

**THE PROPORTION OF PULMONARY EMBOLISM
IN COVID-19 PNEUMONIA DIAGNOSED BY
COMPUTED TOMOGRAPHY PULMONARY
ANGIOGRAPHY WITH ITS ASSOCIATED
IMAGING FEATURES AND MARKER IN
HOSPITAL SULTANAH BAHYAH (HSB)**

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LIST OF SYMBOLS, ABBREVIATIONS, AND ACRONYMS

BNP	Brain Natriuretic Peptide
COVID-19	Coronavirus Disease 2019
CRP	C-Reactive Protein
CT	Computed Tomography
CTPA	Computerized Tomography Pulmonary Angiography
DCF	Data Collection Form
ECG	Electrocardiography
EP	Embolisme Peparu
eHis	Electronic Hospital Information System
GGO	Ground Glass Opacities
HRCT	High Resolution Computed Tomography
HSB	Hospital Sultanah Bahiyah
ICU	Intensive Care Unit
LIS	Laboratory Information System
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
PACS	Picture Archiving and Communication System
PE	Pulmonary Embolism
pro-BNP	Pro-Brain Natriuretic Peptide

ROI	Region of Interest
RT-PCR	Real Time Polymerase Chain Reaction
SARS-CoV-1	Severe Acute Respiratory Syndrome Coronavirus 1
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SPSS	Statistical Product and Service Solution
VTE	Venous Thromboembolism
WHO	World Health Organization

ABSTRAK

Latar belakang: COVID-19 merupakan jangkitan virus yang menjangkiti sistem pernafasan dan boleh mengakibatkan kesukaran bernafas. Kajian mendapati risiko untuk embolisme peparu (EP) semakin tinggi dalam kalangan pesakit jangkitan paru-paru COVID-19, seterusnya meningkatkan tahap morbiditi and mortaliti. Kajian mengenai perkadaran, ciri pengimejan dan ujian makmal mengenai EP pesakit jangkitan paru-paru COVID-19 masih belum dibuktikan di Malaysia. Tujuan kajian ini adalah untuk mengenal pasti perkadaran EP, peringkat klinikal jangkitan paru-paru COVID-19, bacaan D-dimer, ciri pengimejan yang berkaitan dan kematian pesakit jangkitan paru-paru COVID-19.

Metodologi: Bertempat di Hospital Sultanah Bahiyah (HSB), Alor Setar, Kedah, Malaysia, satu kajian keratan rentas menggunakan data retrospektif telah dijalankan atas 949 pesakit jangkitan paru-paru COVID-19. Kesemua pesakit ini telah menjalani pengimejan diagnostic CTPA kerana disyaki mengalami komplikasi EP. Kesemua CTPA imej telah dianalisis untuk mengesan darah beku yang menyebabkan EP dan seterusnya dibuat pelaporan mengenai ciri pengimejan yang berkaitan oleh pakar radiologi. Data demografi, peringkat klinikal jangkitan paru-paru COVID-19, bacaan D-dimer dan status mortaliti telah dikumpulkan dan direkodkan. Kadar perhubungan antara EP dalam kalangan pesakit COVID-19 dan status mortaliti dianalisis menggunakan Pearson Chi-Square Test. Independent T-test digunakan untuk menganggarkan perbezaan purata untuk umur dan bacaan D-dimer antara PE dan tanpa PE dalam jangkitan paru-paru COVID-19.

Keputusan: Seramai 216 (22.8%) daripada 949 subjek yang menghidapi jangkitan paru-paru COVID-19 telah mengalami komplikasi EP berdasarkan CTPA yang dijalankan, dimana darah beku paling kerap ditemui di salur darah arteri segmental dan subsegmental. Ciri pengimejan yang paling tinggi dijumpai adalah ground glass appearance (GGO).

Jangkitan paru-paru COVID-19 dengan EP menunjukkan bacaan D-dimer yang tinggi dengan purata 6.74 berbanding dengan purata 3.93 untuk pesakit yang negatif untuk EP ($p = <0.001$). Seramai 121 dari 216 kematian pesakit COVID-19 dengan EP telah disumbangkan oleh subjek yang dikategorikan tahap 4 (56.0%), selebihnya oleh tahap 5 iaitu 90 (41.7%). Perkadaran mortaliti antara pesakit COVID-19 dengan EP adalah 32.4%, menunjukkan perhubungan yang ketara secara statistik antara peratusan kematian dan EP ($p < 0.001$).

Kesimpulan: Kajian kami menunjukkan terdapat 1 dalam 5 pesakit mengalami EP yang didiagnosis melalui CTPA dalam kalangan pesakit COVID-19. Kajian ini juga menekankan kepentingan penilaian keputusan makmal dalam mengenalpasti subjek yang berisiko untuk EP. Dengan mengenal pasti ciri pengimejan dan keputusan makmal yang berkaitan untuk pesakit yang mengalami komplikasi EP dalam pesakit COVID-19, ini dapat membantu dalam diagnosis pesakit, seterusnya dapat memberi rawatan sewajarnya dan menghindari dari risiko mortaliti.

Kata kunci: pneumonia COVID-19, tomografi berkomputer angiografi pulmonari, embolisme peparu, D-dimer

ABSTRACT

Background: COVID-19 pneumonia is a viral infection that primarily affects the respiratory system and can lead to severe respiratory distress. Recent studies have suggested an increased risk of pulmonary embolism (PE) in COVID-19 pneumonia which could lead to morbidity and mortality. However, the proportion, imaging features, and biomarkers such as D-dimer level of PE in COVID-19 pneumonia are yet to be established in Malaysia. The purpose of this study is to determine the proportion of PE, clinical staging of COVID-19 pneumonia, D-dimer levels, associated imaging features and the mortality rate among COVID-19 pneumonia.

Methods: A cross-sectional study that using retrospective data conducted in Hospital Sultanah Bahiyah (HSB), Alor Setar, Kedah, Malaysia, on 949 patients with COVID-19 pneumonia suspected with PE underwent CTPA. All the CTPA images were reviewed and reported for the presence of PE and associated imaging features by radiologists in the Radiology Department at HSB. The demography, clinical staging of COVID-19 pneumonia, D-dimer levels and mortality status were collected. The association between PE in COVID-19 pneumonia and mortality status were tested using Pearson's Chi-Square Test. The independent T-test was used to estimate the mean difference age and D-dimer levels between PE and without PE in COVID-19 pneumonia.

