Clinical and computed tomography pulmonary angiogram (CTPA) characteristics of COVID-19 related pulmonary artery thromboembolism

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LIST OF ABBREVIATIONS

DVT – Deep vein thrombosis

PE – Pulmonary Embolism

RV – Right Ventricle

CTPA – Computed Tomography Pulmonary Angiogram

CTV – Computed Tomography Venography

MRPA – Magnetic Resonance Pulmonary Angiography

PERC – Pulmonary embolism rule-out criteria

MRA – Magnetic Resonance Angiography

PTE – Pulmonary Thromboembolism

CT – Computed Tomography

ACE – Angiotensin Converting Enzyme

TMPRSS2 – Transmembrane protease serine protease-2

RAAS – Renin-Angiotensin-Aldosterone-System

ACE2 – Angiotensin-converting enzyme 2

Ang – Angiotensin

Ang II – Angiotensin 2

hACE2 – human angiotensin-converting enzyme 2

RBD – Receptor-binding domain

ADAM17 – A disinterring and metalloprotease 17

ARDS – Acute Respiratory Distress Syndrome

DIC – Disseminated intravascular coagulation

IL – Interleukin

CRP – C-reactive protein

HRCT – High-resolution computed tomography

1. INTRODUCTION

1.1. Pulmonary Artery Thromboembolism

1.1.1 Definition

Pulmonary artery thromboembolism is an embolic occlusion in the area of the pulmonary arteries. The most common cause is a deep venous thrombosis (DVT) on top of other underlying risk factors. Other reasons for the development of pulmonary artery thromboembolisms are particles of air, fat, bone marrow, amniotic fluid which travel via the bloodstream and get trapped in the lungs (1).

Acute pulmonary thromboembolism is virtually always associated with a poor prognosis, and it is one of the main factors leading to death among hospitalized patients (1,2).

It is characterized by an early lethality, 45-90% of deaths occur within 1-2 hours after the symptoms have started (1). Patients who survived embolic incidents, are more likely to suffer from pulmonary hypertension afterwards (1,2).

1.1.2. Risk Factors

Primary risk factors are factor-V-Leiden, APC-resistance, prothrombin-20210A-mutation, hyperhomocysteinemia, antithrombin deficiency, protein-C or protein-S deficiency, anticardiolipin-antibodies, congenital dysfibrinogenemia, factor XIII deficiency, plasminogen deficiency and dysplasminogenemia (1).

Secondary risk factors are trauma, surgery, immobilization, age, adiposity, malignant diseases, chemotherapy, nephrotic syndrome, Crohn´s disease, glucocorticoid therapy, apoplexy, myocardial infarction and cardiac failure, chronic venous insufficiency, smoking, pregnancy, oral contraceptives, previous thromboembolic diseases, hyper viscous changes and long flights (1).

It has been noticed by radiologists that one of the newer risk factors is the presence of an underlying Covid-19 pneumonia. Pulmonary embolism (PE) occurred even though thromboprophylaxis was given. However, it was mostly observed in severely ill patients (3). Compared with the general population pulmonary emboli occur nine times more often in patients with underlying Covid-19 (4).

1.1.3. Signs and Symptoms

The signs and symptoms in patients with pulmonary artery thromboembolism are unspecific and they vary, which makes the diagnosis difficult. Small emboli could even be physiologically insignificant and cause no symptoms at all. Symptoms depend on the severity of pulmonary artery thromboembolism, the extent of occlusion and on the individual patient's cardiopulmonary history and function.

The most common signs in a patient suffering from acute PE are tachycardia and tachypnea. Possible symptoms are dyspnea, chest pain, syncope, leg pain, signs of thrombosis, fever, cyanosis, cough, hemoptysis, rales, 4th heart sound, pronounced 2nd heart sound, pleural friction and wheezing.

There is no single symptom, risk factor or test that could prove or rule out pulmonary artery thromboembolism. In majority of the cases, it is the combination of the most common symptoms that leads to the suspected diagnosis. In patients with other comorbidities, even small emboli may cause cardiopulmonary decompensation (1).

If diagnosis is delayed, the patient may have a worse outcome. To support the physician in the diagnostic process, scoring systems have been established. Wells score and the Geneva score are most widely used (2,5), Table 1 and 2.

Table 1. Wells score. Taken and modified from reference (5).

Factor	Points
Suspected deep venous thrombosis	3
Alternative diagnosis less likely than PE	3
Heat rate >100bpm	1.5
Prior venous thromboembolism	1.5
Immobilization within prior 4 weeks	1.5
Active malignancy	1
Hemoptysis	1

If less than 4 points are reached, D-dimer testing can be performed, and exclusion of pulmonary embolism should be considered.

Table 2. Geneva score. Taken and modified from reference (5).

Clinical variable	Points
Age>65y	1.0
Previous venous thromboembolism	1.0
Surgery requiring anesthesia or fracture of lower limb in past month	1.0
Active malignancy	1.0
Unilateral leg pain	1.0
Hemoptysis	1.0
Pain on lower-limb venous palpation and unilateral edema	1.0
Heart rate	
75-94 bpm	1.0
>95 bpm	2.0

Clinical probability is low if 0-1 points are reached. 2-4 points indicate intermediate risk. A score of 5 points and more refers to a high risk of PE.

1.1.4. Pathophysiology

Acute pulmonary embolism causes a sudden rise in pulmonary vascular resistance and RV afterload due to direct physical blockage, hypoxemic vasoconstriction and the release of pulmonary artery vasoconstrictors. Acute increases in RV afterload can result in acute right ventricular failure through tricuspid regurgitation, RV dilatation, and hypokinesis. Systemic arterial hypotension, cardiogenic shock and cardiac arrest can lead to decompensated heart failure (5).

1.1.5. Diagnostic Methods and Imaging Findings

Imaging modalities available to assess acute pulmonary embolism are chest radiography, CTPA, CT venography (CTV), MRPA, nuclear medicine ventilation/perfusion scan, venous ultrasonography, echocardiography and catheter pulmonary angiography (6).

The wide range and diversity of pulmonary embolism symptoms make the diagnosis difficult. The high fatality is linked to recurrent pulmonary embolism. Even individuals with modest symptoms are at risk of developing recurrent pulmonary emboli, thus early detection is crucial. Having a normal D-dimer concentration and a low clinical likelihood score offers a reliable screening strategy that makes it possible to rule out pulmonary embolism without the need for diagnostic imaging (7).

The most effective noninvasive diagnostic method for detecting acute pulmonary embolism is a CT pulmonary angiography (CTPA), whose usefulness is not limited to identifying or ruling out the condition. It is a feasible and reliable imaging technique for evaluating the effectiveness of treatment in acute pulmonary embolism (8). Due to its high accuracy, widespread availability, quick turnaround, strong spatial resolution, and multi-planar reconstruction capabilities, CTPA is now the gold standard in the assessment of acute PE (9). The PIOPED II study showed that CTPA has a sensitivity of 83% and specificity of 96%. When clinical probability was included, the positive predictive value increased to 92% in patients with moderate clinical risk and as high as 96% in patients with low or high clinical risks (6). Since CT can visualize the whole thorax, it is advantageous for diagnosing clinical states that might be misinterpreted for pulmonary embolism such as pneumonia, aortic dissection, cancer, musculoskeletal injuries, pericardial abnormalities, and vascular pathologies (6,7). The form, quantity and location of pulmonary emboli may all be clearly and easily visualized with CTPA (8).

