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# Relationship Between Pulmonary Vascular Dilatation and Clinical Symptoms on Chest Computed Tomography in Patients with Confirmed COVID-19

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**Abstract**

**BACKGROUND:** Chest computed tomography (CT) is important in establishing a diagnosis, including detecting pulmonary vascular dilatation as a radiological feature of COVID-19, and consequently in providing comprehensive treatment.

**AIM:** This study aimed to analyze the relationship between pulmonary vascular dilatation and clinical symptoms on chest CT in patients with confirmed COVID-19.

**PATIENTS AND METHODS:** This retrospective and cross-sectional study was conducted at the Radiology Department of Dr. Wahidin Sudirohusodo Hospital and Hasanuddin University Hospital, Makassar, Indonesia, from July to September 2021 in a total of 231 patients with confirmed COVID-19. The Chi-squared correlation test was used to analyze the data, with $p < 0.05$ considered significant.

**RESULTS:** Pulmonary vascular dilatation was observed in 31 (37.8%) of the 82 patients with confirmed COVID-19 with mild-to-moderate clinical symptoms and in 51 (69.8%) of the 73 patients with confirmed COVID-19 with severe-to-critical clinical symptoms. The incidence of pulmonary vascular dilatation increased in the patients with confirmed COVID-19 with severe-to-critical clinical symptoms. The chief complaints of most patients were cough, shortness of breath, and fever. In the patients with mild-to-moderate clinical symptoms, the most common chief complaint was cough (n = 53; 64.63%), while in those with severe-to-critical clinical symptoms, the most common chief complaint was shortness of breath (n = 60; 82.19%).

**CONCLUSIONS:** Based on chest CT findings, pulmonary vascular dilatation is related to clinical symptoms in patients with confirmed COVID-19.

## Introduction

A total of 152 studies involving 41,409 patients from at least 23 countries have reported 26 different clinical manifestations of COVID-19 [1], [2]. Identification of all clinical manifestations of this disease is essential for early diagnosis and implementation of treatment measures [3]. Radiological imaging methods, especially chest computed tomography (CT), have been widely used in the diagnosis of COVID-19 because RT-PCR examination is not readily available, and the results may take several days to obtain. Although it is not a screening method, chest CT can provide valuable diagnostic information according to international radiology associations [4].

Since the outbreak of COVID-19, changes in the small segmental or subsegmental pulmonary vasculature have been reported in 70–89% of cases of COVID-19 pneumonia on non-contrast-enhanced chest CT in addition to imaging findings typical of viral pneumonia, such as ground-glass opacities (GGOs), crazy-paving patterns, and consolidations. Among these CT features, vascular thickening was found to be a promising hallmark of early COVID-19 [5]. At present, new imaging findings of small pulmonary vascular changes are variously described as vascular thickening. This is believed to be a unique feature of COVID-19 pneumonia that has rarely been previously described in any infectious disease setting [5].

The typical chest CT findings of patients with COVID-19, such as GGO and consolidation, are non-specific and can be observed in a variety of patients with other diseases, including other viral pneumonia, atypical bacterial pneumonia, drug toxicity, eosinophilic pneumonia, or cryptogenic organizing pneumonia. Interestingly, vascular dilatation on chest CT is often more commonly found in patients with COVID-19 than in those with non-COVID-19 pneumonia, thus highlighting the potential implications of COVID-19 on the pulmonary vasculature [6], [7].

Chest CT is important in establishing a diagnosis, including detecting pulmonary vascular dilatation as one of the radiological features of COVID-19, and consequently in providing comprehensive treatment. Therefore, this study aimed to examine the relationship between pulmonary vascular dilatation and clinical symptoms on chest CT in patients with confirmed COVID-19. We hypothesized that pulmonary vascular dilatation is a significant radiological finding in patients with confirmed COVID-19 in addition to the presence of GGO and consolidation on chest CT.

## Patients and Methods

This retrospective and cross-sectional study determined the relationship between pulmonary vascular dilatation and clinical symptoms on chest CT in patients with confirmed COVID-19. It was conducted at the Radiology Department of Dr. Wahidin Sudirohusodo Hospital and Hasanuddin University Hospital, Makassar, Indonesia, from July to September 2021. This study was approved by the Health Research Ethics Committee of Hasanuddin University (No. 437/UN4.6.4.5.31/PP36/2021). The study population included patients who were confirmed to have COVID-19 by clinicians and had undergone chest CT. The sampling method used was consecutive sampling. We performed CT using the GE LightSpeed VCT 64 Slice CT Scanner (model number 5114671-2; General Electric, IL, US).

We recorded and analyzed the chest CT findings of the patients with confirmed COVID-19 with and without clinical symptoms to determine the presence of vascular thickening. The findings were further confirmed by two other radiology specialists with more than 10 years of clinical experience.