Result: A total of 216 (22.8%) were diagnosed with PE by CTPA and commonly found in segmental and subsegmental pulmonary arteries. The most common associated imaging feature was ground-glass opacities. COVID-19 pneumonia with PE showed elevated D-dimer levels, with a mean of 6.74 (SD 7.34) vs. 3.93 (SD 5.51) without PE ($p = <0.001$). Out of the 216 death in COVID-19 pneumonia with PE, the clinical staging in stage 4 were 121 (56.0%) and followed by stage 5 which

demonstrated 90 (41.7%). The mortality rate (32.4%) among the PE in COVID-19 pneumonia was statistically significant association with PE ($p < 0.001$).

Conclusion: Our study demonstrated that one-fifth of COVID-19 pneumonia were diagnosed with PE by CTPA and highlights the importance of evaluating clinical biomarkers to identify those at risk for this complication. The identification of imaging features and biomarkers associated with PE in COVID-19 pneumonia could improve the diagnosis and treatment of this potentially life-threatening condition and thus prevent mortality.

Keywords: COVID-19 pneumonia, computed tomography pulmonary angiography, pulmonary embolism, D-dimer

CHAPTER 1: BACKGROUND

1.1 Introduction

COVID-19 pneumonia is a respiratory illness caused by the SARS-CoV-2 virus and was first detected in Wuhan, China in December 2019 (Astuti and Ysrafil, 2020). It was declared a global pandemic by the WHO in 11 March 2020 (Cucinotta and Vanelli, 2020). While most people with COVID-19 experience mild to moderate symptoms, some may develop more severe disease with a higher risk of complications. These complications include lung fibrosis, venous thromboembolism (VTE), arterial thromboses, myocarditis, stroke, "brain fog," skin rashes, and overall mood dysfunctions (Desai et al., 2022).

PE occurs when a thrombus formed and lodged in one of the arteries of the pulmonary vasculature, leading to impaired blood flow and oxygenation. Non-COVID-19 pneumonia cases have a PE incidence of 60 to 70 per 100,000, however exact epidemiological data on PE is currently unavailable (Bělohávek et al., 2013).

Studies have shown that PE is a complication of COVID-19 pneumonia (Desai et al., 2022). However, the actual prevalence of PE in COVID-19 pneumonia is not well established and can vary depending on various factors such as patient population, diagnostic criteria, and study design (van Twist et al., 2021).

The pathophysiology of PE in COVID-19 pneumonia is not entirely clear, but there are various suggested mechanisms that may contribute to its development. The factors that contribute to the formation of PE in COVID-19 pneumonia are likely multifactorial and include hypercoagulability due to inflammation, endothelial dysfunction, and activation of prothrombotic factors, as well as direct and indirect damage from the virus and comorbidities (Fu et al., 2022).

The diagnosis of PE typically involves a combination of clinical evaluation, imaging tests, and laboratory tests. Clinician will start by assessing the patient's symptoms. Symptoms of PE may include sudden onset of respiratory distress, desaturation or hypoxia should raise the suspicion of PE. Clinical work-up include electrocardiography (ECG), chest radiograph, echocardiography, laboratory investigation primarily D-dimer and imaging such as CTPA or ventilation-perfusion scintigraph (Estrada-Y-Martin and Oldham, 2011; Gayed et al., 2022).

Several unknown aspects of PE in COVID-19 pneumonia include:

Prevalence and incidence: The exact prevalence and incidence of PE in COVID-19 patients are not yet well-established. Further research is needed to determine the frequency and magnitude of this complication in individuals with COVID-19 pneumonia.

The higher incidence of PE in men than women. The observation that PE appears to be more common in males with COVID-19 pneumonia is an area of ongoing investigation, and the exact reasons for this gender disparity are not yet fully understood. However, several potential factors have been proposed such as underlying comorbidities, coagulation differences, immune response, behavioural and lifestyle factors and hormonal influences (Capuano et al., 2020).

The underlying pathophysiology by which COVID-19 pneumonia contributed to an increased risk of PE are not fully understood. It is crucial to investigate the pathophysiological processes and potential mechanisms involved in the development of PE in COVID-19 pneumonia (Angelini et al., 2022; Dayanand and Olivia E. Atherton¹, Jennifer L. Tackett², Emilio Ferrer¹, 2018).

Computed Tomography Pulmonary Angiography (CTPA) is commonly used to diagnose PE and is considered the gold standard imaging modality. However, its

usefulness in cases with low or intermediate pretest probability of PE requires careful consideration.

CTPA involves the use of ionizing radiation, which carries a potential risk of cumulative radiation exposure, particularly in young patients or individuals who may require multiple imaging studies. The risks associated with radiation should be weighed against the potential benefits of diagnosing or ruling out PE in low or intermediate pretest probability cases (Korevaar et al., 2021).

CTPA is a resource-intensive imaging technique that may require intravenous contrast administration and skilled interpretation by radiologists. Using CTPA as the primary screening tool for every patient with low or intermediate pretest probability of PE may lead to increased healthcare costs and strain on resources (Korevaar et al., 2021).

Optimal management strategies for PE in COVID-19 pneumonia require further investigation. This includes determining the most appropriate anticoagulation regimens, evaluating the role of thrombolysis or other interventions, and assessing the impact of different treatment approaches on patient outcomes (Nishimoto et al., 2022).

The long-term consequences and outcomes of PE in different novel strains of COVID-19 survivors are not well-documented. Long-term follow-up studies are necessary to understand the potential long-term complications, recurrence rates, and overall prognosis in individuals who have experienced PE during their COVID-19 illness (Desai et al., 2022).