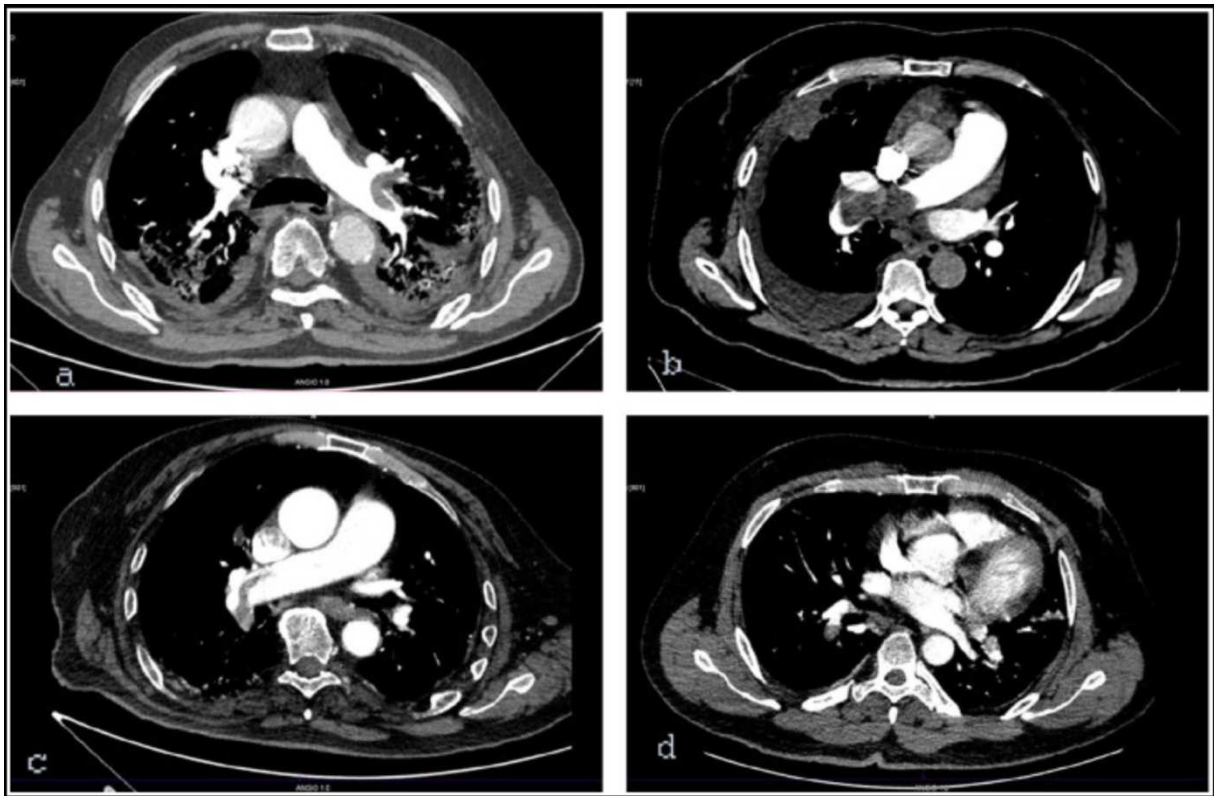

Figure 1. CT angiography scans with pulmonary emboli in Covid-19 patients in acute state (a and b) and after recovering (c and d).
Source: Budimir Mršić D, Perković-Tabak L, Ćavar M, Luetić A, Petričević M, Dolić K. Pulmonary Embolism Associated with COVID-19 Occurs in Predominantly Elderly Patients with Comorbidities: A Single Center Retrospective Study. Gerontol Geriatr Med. 2017;18;7

Following the delivery of 50 to 100 ml of intravenous contrast at a rate of 4-5ml/s, a saline chaser is added and CTPA is carried out utilizing multi-detector CT scanners. The volume of contrast is determined by the patient´s physique and the type of scanner used. In order to reduce motion artifacts, the scan is carried out in a caudocranial direction and the patient is either holding his breath after inspiration or finds himself in a resting expiratory position. Furthermore, the patient is given specific breathing instructions to prevent a quick inspiration of the Valsalva maneuver, which might result in a temporary contrast disruption and an artifactual defect. Even in emergency situations arms should always be held above the head to enhance image quality and lower radiation exposure. When this is not practicable, the arms should be placed in front of the abdomen rather than to the side of the body (9).

The potential danger of cancer from ionizing radiation is the most well-known and common worry associated with utilizing CT. Nevertheless, developments in protocols and technique, may now produce diagnostic scans with the least amount of ionizing radiation possible.

Moreover, it is important to consider the benefit-to-risk ratio of CTPA. The rate of positive pulmonary CTPA tests can be increased with the use of clinical prediction tools, such as the Geneva score and modified Wells criteria (6,10). The idea that untreated PE carries a high mortality risk of about 30% is frequently used to justify the radiation risk associated with CTPA (10,11). In the emergency department, the pulmonary embolism rule-out criteria (PERC) rule was introduced. It is a clinical prediction rule which helps to identify individuals in whom further examination was unnecessary because they had such a low clinical risk of PE (12,13).

A negative PERC rule combined with low clinical probability of having PE can accurately predict a PE. Like everything in medicine, it is not 100% sensitive, and the PERC rule can be negative at a rate of 1 in 100 in the case of a small PE and even less often in the presence of a bigger PE.

The PERC rule is determined by nine factors as seen in the table below.

1.Clinical low probability

2.Age <50 years

3.Pulse <100bpm during the stay in the emergency room

4.Pulse oximetry >94% at near see level

5.No hemoptysis

6.No prior VTE history

7.No surgery or trauma requiring endotracheal or epidural anesthesia within the last 4 weeks

8.No estrogen use

9.No unilateral leg swelling

In order to exclude PE, all nine factors must be present (12).

There is little doubt that CTPA has an advantage over MRA since the embolus itself exhibits a signal on CT, whereas MRA sequences with short echo times show no signal. Emboli in acute PTE typically create acute angles with the vessel wall and are seen near the vessel bifurcation (9,14). The arteries distal to the embolus may have a decreased diameter due to poor perfusion, while they might also be completely occlusive and cause an expansion of the afflicted vessel. Contrarily, chronic PTE displays intraluminal webs or bands, recanalized thrombi and filling defects adhering to the vessel wall and generating obtuse angles (9).

It is important to check the oxygenation of the patient since hypoxemia can be a sign of pulmonary embolism. On ECG tachycardia and unspecific ST-T wave changes can be noticed. A sudden rise in RV size can affect the conduction pathways and are shown by S1Q3T3.

Ventilation/perfusion (V/Q) scanning is helpful to determine areas in the lung that are ventilated but not perfused. It is usually indicated in patients who have a contraindication for using contrast. Other possibilities of mismatched perfusion should be ruled out.

Doppler Sonography is used for detection of thrombi in the limbs. By demonstrating poor vein compressibility or decreased flow, a clot can be found. Sensitivity and specificity are both 95% (15).

1.1.6. Management of pulmonary thromboembolism

It is important to determine the severity of a pulmonary embolism in a patient. If the patient is hemodynamically unstable it immediately categorizes him as being high-risk. A hemodynamically stable patient with high-risk clinical features, abnormal RV, and elevated troponin levels is considered intermediate to high-risk PE. An intermediate to low-risk PE is characterized by a hemodynamically stable patient, having high-risk clinical features, and present or absent elevated troponin levels and abnormal RV. In low-risk PE, the patient is hemodynamically stable, has low-risk clinical features, normal RV and normal troponin levels (16). A high probability of a negative clinical outcome despite anticoagulation is predicted by hemodynamic instability, RV dysfunction on echocardiography, RV enlargement on chest CT, or elevation of the troponin level due to RV microinfarction.

