also be used as an add on to saline if blood pressure of the patient is not increasing. Norepinephrine is the first line agent which is commonly used.

Anticoagulation therapy: Generally, patients with low risk PE, only anticoagulation. But high risk PE patients: requires anticoagulation with some additional interventions like systemic thrombolysis or surgical or catheter-induced therapy.

Intermediate risk PE patients are most commonly treated with anticoagulation alone. But they require wise clinical assessment like

- Clinical signs and symptoms
- ECHO for severity of right ventricle dysfunction
- Levels of cardiac troponins
- Size and location of thrombus

Anticoagulation therapy for acute PE should be started as soon as diagnosis of PE is made, but only after risk of bleeding has been excluded in those patients.

- **Intravenous unfractionated heparin:** it has a short life span. Given initially as bolus and further infusion of heparin as per the protocol. Patient may require hospitalisation for further management.
- **Subcutaneous LMWH:** It has got various advantages over unfractionated heparin like more bioavailability, better outcomes, less risk of bleeding, less side effects (thrombocytopenia).
- Factor 10a inhibitors like Fondaparinux, Edoaxaban and Betrixaban etc.

Fondaparinux (subcutaneous) helps to prevent recurrence in patients. Fixed dose administration and no side effect like heparin makes it more suitable to use for the patients. Edoaxaban and betrixaban are other example which has got fixed oral dose administration. They can be used as maintenance anticoagulation. But the major disadvantages of these drugs are their drug interactions [17].

Maintenance anticoagulation drugs like

- Oral warfarin (vitamin k antagonist)
- Oral factor 10a antagonists like Edoaxaban, Rivaroxaban and Betrixaban
- Oral Dabigatran (direct thrombin inhibitor)

Vitamin k antagonist like Warfarin has got a significant role in pulmonary embolism treatment, most commonly in patients suffering from renal insufficiency disorders and patients who are not able to afford Direct Oral Anticoagulants drugs [12].

Patients who are on warfarin therapy require vigorous monitoring which is done by monitoring INR or International Normalized Ratio [17].

Duration of anticoagulation therapy: It can range from 3 months to lifetime depending on various factors like risk factors of PE, risk of bleeding etc.

In case of short-term risk factors (immobilisation, recent trauma or surgery) requires only 3 months of treatment. For long term risk factors (malignancy, any blood coagulative disorder) requires lifelong treatment keeping in mind the risk of bleeding.

Risk factors for bleeding in COVID-19 patients include:

- Age-more than or equal to 85 years
- Thrombocytopenia<50,000/cubic mm
- Any coagulation disorder
- Previous history of bleeding episodes
- Underlying diseases like uncontrolled bleeding peptic ulcer, uncontrolled hypertension, stroke, diabetes etc.
- Medications like antiplatelet, thrombolytic drugs or anticoagulants [18-20].

Inferior vena cava filters

IVC filters can be used in patients who are at higher risk of iatrogenic thromboembolism during systemic endovascular intervention.

It should be used with anticoagulation therapy since it may decrease long term filter related complications.

Systemic thrombolytic therapy

- It includes use of tissue plasminogen activator like ATPase
- Streptokinase and Urokinase are no longer used.
- Systemic thrombolysis is the mainstay treatment for acute PE. But it has got high risk of bleeding that can be controlled by giving FFP (Fresh Frozen Plasma).

Certain contraindications for this therapy include:

- History of prior stoke (haemorrhagic)
- History of prior ischemic stroke in 1 year
- Any brain tumour
- Any surgery within 2 months
- Any active bleeding (internal or external)

Presence of these contraindications and potential risk of bleeding by this therapy has led to the implementation of Catheter induced thrombolysis.

Catheter induced thrombolysis (for massive or high risk PE)

- There are four main types of catheter induced thrombolysis.
- Standard Catheter Induced Thrombolysis (CDT),
- USG guided catheter induced thrombolysis
- Pharmaco-mechanical catheter induced thrombolysis
- Mechanical thrombectomy with thrombolysis

Out of all, USG guided thrombolysis is most widely used modality. According to American Heart Association guideline, goals of catheter induced thrombolysis include:

- Rapid reduction of pulmonary artery pressure resulting into decreased right ventricle load and decreased resistance in pulmonary vasculature.
- To stimulate systemic perfusion
- To encourage early right ventricle recovery [14,15].

A catheter is placed in pulmonary artery *via* right heart catheterization and thrombolytic are directly administered to the large emboli present proximally. Dose of thrombolytic (TPA) is 20-24 mg over>15 hours.

DISCUSSION

Other technique involves catheter induced suction embolectomy. This is used for the emboli present in vena cava, right atria and right ventricle. This therapy helps in quick reduction of pulmonary vascular obstruction and that too without any use of fibrinolytic agents. A large bore catheter is used and blood which is suctioned out has to be get back to the body *via* veins (most commonly femoral). But the risk with this method is distal embolization in the normal functioning pulmonary vasculature.

Surgical embolectomy

It is indicated in patients who are persistently hypotensive despite of vasopressors and fluids therapy (SBP=less than 90 mm of hg). Patients who are contraindicated for thrombolysis are treated by this method.

Extracorporeal Membrane Oxygenation (ECMO)

It is used in case of catastrophic pulmonary embolism when thrombolysis has failed. It provides some time for anticoagulation therapy to work and also bridges the gap between catheter induced thrombolysis and surgical embolectomy.