D-dimer test is a commonly used screening tool for PE in COVID-19 pneumonia. However, it is important to note that while D-dimer test is a valuable tool, it is not considered the definitive or best screening tool for PE in COVID-19 pneumonia (Elberts et al., 2021). Several knowledge gaps of D-dimer levels in PE with COVID-19 pneumonia. These include:

Optimal cut-off values: The determination of an optimal cut-off value for D-dimer levels in PE with COVID-19 pneumonia is still an area of uncertainty. Different studies have proposed varying thresholds, and further research is needed to establish a universally accepted cut-off value (Korevaar et al., 2021; Revel et al., 2022).

Predictive value: While elevated D-dimer levels have been observed in COVID-19 pneumonia with PE, the predictive value of D-dimer levels for the diagnosis of PE and assessing its severity in COVID-19 pneumonia is not well-defined. More research is needed to understand the accuracy and reliability of D-dimer levels as a diagnostic and prognostic marker (Cidade et al., 2022).

Role of anticoagulation: The optimal management strategy for COVID-19 pneumonia and elevated D-dimer levels, including the initiation and duration of anticoagulation therapy, is still a matter of debate. Further studies are needed to determine the benefits and potential risks associated with anticoagulation in this population (Chandra et al., 2022; Lehmann et al., 2021).

Long-term outcomes: The long-term implications of elevated D-dimer levels in COVID-19 pneumonia with PE are not yet fully understood. It is unclear whether these patients have a higher risk of recurrent thromboembolic events or other long-term complications (Townsend et al., 2021).

By identifying these gaps, we can design studies and experiments that address these unanswered questions, which can lead to new insights and discoveries have significant implications for clinical practice, helping healthcare professionals to better manage COVID-19 pneumonia at risk of developing thromboembolic complications.

The objective of this study was to investigate the proportion of PE in COVID-19 pneumonia and identified the risk factors associated with an increased risk of developing PE in this population. We conducted a cross sectional study using

retrospective data retrieved from electronic health records of COVID-19 pneumonia admitted to hospital who underwent CTPA. We analysed the data to identify the proportion of PE in COVID-19 pneumonia and assessed the impact of various risk factors such as age, gender, disease severity and D-dimer levels on the development of PE.

1.2 Objectives

1.2.1 General Objective

To investigate PE in COVID-19 and its association.

1.2.2 Specific Objectives

1. To determine proportion of PE and at each clinical staging of COVID-19 pneumonia.
2. To determine the vessel involvement in PE within the lungs in COVID-19 pneumonia.
3. To determine the associated imaging features besides PE in COVID-19 pneumonia.
4. To determine the mean difference in D-dimer between PE and without PE
5. To determine the mortality rate for PE in COVID-19 pneumonia.

1.3 Hypothesis

Null Hypothesis: There is no significant difference in D-dimer level between COVID-19 pneumonia with and without PE.

Alternative Hypothesis: There is significant difference in D-dimer level between COVID-19 with and without PE.

1.4 Research Question

1. What is the proportion of PE and at each clinical staging in COVID-19 pneumonia in Malaysian population?

2. Which are the vessels involvement in PE in COVID-19 pneumonia?
3. What are the associated imaging features apart from PE in COVID-19 pneumonia?
4. What is the different level of D-dimer between COVID-19 pneumonia with and without PE?
5. What is the mortality rate for PE in COVID-19 pneumonia?

CHAPTER 2: LITERATURE REVIEW

2.1 Proportion of PE in COVID-19 Pneumonia

The prevalence of PE in COVID-19 pneumonia varies depending on the study and population examined. Some studies have reported a relatively low prevalence of PE in COVID-19 pneumonia while others have reported a higher prevalence.

The actual prevalence of PE in COVID-19 remains unclear (van Twist et al., 2021). Studies showed that PE in COVID-19 pneumonia were range of 23 to 30% (Sakr et al., 2020). These studies had varying inclusion criteria such as only those referred by physician undergone CTPA, patient populations such as CTPA only performed in COVID-19 pneumonia with clinical suspicion of PE, and diagnostic methods such as specific cut-off D-dimer levels to exclude PE, which may contribute to the differences in reported prevalence rates .

Some studies have suggested that COVID-19 pneumonia associated with a higher risk of thromboembolic events, including PE, compared to other viral respiratory infections.

A study showed that the incidence of thrombosis in patients hospitalized with non-COVID-19 pneumonia acute viral respiratory illnesses compared to the incidence among hospitalized COVID-19 pneumonia. The proportion of hospitalization complicated by thrombosis was lower in patients with viral respiratory illness than in COVID-19 pneumonia (5% vs 16%) (Smilowitz et al., 2021).

Another study clarified that thrombosis is not only limited to COVID-19 pneumonia but also a complication with influenza in adults and children. Thrombosis can occur despite thromboprophylaxis in hospitalized patients. The SARS-CoV-2 and influenza viruses share many similarities, including the route of transmission and the clinical

manifestations. Similar to SARS-CoV-2, the influenza virus has significant effects on the inflammatory and coagulation pathways and may contribute to cardiovascular disease (Rubino et al., 2022).

The SARS-CoV-1 virus, which caused an epidemic in 2003, had similar hematologic manifestations and thrombotic complications as COVID-19 pneumonia. Nicholls et al. found edema and fibrin thrombi in the pulmonary vasculature of an infected patient, while autopsies revealed thrombi in pulmonary, bronchial, and small lung veins. A Singaporean study found pulmonary embolism, deep vein thrombosis, and multi-organ infarcts due to thrombi in some SARS-CoV-1 patients. A 57-year-old patient showed multiple organ thrombosis and microcirculation disturbance. Additionally, a study by Umapathi et al. reported ischemic strokes in 5 out of 206 patients, and around 30% of critically ill patients had VTE. (Giannis et al., 2020).

Microthrombi in pulmonary vasculature was observed in mice infected with MERS-CoV pneumonia, according to Li et al.'s findings. Thrombocytopenia was found to be a common clinical feature in MERS patients by Assiri et al., and Hwang et al. reported that MERS pneumonia often have lower platelet counts. These studies suggested that coagulation disorders and PE may be linked to the poor prognosis of MERS pneumonia (M. Yao et al., 2020).