A positive clinical outcome can be achieved with anticoagulation alone when RV function is normal and when the patient is hemodynamically stable (17).

For both intermediate- and high-risk PE, immediate therapeutic anticoagulation is the basic treatment. Advanced therapy is needed in patients who later aggravate despite anticoagulation. These therapies are usually based on pulmonary artery reperfusion, which is achieved with systemic fibrinolysis, surgical pulmonary embolectomy and an expanding range of catheter-based therapeutic alternatives (16).

Anticoagulation is the most important factor in treating DVT and PE. Initial anticoagulation includes intravenous unfractionated heparin, subcutaneous low molecular weight heparin, subcutaneous fondaparinux, factor Xa inhibitors and direct thrombin inhibitors. Maintenance anticoagulation consists of oral vitamin K antagonist (warfarin), oral factor Xa inhibitors (apixaban, rivoroxaban, edoxaban), oral direct thrombin inhibitor (dabigatran) and rarely subcutaneous low molecular weight heparin.

1.2. SARS-CoV-2 infection

Coronaviruses belong to the order *Nidovirales,* family *Coronoaviridae*, and subfamily *Orthocoronavirinae* (18). They are classified into six genera: Alphacoronavirus, Betacoronavirus, Gammacoronavirus, Delta coronavirus, Bafinivirus, and Toro virus. Humans can be infected with viruses from the first two and the last genera. The former are connected to respiratory tract diseases and the latter one to diarrheal diseases. Coronaviruses are particles with the size of 120- to 160-nm. They contain an unsegmented genome of single-stranded positive-sense RNA (27-32 kb), which makes them the RNA viruses with the largest genome. Four structural proteins make up a coronavirus: the nucleocapsid (N), spike (S), membrane (M), and envelope (E) proteins. The coronavirus gets its name from the enormous protrusions that the spike proteins create from the surface of the virus, which resemble a crown (18,19).

The disease Covid-19 is a consequence of an infection with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), which gained its global attention in December of 2019 (20). It was first detected in Wuhan, China, when multiple cases of pneumonia of unknown etiology appeared (21). Patients presented with fever, dyspnea and pulmonary infiltrates on chest radiography (22). It is believed that the disease might have originated from wild animals and was then transferred to humans, but the exact origin of the virus remains unknown (23).

After the breakout of SARS-CoV in 2002 and MERS-CoV in 2012, SARS-CoV-2 has become the third coronavirus that posed a challenge to the entire world. Compared to the first two outbreaks, this one has become of greater concern because of its high speed of spread. However, its overall fatality is lower than in SARS-CoV and MERS-CoV (24).

1.2.1. Route of Transmission

As seen in Figure 2, SARS-CoV-2 is typically spread by respiratory droplets. Aerosol, direct contact with infected surfaces and fecal-oral transmission were also reported (25).

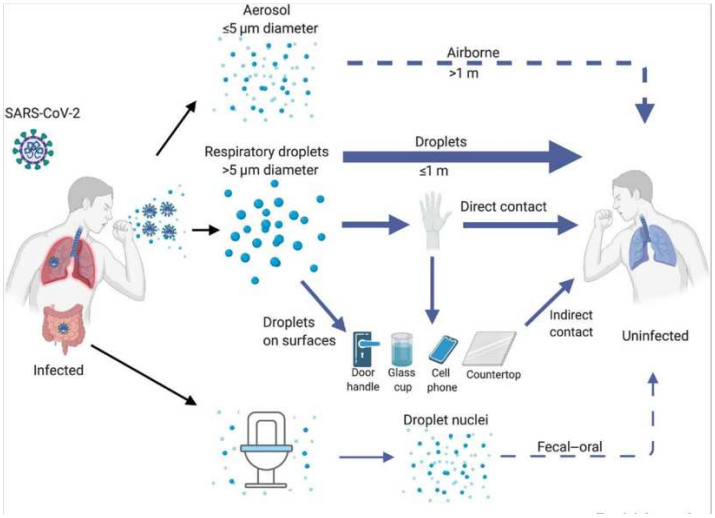

Figure 2. Route of transmission of SARS-CoV-2 (25).
Source: Harrison AG, Lin T, Wang P. Mechanisms of SARS-CoV-2 Transmission and Pathogenesis. Trends Immunol. 2020;41:1100-1115.

1.2.2. Pathogenesis

In order to enter cells, SARS-CoV-2 interacts with the angiotensin converting enzyme (ACE) 2 receptor and the transmembrane protease serine protease-2 (TMPRSS2). The membrane-bound protein ACE2 is expressed in type II alveolar cells, cardiovascular system, adipose tissue, the gut, epithelial cells in the tongue and esophagus, kidneys, lungs, cholangiocytes, bladder urothelial cells, testis, uterus epithelial cells, ovary and breast and the central nervous system (19). It is essential in the renin-angiotensin-aldosterone system (RAAS) as it prevents angiotensin II from having vasoconstrictor effects by converting it to vasodilatory angiotensin (1-7) in various organs. The major enzyme product, Ang (1-7), binds to the Mas receptor. Through vasodilation, oxidative stress resistance and cell proliferation, it contributes to blood pressure reduction and thereby blunts the effects of Angiotensin II. As a result, an important regulatory mechanism of the RAAS is the ACE2/Ang (1-7)/Mas axis, which balances

the ACE/Ang II/AT1R axis. Furthermore, it has a regulatory function in cellular biology (19,26,27). SARS-CoV-2 and Ang II compete for binding with ACE-2.

When SARS-CoV-2 binds to the ACE-2 protein it can inactivate its activity and its converting effects. Additionally, it lowers the expression of the enzyme in the membrane. This can lead to increased vascular inflammation and local arterial thrombosis, which furthermore can result in stroke and digital ischemia (19).

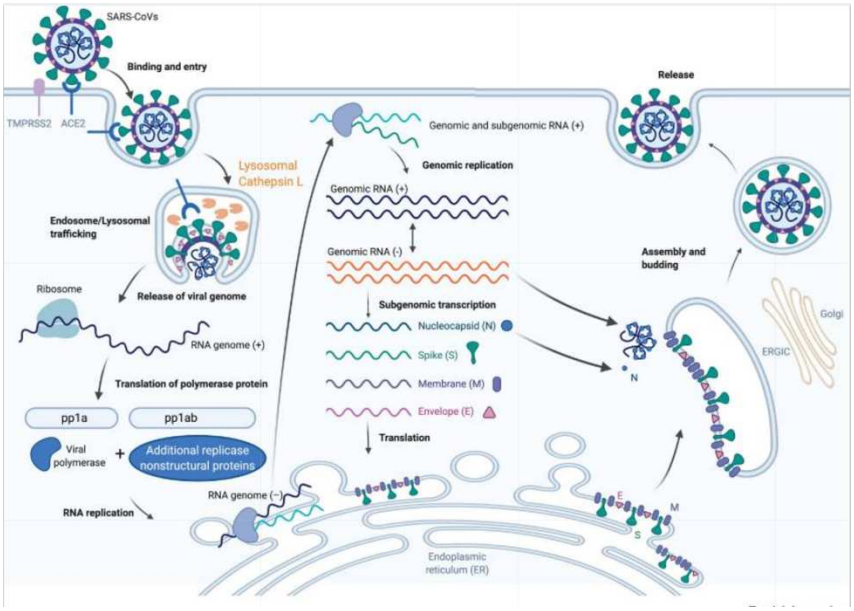

Figure 3. Pathogenesis of SARS-CoV-2 (25).
Source: Harrison AG, Lin T, Wang P. Mechanisms of SARS-CoV-2 Transmission and Pathogenesis. Trends Immunol. 2020;41:1100-1115.