Post COVID-19 thromboprophylaxis

For prophsylaxis, Heparin (LMWH as well as unfractionated) is preferable than using Direct Oral Anticoagulant drugs. It is preferred because of presence of drug interaction with administered anti-viral drugs such as anti-HIV protease inhibitors like ritonavir or antibiotics like Azithromycin. These drugs might intervene with CYP3A4 and/or P-GP pathways and could possibly increase the risk of bleeding or decrease the anti-thrombotic effects of DOACs. Generally, in the absence of the need to alter the dose of LMWH when there is concomitant thrombocytopenia, in general, an optimal balance between thrombotic complications and the risk of bleeding should be attempted. Initial results suggest LMWH has a positive effect in VTE prevention and its related complications.

Venous thrombo-embolism prophylaxis is not advised for COVID-19 patients. However, Patients treated for COVID-19 and having moderate or severe PE, a computed tomography Pulmonary Angiogram (CT-PE) within 1 month of being negative for COVID-19 may be advised. In patients with high risk of PE, a follow-up and 3 months of thromboprophylaxis may be advised. FDA has approved Rivaroxaban 10 mg daily for almost 2 months.

Function of vitamin d in regulation of thrombosis

Vitamin D has got an effective anticoagulation property and it helps in regulation of various pro and anti-thrombotic agent of coagulation pathway. Vitamin D plays an important role in upregulation of antigen expression and also increases levels of mRNA or anticoagulation. There is also a downregulation of antigen expression, activity, and mRNA levels of the important coagulation factor TF that helps in initiation of coagulation [17].

CONCLUSION

Patient suffering from COVID-19 have got a very at high possibility for DVT or PE. Pulmonary embolism is the presence of thrombus in pulmonary artery occluding it and that has originated somewhere else in the body (mainly in large veins of lower limbs). Risk factors include some hypercoagulable state, endothelial injury or dysfunction and impaired venous return. Symptoms are generally non-specific including breathlessness, chest pain (pleuritic in nature), and giddiness due to pre-syncopal attacks. Signs are also non-specific like tachycardia, tachypnoea, syncope or in severe cases cardiopulmonary arrest. Diagnosis of PE can be made with initial clinical assessment (various scores can be used), estimation of D-dimer, duplex scan (B-mode ultrasonography+colour Doppler) of lower limbs to rule out DVT, V/Q scan and CTPA. Treatment includes supportive therapy, anti-coagulation therapy (initiation and maintenance both) and with systemic thrombolysis or catheter induced thrombolysis. Surgical embolectomy also plays role in patients in which thrombolysis is contraindicated.

REFERENCES

1. Kollias A, Kyriakoulis KG, Stergiou,GS, et al. Heterogeneity in reporting venous thromboembolic phenotypes in COVID-19: methodological issues and clinical implications. Br J Haematol 2020; 190:529–532.
2. McGonagle D, Sharif K O'Regan A, Bridgewood C, et al. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autoimmun Rev 2020; 19:102537.
3. Fogarty H, Townsend L, Ni Cheallaigh C, et al. COVID-19 coagulopathy in Caucasian patients. Br J Haematol 2020; 189:1060-1061.
4. McGonagle D, O'Donnell JS, Sharif K, et al. Why the immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia are distinct from macrophage activation syndrome with disseminated intravascular coagulation. Lan Rheum 2020; 2:460-461.
5. Tay MZ, Poh CM, Rénia L, et al. Review The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol 2020; 20:363-374.
6. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020; 395:1033-1034.
7. Mancini I, Baronciani L, Artoni A, et al. The ADAMTS13-von Willebrand factor axis in COVID-19 patients. J Thromb Haemost 2021; 19:513-521.
8. Goshua G, Pine AB, Meizlish ML, et al. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study. Lan Hae 2020; 7:575-582.
9. Iba T, Levy JH. Inflammation and thrombosis: roles of neutrophils, platelets and endothelial cells and their interactions in thrombus formation during sepsis. J Thromb Haemost 2018; 16:231-241.
10. Duffett L, Castellucci LA, Forgie MA, et al. Pulmonary embolism: update on management and controversies. BMJ 2020; 370:2177.
11. McFadyen JD, Stevens H, Peter K, et al. The Emerging Threat of (Micro) Thrombosis in COVID-19 and Its Therapeutic Implications. Circ Res 2020; 127:571-587.
12. Edwards E., Wayant C., Besas J. How Fragile are clinical trial outcomes that Support the CHEST clinical Practice guidelines for VTE? Chest. 2018;154:512-520.
13. Kollias A, Kyriakoulis KG, Dimakakos E, et al. Thromboembolic risk and anticoagulant therapy in COVID-19 patients: emerging evidence and call for action. Br J Haematol 2020; 189:846-847.
14. 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; 395:1054-1062.
15. Zhang L, Yan X, Fan Q, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost 2020; 18:1324-1329.
16. Koyama T, Shibakura M, Ohsawa M, et al. Anticoagulant effects of 1 alpha, 25-dihydroxyvitamin D3 on human myelogenous leukemia cells and monocytes. Blood 1998; 92:160-167.
17. Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. Blood Adv 2018; 2:3198-3225.
18. Levy MM, Baylor MS, Bernard GR, et al. National Heart, Lung, and Blood Institute; Centers for Disease Control and Prevention; Institute of Allergy and Infectious Diseases. Clin res in respiratory failure from severe acute respiratory syndrome. Am J Respir Crit Care Med 2005; 171:518-526.
19. Bikdeli B, Madhavan MV, Jimenez D, et al. Global COVID-19 Thrombosis Collaborative Group, Endorsed by the ISTH, NATF, ESVM, and the IUA,

Supported by the ESC Working Group on Pulmonary Circulation and Right Ventricular Function. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020; 75:2950-2973.

20. Guyatt GH, Akl EA, Crowther M, et al. American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141:17-47.