The incidence of thrombotic events, both venous and arterial, were unexpectedly similar between COVID-19 and MERS-CoV, with COVID-19 having a higher rate of venous thrombosis and MERS-CoV having a higher rate of arterial thrombosis. This suggested that thrombotic complications were a distinctive complication of coronaviruses (Al Raizah et al., 2022).

2.2 Risk factors of PE in COVID-19 Pneumonia

Some of the risk factors for developing PE in COVID-19 pneumonia may include age, male gender, comorbidities such as obesity, diabetes, cardiovascular and cerebrovascular diseases, immobilization, critical ill requiring intensive care unit (ICU) admission or elevated D-dimer level (Gómez et al., 2021; Sakr et al., 2020).

COVID-19 pneumonia has been classified into several stages due to its natural history of disease progression through several clinical phases. The purpose of staging systems in COVID-19 pneumonia is to offer useful guidelines and standards for clinical judgement in patient care, better prognostication, and the selection of evidence-based treatments.

According to the guidelines provided by Malaysia Ministry of Health for the clinical management of confirmed COVID-19 pneumonia in adults, these patients are classified into 5 categories as stated in the table below. The clinical management of COVID-19 pneumonia is based on these categories (Ministry of Health, Malaysia).

Table 2.1: Clinical Staging of COVID-19 Pneumonia

Clinical Stage	Disease Severity
1	Asymptomatic
2	Symptomatic, No Pneumonia
3	Symptomatic, Pneumonia
4	Symptomatic, Pneumonia, Requiring supplemental oxygen
5	Critically ill with or without other organ failures

Adapted from Ministry of Health, Malaysia

2.3 Imaging of PE in COVID-19 Pneumonia

Imaging plays a critical role in the diagnosis of PE in COVID-19 pneumonia, as the clinical presentation of PE in these patients can be atypical and nonspecific. CTPA is

considered the gold standard and recommended for diagnosis of PE. Other diagnostic tests that may be used to diagnose PE include ventilation-perfusion (V/Q) scans and pulmonary angiography. However, CTPA is generally preferred because it is non-invasive, widely available, provides high-quality images and disease severity that can be used to guide treatment decisions (R. M. Kwee et al., 2021; Yassin et al., 2021).

It is used to detect location of the PE as in main, lobar, segmental, or subsegmental pulmonary arteries (Yassin et al., 2021). Studies showed that most of the PE in COVID-19 pneumonia most commonly involved the segmental and subsegmental pulmonary arteries (Valle et al., 2021).

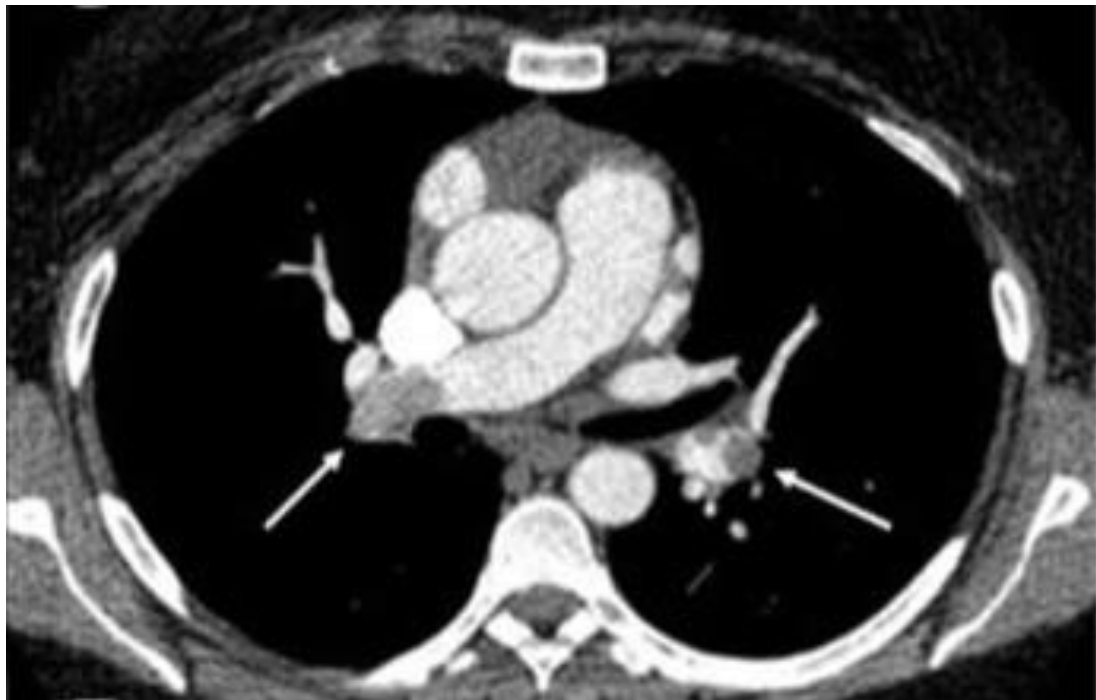


Figure 1: Axial CTPA demonstrated a saddle PE involving the right and left main pulmonary arteries (Adapted from Yassin et al., 2021)