The previously mentioned S protein has two subunits, S1 and S2. They are in charge for membrane fusion and attachment. S1 subunit of the receptor-binding domain (RBD) allows the spike to bind to human ACE2 (hACE2) in the cell membrane (19). It has been established that the SARS-CoV-2 RBD binding capacity has a 10 to 20-fold greater affinity to hACE2 than SARS-CoV RBD. This might explain the higher infectivity of Covid-19 when compared to the previous SARS-CoV outbreaks.

The S2 subunit enables fusion of the viral and host membranes. For that, the host cell´s TMPRSS-2 and ADAM metallopeptidase domain 17 (ADAM17) are both necessary (19). TMPRSS-2 is mainly expressed in the prostate, but it has also been found in the kidney, liver, testicles, gastrointestinal tract, lungs and type II alveolar cells (19, 26). It has a role in in priming of the S protein (28).

After internalization of the pathogen by endocytosis, the viral RNA is released for host cell machinery to carry out viral particle assembly and exocytosis as well as replication and translation. Clinical manifestations may be explained by ACE2 and TMPRSS2 expression, which happens to be in the same target tissues (19).

Nearly 50% of patients also suffer from a chronic underlying cardiovascular or cerebrovascular illness or diabetes (29). The outcome of the disease is determined by the host´s immune status and the virulence factors of the pathogen. Severely ill patients might also have bacterial and fungal co-infections.

The pathogenesis of SARS-CoV-2 (Figure 2) results in inflammatory endothelial processes and leads to diffuse alveolar damage, interstitial fibrosis and exudative inflammation with extensive serous and fibrin exudates, macrophage infiltration and abundant production of inflammatory factors and disseminated vascular coagulopathy, both being significant for the severe outcome of Covid-19. Especially microvascular thrombosis may result in abnormalities of microcirculation and lethal multiple organ disorders (30).

1.2.3. Clinical Presentation

The initial viral load, the integrity of the immune system and the number and configuration of the ACE-2 metalloprotein determine the clinical response to SARS-CoV-2 infection. SARS-CoV-2 has a variety of clinical manifestations ranging from asymptomatic infection to serious pneumonia. Infection manifests as a flu-like disease with the most common symptoms being fever, cough, chills, sore throat, dyspnea, myalgia and loss of smell and taste. Multiple body systems can be affected, exhibiting a wide range of severity and onset. Other symptoms are chest pain, sinusitis, rhinitis, rhinorrhea, dizziness, headache, arthralgia, malaise, neck and back pain. Gastrointestinal complaints such as abdominal pain, nausea, diarrhea and vomiting may also be present (23–25). Covid-19 has a brief incubation period of around 5-6 days.

As time is passing by, it is becoming more and more evident that Covid-19 comprises not just short-term respiratory and gastrointestinal symptoms but also long-term effects including fatigue, dyspnea, cognitive and intellectual degradation, myalgia, chest and joint pains, myocardial inflammation, palpitations, and other cardiac disorders, smell and taste dysfunctions, cough, headache, and gastrointestinal conditions (25,31). Most Covid-19 patients have a mild or moderate illness. In 5-10% the flu-like symptoms can furthermore develop into acute respiratory distress syndrome (ARDS), pneumonia, kidney failure, and even death (25,32). Moreover, venous and arterial thromboembolic conditions can occur as a result of severe inflammation, hypoxia, immobilization and diffuse intravascular coagulation (DIC) (33).

1.2.4. Risk Factors

Risk factors are male gender, advanced age, obesity, higher C-reactive protein and ferritin levels. The presence of comorbidities and higher Pulmonary Disease Severity Index scores are predictors of a worse outcome (34). Females tend to be less susceptible to viral infections than men. This might be due to the protective effects from sex hormones and the additional X chromosome, which both have significant roles in innate and adaptive immunity. Innate immune cells such as monocytes, macrophages, dendritic cells, and cytotoxic T cells are more numerous and active in women (29,35). According to studies, estrogen inhibits proinflammatory cytokines including IL-1 and IL-6, which enhances its protective action. The sex disparities in Covid-19 incidence may also be attributed to differences in activities and behavior. Men show greater rates of drinking and smoking while hand washing and healthcare seeking happen at a lower rate (35).

1.2.5. Diagnosis

Covid-19 can be suspected when there is a known case of infection at the same time and in the same area, and when other individuals present with fever or symptoms of respiratory tract infection within two weeks. It is also possible to be infected with SARS-CoV-2 without exhibiting any symptoms. The epidemiological history, clinical signs and confirmation by several laboratory techniques, including nucleic acid amplification tests (NAAT), radiologic imaging studies, and serological tests are the main components of the clinical diagnosis of Covid-19 (34).

1.2.5.1. Real-time RT-PCR

Reverse polymerase chain reaction (Real-time RT-PCR) has been considered the gold standard for detection of SARS-CoV-2 (34). Specimens from the upper respiratory tract (naso- and oropharyngeal) can be obtained as well as specimens from the lower respiratory tract (expectorated sputum, bronchoalveolar lavage, or endotracheal aspirate) (36). However, the RT-PCR test depends on sampling technique with positive detection rate ranging between 30-60% (37). Therefore, radiologic imaging, especially CT scanning has become an important tool in the diagnosis and management of patients with Covid-19, primarily in severe cases (38). Rapid Antigen Testing using naso- and oropharyngeal swabs is also widely used.

1.2.5.2. Blood tests

In early stages of the disease, the number of leukocytes may stay normal or even decline. Lymphocytes may decrease, and monocyte levels may rise or stay within the normal range (36). Thrombocytopenia can be seen (28). Additional laboratory information should be gathered to aid in the clinical assessment of the illness. Elevation of levels of ferritin, lactate dehydrogenase, liver enzymes, interleukin-6, and D-dimer levels are possible as well as elevation of other inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). In cases where a superimposed bacterial infection is present, procalcitonin can be high (28). Measuring arterial blood gases and oxygen saturation levels is crucial to determine the degree of oxygenation (36,39)

1.2.5.3. Imaging Studies

In patients who develop pneumonia, typical chest X-ray findings show bilateral peripheral patchy opacities. In early stages a high-resolution CT of the chest (HRCT) is more sensitive in comparison to conventional X-ray imaging (28). Patchy ground-glass opacities in the periphery and predominantly in the lower lobe, are frequent manifestations, Figure 3. Consolidation may occur in certain areas, especially as the illness worsens.

It is important to mention that HRCT should be used to assess clinical worsening rather than as a screening test for individuals with suspected Covid-19 (28). Beyond this it must be emphasized that HRCT does not prove the presence of SARS-CoV-2 even in cases with typical pattern as there is a very wide range of other viral and non-viral diseases which may cause a very similar findings in the lung. This includes ground glass-opacities (Figure 4), lymph node enlargement (Figure 5), pleural and basal thickening and infiltrations of various morphology. Table 3 shows typical findings found in patients with Covid-19 (40).

Table 3. CT findings in Covid-19 patients

Ground glass opacifications	83%
Ground-glass opacifications with mixed consolidation	58%
Adjacent pleural thickening	52%
Interlobular septal thickening	48%
Air bronchograms	46%

Autopsy cases show correspondently diffuse alveolar damage, interstitial fibrosis and exudative inflammation with extensive serous and fibrin exudates, macrophage infiltration and abundant production of inflammatory factors. SARS-CoV-2 and ACE2 were co-localized in the alveoli and bronchioles (30).

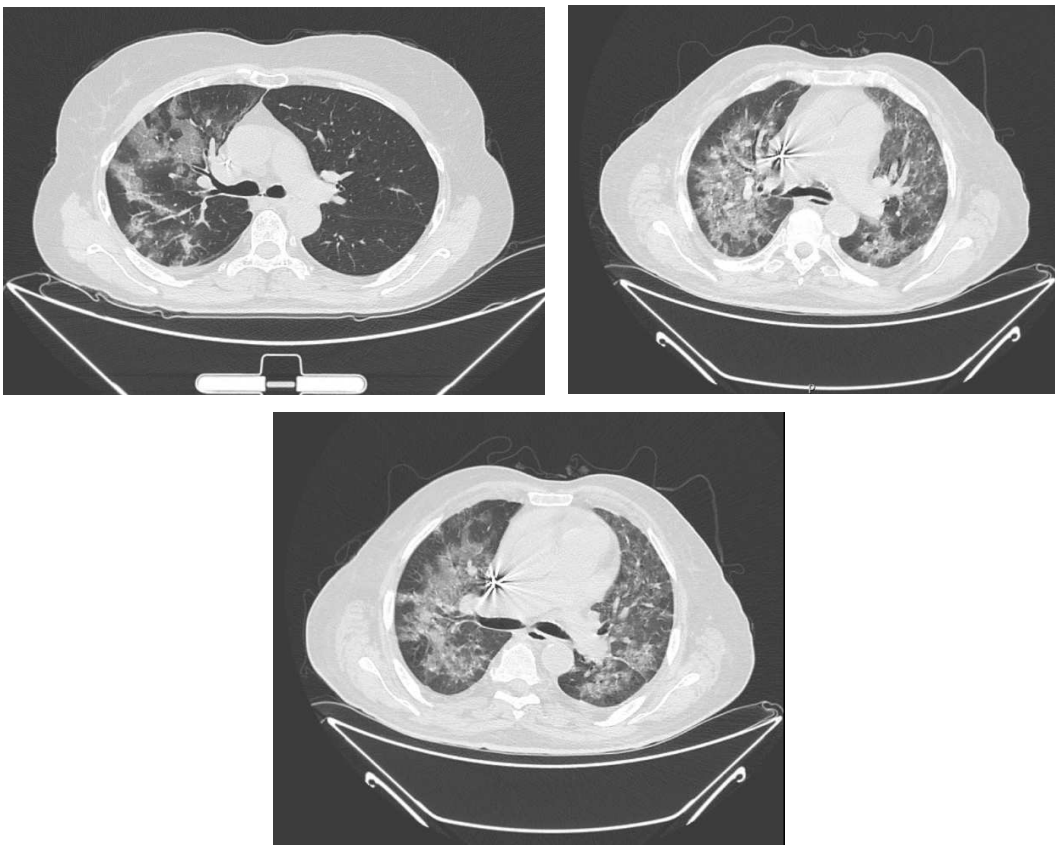

Figure 4. Extended ground glass opacities. (Department of Radiology, University Hospital Split).

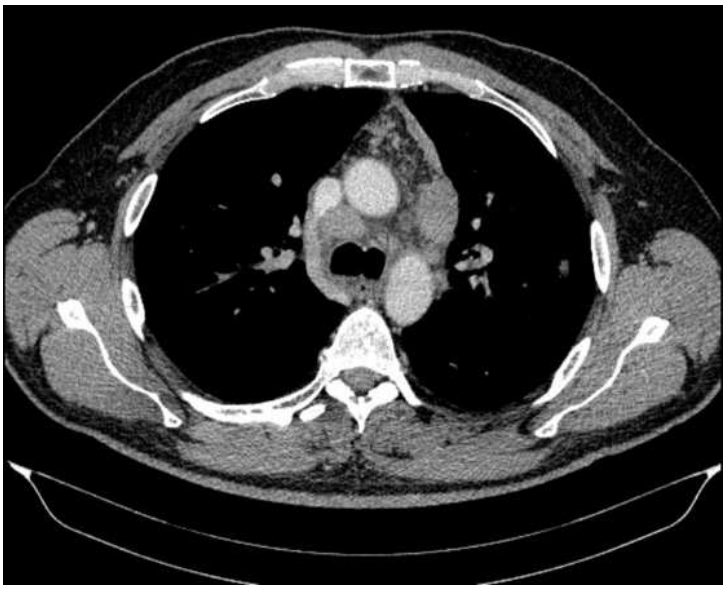

Figure 5. Enlarged retrocaval lymph nodes (Department of Radiology, University Hospital of Split).

1.2.5.4. Ultrasound

It is beneficial for patients in intensive care units to evaluate the lung and heart function without the danger of having to transfer seriously sick patients for radiologic treatments (28). In addition, ultrasound has proved to be of value for evaluation of lung involvement in patients suffering from Covid-19 in the absence of other imaging resources for various reasons. These findings include thickening, discontinuation, and interruption of the pleural line; B lines visible under the pleura that appear discrete, multifocal, or confluent; patchy, strip, and nodular consolidations; and air bronchogram signs in the consolidations (41–43).

Although ultrasound appears to be relatively sensitive for the detection of Covid-19, some studies have reported low specificity. In a systematic review of five studies, the pooled sensitivity and specificity were 86 and 55 percent, respectively (41,44). Ultrasound can help in early risk stratification in Covid-19 patients, guiding further clinical and therapy decisions (45).

1.2.6 Treatment

As diverse as the symptoms can be, as wide is the range of treatment options. Bed rest, monitoring of vital signs and supportive therapy are the cornerstone of a good recovery. It is important to stay hydrated and to ensure sufficient energy intake. Fever can be reduced with antipyretics, preferably paracetamol. In patients with severe respiratory infections, distress, hypoxemia or even shock, oxygen therapy is the first treatment option. The desired oxygen saturation in adults is SpO2 >90% for non-pregnant patients and SpO2> 92-95% in pregnant patients. SpO2>94% should be achieved in children having a severe clinical picture, SpO2>90% in other children (39). High flow nasal oxygen therapy (HFNO) and non-invasive ventilation (NIV) or invasive mechanical ventilation are recommended when nasal cannula or mask oxygen therapy are insufficient (39).

Glucocorticoids may be administered locally or systemically to control inflammation-mediated lung damage and slow the development of respiratory failure and mortality. The recombinant-humanized monoclonal antibody tocilizumab targets IL-6 receptors and prevents IL-6 from binding to it. Elevated IL-6 levels are linked to poorer outcomes (35).

Other treatments may include antiviral drugs, antibiotics in cases of superimposed bacterial infection, prophylactical administration of anticoagulants (35,46).

2. OBJECTIVES

The aim of this study was to evaluate the clinical and computed tomography pulmonary angiogram characteristics of pulmonary embolism seen in patients hospitalized because of a SARS-CoV-2 infection.

Hypothesis:

1. Pulmonary embolism in patients with Covid-19 occurs equally in all pulmonary vessels.

2. It occurs in seriously ill patients with Covid-19.

3. MATERIALS AND METHODS

The present thesis is based on the retrospective observational research carried out in the Department of Radiology at the University Hospital Split (Klinički bolnički centar, Split). Data were collected from the period of March 23, 2020 to January 31, 2021 from the hospital electronic records (3). Data collection was approved by the ethical committee of University Hospital of Split, by decision 2181-147/01/06/M.S.-22-02. Infection with Sars-CoV-2 was verified by a positive qRT-PCR test (LightMix® Modular SARS and Wuhan CoV E-gen and RdRP-gen kit, Cobas 480 Roche).