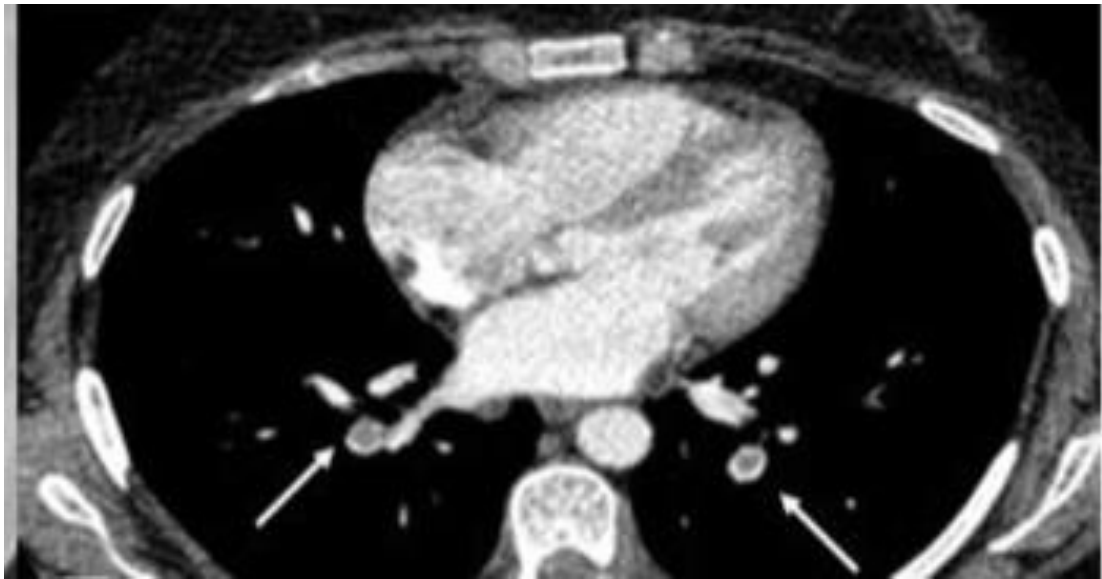


Figure 2: Axial CTPA demonstrated PE involving the right and left lobar pulmonary arteries (Adapated from Yassin et al., 2021)

The associated imaging features included ground-glass opacities (GGO), consolidations, crazy paving pattern, air bronchogram, halo sign, reversed halo sign, vascular enlargement or vascular angiopathy, fibrosis, pericardial effusion, extra-pulmonary signs included pleural effusion and mediastinal lymphadenopathy (Hefeda, 2020; T. C. Kwee and Kwee, 2020; Landete et al., 2020; Sun et al., 2020).

2.4 D-dimer levels in PE with COVID-19 Pneumonia

D-dimer is a fibrin degradation and is a commonly used biomarker to evaluate the risk of PE in COVID-19 pneumonia. However, the diagnostic value of D-dimer in predicting PE in COVID-19 pneumonia is still a subject of debate (Zhan et al., 2021). Studies have shown that elevated D-dimer levels in COVID-19 pneumonia is associated with an increased risk of PE (Gómez et al., 2021). A prospective study found that the pooled prevalence of PE in COVID-19 pneumonia had higher D-dimer levels (Alonso-Fernández et al., 2020). Another study found that among COVID-19 pneumonia who underwent CTPA, those with PE had significantly higher D-dimer levels than those without PE (R. M. Kwee et al., 2021).

However, the diagnostic value of D-dimer in predicting PE in COVID-19 pneumonia is limited by its low specificity. A normal D-dimer level makes PE unlikely and has a high negative predictive value and a positive predictive value of elevated D-dimer level is low. This means that while elevated D-dimer levels are associated with an increased risk of PE in COVID-19 pneumonia, it may not be specific enough to confirm the diagnosis of PE (Vivan et al., 2022). Due to the presence of variations of D-dimer levels in COVID-19 pneumonia, the diagnosis of PE in COVID-19 pneumonia should be confirmed using appropriate imaging modalities such as CTPA or ventilation-perfusion (V/Q) scanning (Ahlers and Said-Hartley, 2022; Gayed et al., 2022).

2.5 Mortality rate in PE with COVID-19 Pneumonia

The mortality rate in PE with COVID-19 pneumonia can vary depending on several factors, such as the age, gender, severity of the disease, the presence of underlying comorbidities, the timeliness and effectiveness of treatment.

A meta-analysis included a total of 50 studies including 10053 COVID-19 pneumonia who were hospitalized with PE, the results indicated that COVID-19 pneumonia with PE experienced significantly higher mortality which was 21.9%. This is higher than the mortality rate reported for patients without PE, which was 10.7% (Fu et al., 2022). Another study published in *Frontiers of Medicine* 2021 found that COVID-19 pneumonia with PE who received anticoagulant therapy had a significantly lower mortality rate compared to those who did not receive anticoagulant therapy (29.1% vs. 62.7%) (Jiang et al., 2021). This highlights the importance of prompt and appropriate treatment for COVID-19 pneumonia with suspected or confirmed PE.

2.6 Conceptual Framework

This conceptual framework for this study was the investigation of PE in COVID-19 pneumonia in terms of the location of the PE and associated imaging features in CTPA. It also evaluated the risk factors, D-dimer levels and the mortality rate in PE with COVID-19 pneumonia (Figure 3).