CT pulmonary angiograms (CTPA) were performed in patients with underlying Covid-19 disease who are suspected to have a pulmonary embolism. Images were taken from an imaging database. CTPAs were analyzed according to the location and the radiological appearance of PE. The patients received i.v. injection of 50-70 mL of high concentration iodinate contrast media. This was performed using a bolus-tracking technique. CT angiograms were acquired on 128 slice multislice CT (Philips, Inguenity Elite). The main pulmonary artery was used as a threshold.

A significant deviation from the normal distribution of all numerical variables was examined by Smirnov-Kolmogorov test. A median (interquartile range, Q1-Q3) was chosen for data description.

4. RESULTS

In total, 280 CTPA were performed in Covid-19 patients and pulmonary embolism was identified in 78 cases. Therefore, prevalence of PE is 27.85%. The majority of patients with PE were elderly people with a median age of 71 (Q1-Q3 62.5-80.5), with a negligible male predominance (n= 49, 62.82%). At least one comorbidity was present in most individuals (n= 64, 82.06%), whereas only 14 (17.94%) were without comorbidities. The most prevalent comorbidity was hypertension, which was present in 34 (43.53%) of PE patients alone or together with other diseases, such as diabetes or cardiac disorders. Diabetes mellitus type II was the second most prevalent condition, occurring in 11 (14.10%) individuals either by itself or in combination with hypertension. Intestinal carcinomas, carcinoma of the urogenital tract and malignancies of the breast were found in 10 (12.82%) patients and was the third most common comorbidity.

Other infrequently discovered comorbidities included autoimmune diseases such as psoriasis, cardiac diseases, gallbladder stones and psychiatric disorders. There was no correlation seen between any specific comorbidity and CT presentation of PE. D-dimer levels were elevated in PE patients (median 12.51, Q1-Q3 8.00-28.04). PE manifested at a median of 14 (Q1-Q3 11-19.5) days after Covid-19 diagnosis was made. Three patients experienced PE symptoms several days to weeks after being released from the hospital after being Covid-19 negative and being clinically recovered. All three individuals previously stayed at the hospital without being in ICU. The remaining patients were tested positive for Covid-19 at the time when CTPA was done. On the day of admission, PE was diagnosed in 50 (61.10%) patients, whereas in 28 (38.90%) patients it was diagnosed during hospitalization. Before onset of PE, all patients were given thromboprophylaxis. Unfortunately, in patients who were diagnosed with PE already at admission data about thromboprophylaxis is not complete and therefore not presented here. Baseline and clinical characteristics of patients are presented in Table 3.

Unilateral distribution of PE in small pulmonary artery branches was common. It occurred in nearly half of the patients who underwent CTPA, the most frequently located in one of the segmental or subsegmental branches (n=23, 29.49% of total number of PE patients), and in 8 (10.25%) cases it was detected in two or more of the segmental branches unilaterally. Typically, these small emboli encompassed areas of Covid-19 inflammation-related CT changes. In contrary, in 33 (42.31%) patients the pulmonary tree affection was bilateral and involved multilobar/multisegmental levels. Branches of all sizes and a wide variety of PE locations were affected. However, they were not necessarily connected to inflammatory alterations on the CT.

As a single vessel, the pulmonary trunk, main, and lobar arteries were the least frequently impacted (n=14, 17.95%). Overall, the right side of the lung was more frequently involved than the left side.

Table 4. Baseline Characteristics of 78 Covid-19 Patients with Pulmonary Embolism

Characteristics	Covid-19 patients with pulmonary emboli, n=78
Age (years)—median (Q1-Q3)	71 (62.5–80.5)
Male—no (%)	49 (62.8)
D-dimers—median (Q1-Q3)	12.51 (8.00–28.04)
Onset of PE (days)—median (Q1-Q3)	14 (11–19.5)

Table 5. CT Pulmonary Angiography Characteristics of 78 Covid-19 Patients with Pulmonary Embolism

Characteristics	Covid-19 patients with pulmonary emboli, n=78
Sites of PE:	
Main pulmonary artery	Truncus pulmonalis, *n*=2 Right main, *n*=2
Lobar artery	RML *n*=3, RLL *n*=4, LLL *n*=2, LUL *n*=1
Segmental	RLL *n*=5, RUL *n*=1, LUL *n*=3, LLL *n*=2
Subsegmental	RLL *n*=2, RUL *n*=2, RML *n*=2 LLL *n*=4, LUL *n*=2
Multilobar/segmental, unilateral:	RUL+RML+RLL *n*=4 RML+RLL *n*=3 left main+LUL+LLL *n*=1
Multilobar/multisegmental, bilateral:	SS in LUL+RLL *n*=2 S LUL+RML *n*=1 RLL and LLL S *n*=2 S and SS RML+RLL *n*=1 S in RUL+LLL *n*=1 RML+RLL+LLL *n*=1 RUL+RML+LLL *n*=2 SS in all lobes *n*=7 S both LL *n*=3 S both UL *n*=3 S LUL+RUL *n*=1 S LUL+RML+RLL *n*=1 Both main+both UL+RML *n*=1 Both main+all lobes *n*=1 L main+both LL *n*=2 R main+both LL *n*=1 R main+both UL *n*=1 R main+both UL+LLL *n*=1 R main+LLL *n*=1

PE = pulmonary embolism; RML = right middle lobe; RLL = right lower lobe; LLL = left lower lobe; LUL = left upper lobe; RUL = right upper lobe; L = left; R = right; UL = upper lobe; LL = lower lobe; S = segmental; SS = subsegmental

5. DISCUSSION

The results of this study illustrate a high incidence of pulmonary embolism in Covid-19 patients mainly in elderly people who suffered from diverse comorbidities (elevated blood pressure in a high percentage, followed by diabetes and malignancies), and had high D-dimer levels. Pulmonary embolism occurred with a median of 14 days from onset of Covid-19, even in a small percentage of Covid-19 negative patients. Small and medium sized branches are more often affected by PE when compared with large pulmonary branches and the main trunk. The findings are in line with previous studies investigating thromboembolic disease in Covid-19, which also showed higher prevalence of peripherally located pulmonary emboli (47,48). Our research shows a similarity to already published papers concerning an embolic manifestation within the lung. These results support the connection between Covid-19 and pulmonary embolism (49).

Chest radiographs and, when needed a native CT examination of the thorax, is an obligatory diagnostic standard when Covid-19 has manifested. Additional CTPA should be performed when there are severe hints for major risk for pulmonary embolism to occur, based on clinical picture, laboratory, and radiological results. D-dimer levels were elevated on admission in patients with pulmonary embolism and rose at time of PE diagnosis (50). Specifically, severe CT-findings, lower level of saturation, and elevated D-dimer levels justify a CTPA. Beyond PE, CT gives valuable information about heart strain and systematic inflammatory response (51).

Usually, higher D-dimer levels are found in PE patients compared with non-PE patients. Elevated D-dimer levels have been reported to be associated with an increased risk of developing PE and may have a predictive value in detecting PE (52, 53). However, high D-dimer levels are not an ultimate diagnostic criterion for PE as they can be elevated in other clinical conditions. In fact, a rise in D-dimer values is frequent in Covid-19 patients, even in the absence of acute pulmonary embolism (54). In patients with detected PE on chest CT, D-dimers had a sensitivity of 67% and specificity of 70% (46). Hence, the increase in D-Dimer values might be related to the intensity and extent of the ongoing inflammation.

Concerning the topographic distribution of pulmonary embolism, every branch of the pulmonary tree can be involved. Our study showed the tendency of PE to be located in the right lung, most often in subsegmental vessels. This might be explained by superior vascularization

of the right lung (47). Another tendency of PE is to occur in areas where Covid-19 caused inflammatory changes which have been detected on CT. This statement remains controversial as there are reports of a lack of relationship between parenchymal disease and PE (55–58). PE more often involves pulmonary branches with small or medium aperture affecting one or both lobes. This higher prevalence of peripherally located pulmonary emboli have been described in many articles (3,47,48,59). These articles speculated about a possible pathogenic mechanism that involved in situ microvascular thrombosis in the affected lung region, primarily linked to Covid-19 inflammatory changes or concurrent endothelial injury effects, leading to a higher incidence of PE in the small-diameter vessels in the involved lung area (60,61).

The fact that there is a significant incidence of PE simultaneously in both lungs and the fact that PE is often a multilocular event should let us assume other reasons than a pure local inflammatory process. Following this assumption researchers detected elevated cytokine levels, where especially interleukin-6 seems to have an impact on the occurrence of thrombosis within the deep venous system (3). On the other hand, some researchers venture a guess that the pulmonary thrombus associated with Covid-19 may primarily originate from the lung since complaints in the leg were less common. As this potential pathogenic mechanism is not known yet maybe a simpler explanation could be the fact that small vessels have a reduced blood flow and therefore are more sensitive for inflammatory processes.

The pathogenesis of Covid-19 associated with PE is unclear. But it has become clear that some Covid-19 patients showed pulmonary vascular involvement. Therefore, some imaging studies reported a vascular involvement in areas of lung opacities, which could indicate an inflammatory response with vascular involvement leading to thrombosis (62–64).

During the different stages of Covid-19, vascular changes have been described, such as endothelial inflammation with microthrombus agglomerations and macrothromobosis of pulmonary arterial vessels (65). According to other researchers, localized immunothrombosis can be the result of the underlying inflammatory process. This is an alternative to the pathogenesis of thromboembolic pulmonary embolism (66–68). We assume that this narrow connection between the topography of thromboembolic manifestations and the region of the consecutive changes of lung density may verify a local origin of the underlying embolic mechanisms in patient with Covid-19. This assumption has been already brought up by other researchers (67–69).

In general, dyspnea is the most common presenting clinical symptom in SARS-CoV-2 infection, followed by cough. Although fever is present in 40% of patients, this is not considered to be a useful factor to determine the severity of illness. As one could expect patients with PE show a minor level of oxygen saturation in comparison to non-PE cohort (70).

The primary radiological findings in Covid-19 patients are diffuse pneumonic infiltrations rather than pulmonary embolism. These infiltrations are characterized by ground glass opacities (Figure 3) with certain patterns, enlargement of the hilar lymph nodes and thickening and enlargement of the vessel wall (30,71). Unfortunately, the radiological pattern of Covid-19 pneumonia is not specific and of little value when trying to determine those patients who are at risk of developing pulmonary embolism, because these patterns can be seen in various viral and non-viral diseases. In patients with PE, CT scans demonstrate a worse score of severity and a larger extent of structural damage accompanied by ground glass opacities when compared with patients who did not suffer from PE. Most of the emboli were found in damaged lung parenchyma where Covid-19 pneumonia took place (72). This may allude to a correlation between the extent of lung parenchymal injuries and a more serious inflammatory reaction resulting in an alveolar damage and to pathomorphological changes of the vascular endothelial cells (69,73). This is in line with current literature regarding prothrombotic change in Covid-19 patients (74,75). These pathomorphological changes are consistent with the clinical picture, which indicates that respiratory distress is the primary cause of Covid-19 related mortality.

Our study shows a prevalence of PE of 27.86%. However, the actual prevalence of PE could be higher than the one found in this presented study. Despite CTPA being the gold standard for diagnosing PE, it is constrained by its spatial and contrast resolution. This furthermore makes it more difficult to detect smaller emboli or thrombi, microvascular inflammation or micro-obstructions.

Pulmonary embolism occurs approximately within a period of two weeks after Covid-19 onset. It has been shown in some other cohorts that a small number of patients developed pulmonary embolism after being discharged from the hospital in a stable condition and some of them did not have inflammatory consolidations detectable at the time when CTPA was obtained (3, 76). We had three of those patients in our study.

Other studies showed cases where pulmonary embolism occurred 110 days and deep vein thrombosis 70 days after Covid-19. This fact indicates that Covid-19 is a risk factor for pulmonary embolism not only in the acute stage but also in the long term (77).

As already mentioned, it is currently unknown if thrombosis would also be encountered commonly if a CTPA was performed earlier. If this assumption proved to be right, it would have a great impact on the timing of the CT examination. In regard to this possibility, further research is required.

One should not forget that elderly people are expected to have more predisposing factors for PE (48,58,59). Possible thrombosis-causing factors in the underlying comorbidities were likely connected to endothelial damage or increased levels of inflammatory markers, which are frequent in the pathophysiology of these individuals. Even though the comorbidities themselves have an impact on the pathophysiology of PE, pathophysiological data indicate that Covid-19 genuinely induces intravascular inflammatory process resulting in microangiopathic endothelial damage (78).

Apart from pulmonary thrombus, two additional CT abnormalities are observed in a significant majority of Covid-19 patients. First, 66% of Covid-19 patients admitted to intensive care unit showed enlarged lymph nodes which in majority could neither have been explained with co-existing pathogens, nor could it have been attributed to the presence of fibrosis. Similarly, pleural effusion is regarded as a non-Covid-19 feature although it is relatively common in Covid-19 cases. In these cases it is discussed to be a feature of comorbidities (79). The second finding is the thickening of pulmonary vessels and enlargement of the pulmonary arteries. The most common radiological finding is “pulmonary vascular enlargement”. Individuals with pneumonias caused by other pathogens than SARS-CoV-2 had pulmonary vascular thickening in 22% and those being infected with SARS-CoV-2 showed this enlargement in 59% of cases. This vessel pathology is due to the failure of normal hypoxic pulmonary vasoconstriction and defective vasoregulation, caused by pulmonary vascular dilatation and rigidity of small vessels. This typically is a result of the diffuse inflammatory process and the consequent over-activation of the regional vasodilatation cascade. It can explain Covid-19-related silent hypoxia in patients with normal lung compliance who develop a significant ventilation/perfusion deficit (38,80).

This raises the discussion about the prevention of thromboembolic events in selected group of patients with mild Covid-19. Having this in mind the question arises if there is a need for contrast enhanced CT scanning in mild forms of Covid-19, which would hopefully result in earlier detection of pulmonary thromboembolism and thus in better clinical outcome. Some authors even consider an immediate thrombosis prophylaxis for up to 14 days after the clinical amelioration in patients with a mild form of Covid-19 that present evidence of lung involvement and increased inflammatory markers (81).

There is a definite necessity for elaborating therapeutic guidelines for patients with mild forms of Covid-19 especially concerning the thromboprophylaxis and diagnostic follow up.

Our study emphasizes the necessity of considering the extent of Covid-19 pneumonia and its severity and potential correlation with the patients in which PE has manifested. With regard to the mild forms further research is necessary to determine the role of CT in this group of patients. We can expect that the indications for CT will be extended

The findings of this thesis must be seen in light of some limitations. The study only included a small number of patients, and data collection was retrospective. The CT scan had been read by experienced specialists, nevertheless some microemboli may be overlooked. Overall, the prevalence of PE might be higher than described in our study.