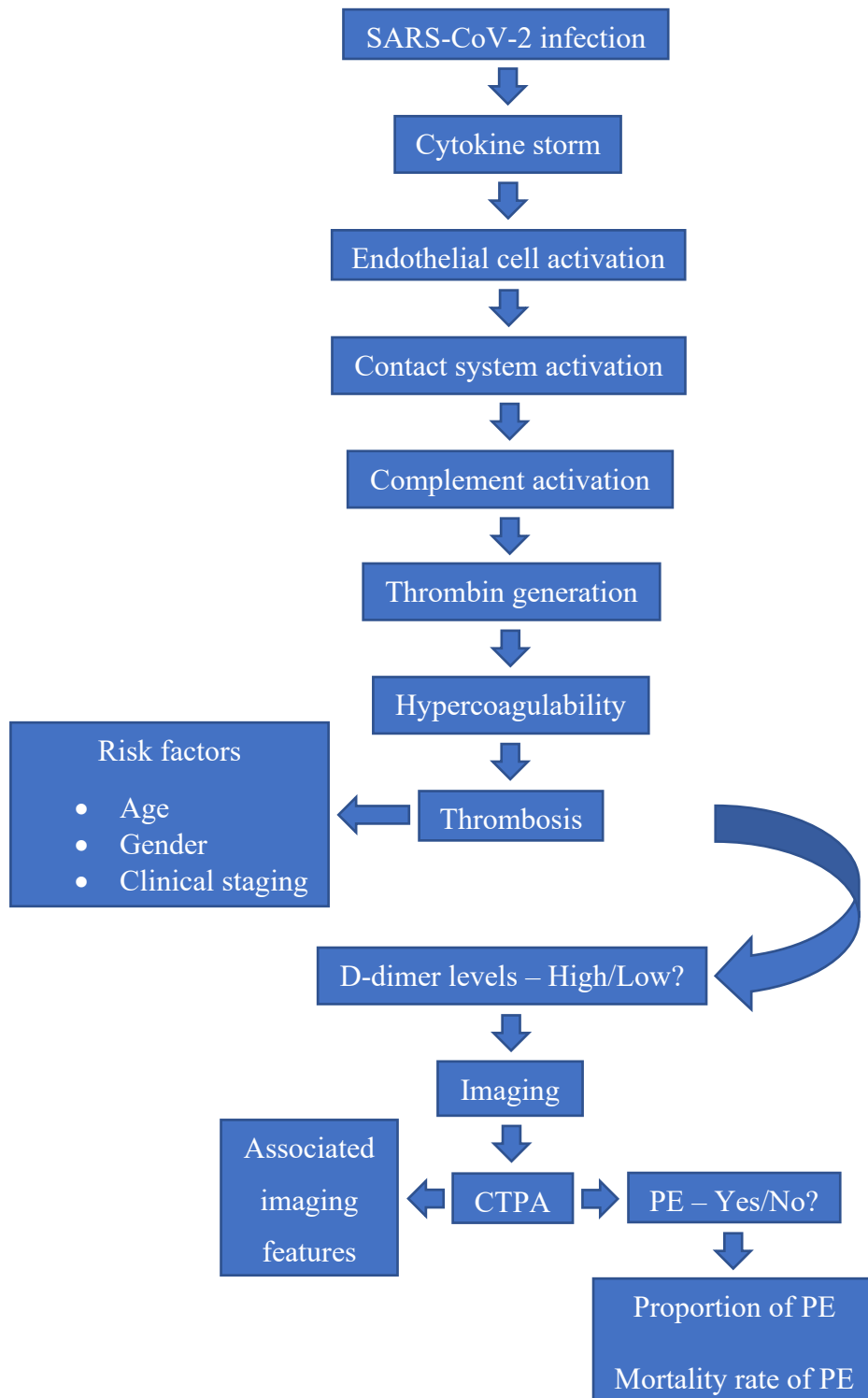


Figure 3: Conceptual framework

2.7 Study Rationale

Literatures suggested that COVID-19 pneumonia has higher risk of PE. No local data yet to establish in Malaysia. The study of PE in COVID-19 pneumonia allows radiologists to understand the characteristics of PE as well as associated imaging features in local population.

Studies have shown that higher D-dimer levels are associated with a higher risk of PE in COVID-19 pneumonia, and that a high D-dimer level can be used to guide further diagnostic testing and anticoagulation therapy. It is worth study the baseline for D-dimer levels in the local population for the similar purposes.

Research concluded that comorbidities such as chronic kidney disease and heart disease are risk factors for PE in COVID-19 pneumonia. It is worth study other risk factors of PE in COVID-19 pneumonia.

CHAPTER 3: METHODOLOGY

3.1 Study Design

A cross-sectional study that collected retrospective data conducted in HSB, Alor Setar, Kedah, Malaysia. Data were collected for a period of 1 year from March 2021 to February 2022.

3.2 Study Population and Sample

The study population were divided into reference, target and sampling population. First, the reference population involved all the COVID-19 pneumonia who were referred for CTPA. The target population included all the COVID-19 pneumonia who underwent CTPA. Finally, sampling population included all COVID-19 pneumonia who underwent CTPA in Department of Radiology, HSB and fulfilled the inclusion and exclusion criteria.

3.3 Sample Size Calculation

To estimate sample size for a first specific objective, a single proportion formula is used. By setting the confidence level at 95%, the margin of error at 5%, and the population size at 30%, the sample size required for the first objective is 323 (Sakr et al., 2020).

To determine sample size for second specific objective, a formula of single proportion is used. By setting the confidence level at 95%, margin of error at 5%, and population size as an unlimited population size. The sample size estimated are stated as table 3.1.

Table 3.1: Sample Size Estimation for Pulmonary Artery Involvement in PE with COVID-19 Pneumonia

Pulmonary Involvement	Artery	Proportion of Pulmonary Artery	Sample Size Estimated
Main pulmonary artery		20%	246
(Thomas et al., 2020)			
Lobar	(Poyiadji et al., 2020)	31%	329
Segmental	(Poyiadji et al., 2020)	51%	385
Subsegmental	(Poyiadji et al., 2020; Thomas et al., 2020)	20%	246

To determine sample size for the third specific objective, a formula of single proportion is used. By setting the confidence level at 95%, margin of error at 5%, and population size as an unlimited population size, the sample size estimated are stated as table 3.2.

Table 3.2: Sample Size Estimation for Associated Imaging Features in COVID-19 Pneumonia

Associated Features	Imaging	Proportion	Sample Size Estimated
Ground glass opacities		91.8%	116
(khalifa et al., 2021)			
Crazy paving pattern		60.3%	368
(khalifa et al., 2021)			

Table 3.2 continued

Consolidation (khalifa et al., 2021)	80%	246
Air bronchogram (Hefeda, 2020)	28 to 80%	246 to 310
Halo sign (Hefeda, 2020)	26%	296
Reverse halo sign (Sales et al., 2021)	5%	73
Vascular angiopathy (Lang et al., 2020)	86.7%	178
Fibrosis (Hefeda, 2020)	20%	246
Mediastinal lymphadenopathy (Hefeda, 2020)	1 to 6%	16 to 87
Pleural effusion (Hefeda, 2020)	2 to 5%	31 to 73
Pericardial effusion (Hefeda, 2020)	1	73

To determine the sample size for fourth specific objective, a previous study was referred. Assuming that the D-dimer level within each group was normally distributed with a standard deviation of 15.77. If the actual difference of D-dimer level in the PE and without PE is 5.04, 155 COVID-19 pneumonia with PE and 155 without PE to be able to reject the null hypothesis that the population means of the PE and without PE

groups are equal with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05 (Gómez et al., 2021).

To determine the sample size for fifth specific objective, a single proportion formula is used. By setting the confidence level at 95%, the margin of error at 5%, and the population size at 21.9%, the sample size required for the fifth objective is 263 (Fu et al., 2022).