6. CONCLUSION

Based on this study and reviewed literature, we can conclude the following:

1. Acute pulmonary embolism is a potential complication of Covid-19. It may occur even in mild forms or late in the course of the disease, when the initial symptoms of SARS-CoV-2 infection have already disappeared.

2. Pulmonary embolism occurs predominantly in elderly patients with various comorbidities and elevated D-dimers.

3. The pulmonary tree is affected at all levels, primarily those of smaller diameters and more often in the right lung.

4. Pulmonary embolism in Covid-19 patients seems to be rather an in-situ thrombosis in the lung than a consequence of a deep venous thrombosis, although an embolic event arising from deep vein thrombosis is possible, especially when comorbidities are present. However, further research is necessary on this question.

5. Patients with SARS-CoV-2 more frequently present with fever, cough and diarrhea, whereas noninfected patients complained about chest pain and painful, swollen legs – so there is a difference in the clinical picture of pulmonary infections between Covid-19 and non-Covid-19 patients.

6. Appearance of the embolism and also imaging of the lungs showed differences between infected and noninfected patients. Due to the infection, lung infiltrates and ground-glass opacities were seen more often as well as lymph node and vessel thickening and enlargement. So, beyond the pulmonary embolism, CT scanning shows common morphological patterns, but it must be emphasized that those patterns are not specific for Covid-19 as they can occur in other viral and non-viral diseases.

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8. SUMMARY

Objectives: The objective of this study was to evaluate the clinical and computed tomography pulmonary angiogram characteristics of pulmonary embolism seen in patients hospitalized because of SARS-CoV-2 infection. Additionally, we intended to describe the distribution of the pulmonary emboli.

Subjects and methods: This study is based on a retrospective observational study which was carried out in the Department of Radiology at the University Hospital Split. A sample of 78 patients was chosen who developed pulmonary embolism after being infected with SARS-CoV-2. CTPAs were analyzed according to location and radiological appearance of PE.

Results: Median age is 71 years and there is a slight male predominance. At least one comorbidity is present in majority of individuals (n= 64, 82.06%), whereas only 14 (17.94%) are without comorbidities. The most prevalent comorbidity is hypertension (n= 34, 43.53%) of PE patients either by itself or together with other diseases, such as diabetes or cardiac disorders. D-dimer levels are elevated (median 12.51, Q1-Q3 8.00-28.04) and PE is manifested at a median of 14 (Q1-Q3 11-19.5) days after Covid-19 diagnosis has been made. Unilateral pulmonary embolism was demonstrated in nearly half of patients who underwent CTPA, mostly located in one of the segmental or subsegmental branches (n=23,29.49% of total number of PE patients). In 8 (10.25%) cases PE involved unilaterally two or more of the segmental or subsegmental branches and typically encompassing areas of Covid-19 inflammation-related CT changes. In 33 (42.31%) patients the pulmonary tree affection was bilateral and involved multilobar/multisegmental levels. Branches at all levels and a wide variety of PE locations were present and were not necessarily linked to inflammatory damage seen on CT. The right lobe of the lung was more often involved than the opposite lobe.

Conclusion: Our results showed that acute PE is a potential complication of Covid-19 even in mild forms or late in the course of the disease, when the initial symptoms of SARS-CoV-2 infection have already disappeared. Pulmonary branches of all sizes were affected, primarily those of smaller diameters and more often in the right lung. PE in Covid-19 patients seems to be rather an in-situ thrombosis in the lung than a consequence of a deep venous thrombosis, although an embolic event arising from dee vein thrombosis is possible, especially when comorbidities are present. There is a difference in the clinical picture of pulmonary infections between Covid-19 and non-Covid-19 patients. Appearance of the embolism and imaging of the lungs showed differences between infected and noninfected patients. Due to the infection, lung infiltrates and ground-glass opacities were seen more often as well as lymph node and vessel thickening and enlargement. So, beyond the PE, CT scanning shows common morphological

patterns, but it must be emphasized that those patterns are not specific for Covid-19 as they can occur in other viral and non-viral diseases.

9. CROATIAN SUMMARY

Naslov rada: Kliničke i CTPA karakteristike plućne tromboembolije povezane s Covid-19

Ciljevi: Cilj rada je evaluacija kliničke slike hospitaliziranih pacijenata oboljelih od Covid-19, te analiza nalaza kompjutorizirane tomografije onih pacijenata s popratnom embolijom pluća.
Materijali i metode: Ovaj se rad prvenstveno temelji na retrospektivnoj opservacijskoj studiji provedenoj na odjelu za Radiologiju u Kliničko bolničkom Centru u Splitu.
U studiji je bilo uključeno 78 pacijenata koji su u okviru infekcije sa SARS-CoV-2 imali emboliju pluća kao popratnu komplikaciju.
Rezultati: Medijan starosne dobi je bio 71 godina s laganom prevagom muškog spola. U većini pacijenata je bio barem jedan komorbiditet (n= 64, 82,06%), samo 14 pacijenata (17,94%) je bilo bez popratnih oboljenja od kojih je najčešća bila hipertenzija (n= 34, 43,53%) kao jedina ili s drugim komorbiditetima kao šećerna bolest ili srčana oboljenja. D-dimeri su bili povišeni (medijan 12,51, Q1-Q3 8,00-28,04) dok se pulmonalna embolija manifestirala s medijanom od 14 (Q1-Q3 11-19,5) dana nakon dijagnoze Covid-19. U skoro polovice pacijenata CTPA je pokazala jednostranu pulmonalnu emboliju, najčešće lokaliziranu u segmentalnim ili subsegmentalnim granama (n=23,29,49% od ukupnog broja pacijenata s plućnom embolijom). U 8 slučajeva (10,25%) embolija je jednostrano obuhvatila dvije ili više segmentalnih ili subsegmentalnih grana i pri tome u pravilu obuhvaćala plućne areale sa znakovima upale u CT-u. U 33 pacijenata (42,31%) embolijom su bila pogođena oba plućna krila pri čemu su bile obuhvaćene multilobarne i multisegmentalne grane raznih veličina s velikom topografskom varijacijom. Pri tome embolija nije nužno bila povezana s arealima u kojima je CT pokazivao znakove upalnog procesa.
Zaključci: Naši rezultati pokazuju da je akutna pulmonalna embolija moguća komplikacija kod Covid-19 čak i u blagim slučajevima te se može manifestirati i u kasnijim stadijima oboljenja kada početni simptomi već jenjavaju. Pogođene su grane svih veličina, prvenstveno one s malim promjerom te češće desno plućno krilo. Postoji osnovana sumnja da je pulmonalna embolija u Covid-19 pacijenata lokalnog uzroka a manje posljedica periferne tromboze, iako je takva moguća posebice u pacijenata s komorbiditetima. Isto tako se razlikuju karakteristike pulmonalne embolije kod Covid-19 te općenito slikovni nalazi u CT-u u usporedbi s pacijentima s drugim infekcijama pluća.
Kod Covid-19 često su prisutni infiltrati te "groundglass" promjene, povećani medijastinalni limfni čvorovi kao zadebljanje i proširenja pulmonalnih arterija. Osim pulmonalne embolije CT

pokazuje morfološke promjene koje ukazuju na prisutnost Covid-19 ali koje nisu specifične za Covid-19 jer su prisutne i kod pulmonalnih infekcija drugih uzroka.

10. CURRICULUM VITAE