After considering the sample size estimation for all the objectives above, the highest sample size was 385.

3.4 Sampling method

All cases that fulfilled the inclusion and exclusion criteria from March 2021 to February 2022 were sampled. All COVID-19 pneumonia in clinical stage 1 to 5, who were admitted to HSB, were referred for CTPA with D-dimer levels extracted from the eHIS.

3.5 Inclusion criteria

1. COVID-19 pneumonia who successfully did CTPA in March 2021 to February 2022 using test bolus protocol,
2. Patients age 18 years old and above,
3. Patients with D-dimer levels, and
4. Patients with small cannula size.

3.6 Exclusion criteria

1. Unsuccessful CTPA such as contrast extravasation,
2. Images of CTPA severely degraded by artefacts such as breathing or motion that interfere the quality of image,
3. Unavailable medical or laboratory records such as D-dimer level, or
4. Inconclusive report.

3.7 Research tool

1. Radiology Information System - Picture Archiving and Communication System (PACS) version 6.0 and eHIS for image acquisition, access to demography or clinical data information.
2. eHis is electronic hospital integrated system. It is an integrated electronic systems that collect, store, retrieve and display overall patients' data and information. This system enhances the ability of health care professionals to coordinate care by providing a patient's health information and visit history at the place and time that it is needed. Patient's laboratory test information also includes visual results such as radiographs, which may be reachable by professionals. eHIS provide internal and external communication among health care providers. It is often composed of one or several software components with specialty-specific extensions for example laboratory information system (LIS), Policy and Procedure Management System, radiology information system (RIS) or picture archiving and communication system (PACS) (Adoption of hospital information system (HIS) in Malaysian public hospitals).
3. Philips Ingenuity Core 128 Multislice CT Scan (Figure 4).
4. Philips IntelliSpace Portal Workstation Version 9.0.
5. Barco 21" medical monitor for image viewing and interpretation (Figure 5).
6. Statistical Product and Service Solutions (SPSS) for Windows, SPSS Inc.© (Version 29, SPSS Inc., Chicago, IL, USA) was used for data analysis.



Figure 4: Philips Ingenuity Core CT scanner



Figure 5: Barco 21" medical monitor

3.8 Operational Definition

1. Air bronchogram is an imaging finding applicable in radiographs and CT scans. An air bronchogram is a pattern of air-filled (low-attenuation) bronchi on a background of opaque (high-attenuation) airless lung (Hansell et al., 2008) (Figure 6).

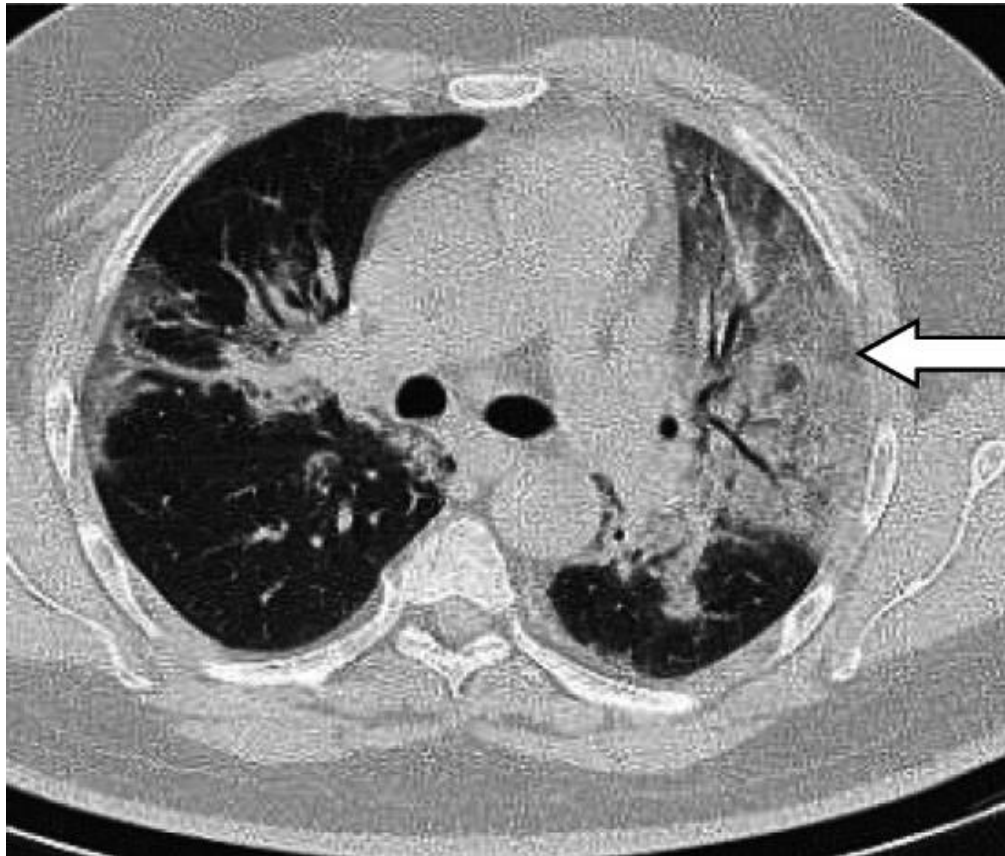


Figure 6: Axial high resolution CT (HRCT) demonstrated wide areas of ground glass infiltration with air bronchogram (Adapted from Hefeda, 2020)

2. BNP is Brain Natriuretic Peptide, which is a neurohormone produced by the heart. BNP is released in response to changes in pressure in the heart, and acts to reduce blood pressure and increase the excretion of salt and water by the kidneys (Arram et al., 2014; Yang et al., 2021)
3. Crazy paving pattern is an imaging finding applicable in CT scans. This pattern appears as thickened interlobular septa and intralobular lines superimposed on

a background of ground-glass opacity, resembling irregularly shaped paving stones. The crazy-paving pattern is often sharply demarcated from more normal lung and may have a geographic outline (Hansell et al., 2008) (Figure 7).

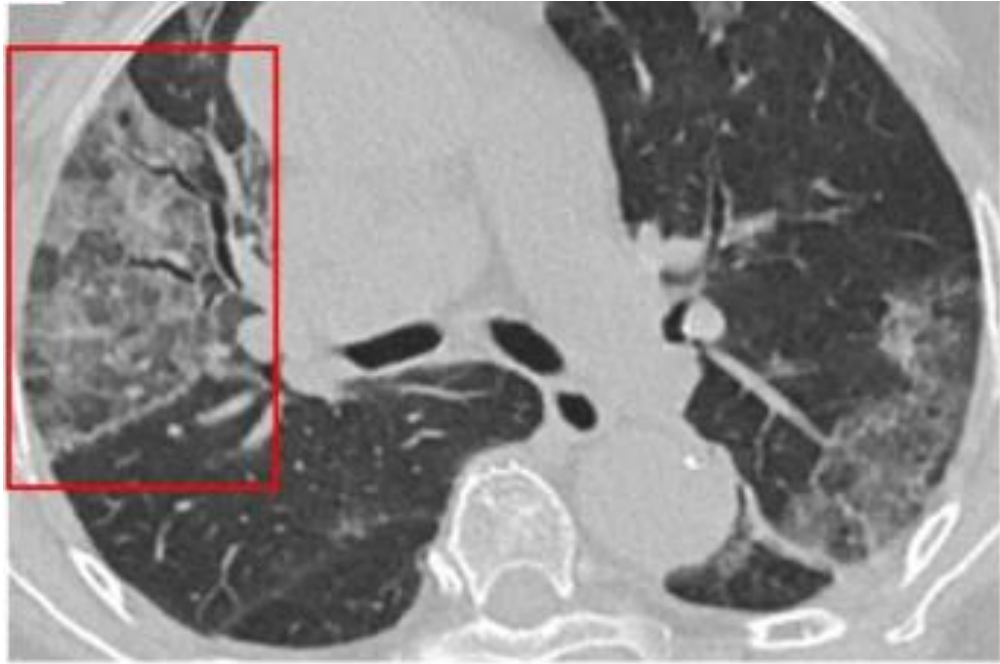


Figure 7: Axial CT demonstrated reticular pattern superimposed on the background of GGO, resembling the sign of crazy paving stones in the right middle lobe (red frame) (Adapted from Ye et al., 2020)

4. Consolidation is an imaging finding applicable in radiographs and CT scans. Consolidation appears as a homogeneous increase in pulmonary parenchymal attenuation that obscures the margins of vessels and airway walls (Hansell et al., 2008).
5. D-dimer is a by-product of the blood clotting and break-down process that can be measured via analysis of a blood sample. D-dimer is released when a blood clot begins to break down (Hansell et al., 2008). The normal D-dimer level is $<0.5 \mu\text{g/ml}$.

6. Fibrosis is a form of interstitial lung disease in which lung parenchyma is replaced by scar tissue (Murray et al., 2014).
7. Ground glass opacities is an imaging finding applicable in radiographs and CT scans. On chest radiographs, ground-glass opacity appears as an area of hazy increased lung opacity, usually extensive, within which margins of pulmonary vessels may be indistinct. On CT scans, it appears as hazy increased opacity of lung, with preservation of bronchial and vascular margins (Hansell et al., 2008) (Figure 8).

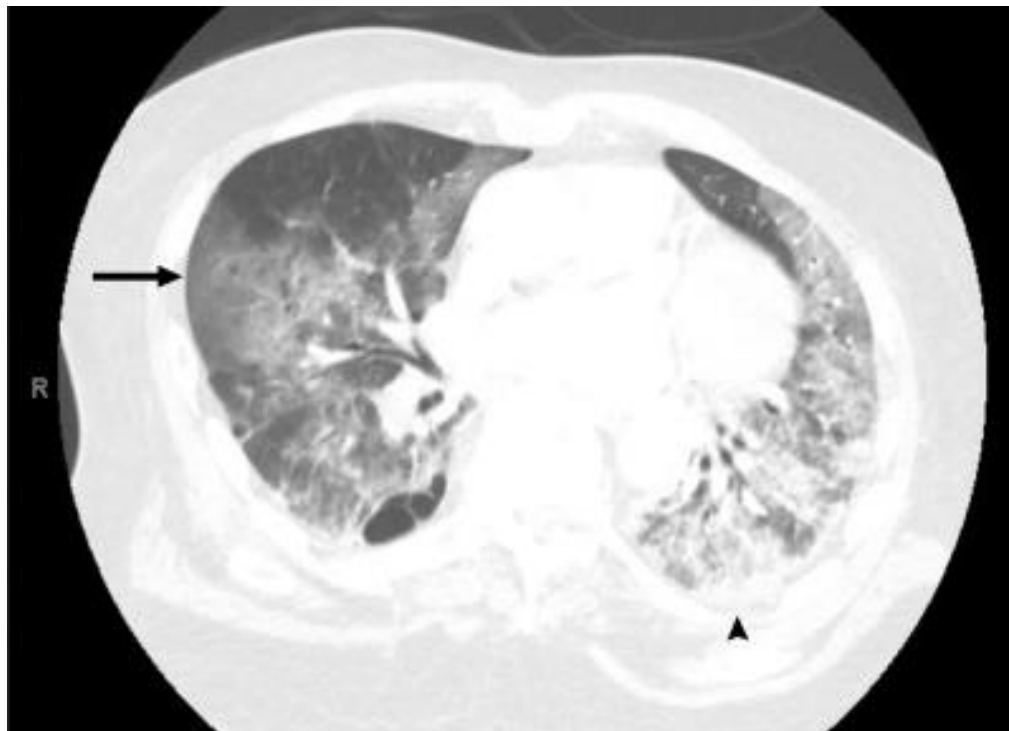


Figure 8: Axial CT demonstrated bilateral ground glass opacities (black arrows), and consolidation. (arrowheads) (Adapted from Poyiadji et al., 2020)

8. Halo sign is a CT finding of ground-glass opacity surrounding a nodule or mass (Fleischner Society: glossary of terms for thoracic imaging. Radiology) (Figure 9).