According to the WHO guidelines, the severity of COVID-19 was divided as follows: Asymptomatic, mild, moderate, severe, and critical. Mild COVID-19 was defined as the absence of pneumonia on lung CT with mild clinical signs; moderate COVID-19 as the presence of fever, cough, and pneumonia on lung CT; severe COVID-19 as the presence of respiratory distress (respiratory rate of >30 breaths/min, oxygen saturation ($SpO_2$) level of 93% at rest, and/or arterial oxygen partial pressure to fractional inspired oxygen ratio of <300 mmHg; and critical COVID-19 as the presence of organ failure other than respiratory failure, intensive care unit hospitalization, shock, and/or respiratory failure requiring mechanical ventilation [8], [9].

Pulmonary vascular dilatation was defined as an increase in the size of the pulmonary blood vessels with vascular thickening on non-contrast-enhanced chest CT [10], [11], [12]. Vascular thickening was described as an increase in the size or diameter of the blood vessels at the vascular branch; its specific characteristics are as follows:

a. The pulmonary blood vessels are larger than the adjacent or directly adjacent areas of the unaffected lung (Figure 1) [10].

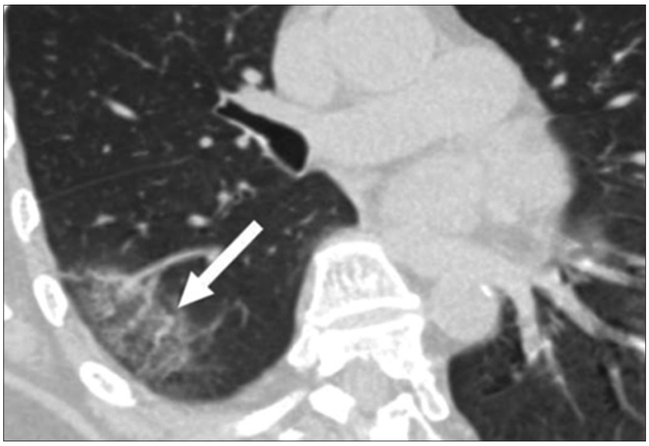

*Figure 1: Vascular dilatation with vascular thickening (arrow) (Axial view)*

b. The vessels are larger than the areas in the unaffected contralateral lung (Figure 2) [11].

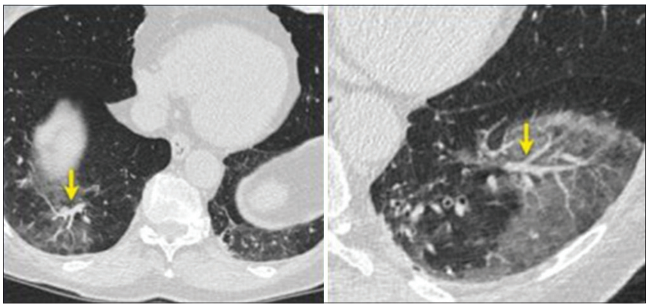

*Figure 2: Axial computed tomography images of a 61-year-old woman with COVID-19 showing a ground-glass opacity with vascular thickening (arrow)*

c. There is focal dilatation or absence of tapering of the blood vessels traveling to the periphery of the lung [12].

We divided the patients into the following age groups: Infants (age: 4 weeks–1 year), children (age: 1–10 years), teenagers (age: 11–20 years), adults (age: 21–50 years), and elderly individuals (>51 years).

### *Statistical analysis*

We recorded the chest CT findings of the patients with confirmed COVID-19 who had vascular thickening and analyzed the data to determine the relationship between vascular dilatation and clinical symptoms on chest CT using the Statistical Package for the Social Sciences program version 21 (IBM Corp., Armonk, NY, US). The Chi-squared correlation test was also used to analyze the data, with $p < 0.05$ considered significant.

## Results

The demographics of the study sample according to age and sex are shown in Table 1.

**Table 1: Frequency distribution of patients with confirmed COVID-19 according to sex and age**

| Category | n | % |
|---|---|---|
| Sex | | |
| Male | 112 | 48.48 |
| Female | 119 | 51.52 |
| Age (year) | | |
| 0–10 | 8 | 3.46 |
| 11–20 | 7 | 3.03 |
| 21–30 | 39 | 16.89 |
| 31–40 | 50 | 21.65 |
| 41–50 | 43 | 18.61 |
| 51–60 | 42 | 18.18 |
| 61–70 | 31 | 13.42 |
| 71–80 | 11 | 4.76 |

Table 1 shows the distribution of the sample frequencies by demographics. The analysis according to sex showed that nearly half of the patients with confirmed COVID-19 were men. Meanwhile, the analysis according to age revealed that most patients with confirmed COVID-19 were aged 31–40 years (21.65%), followed by those aged 41–50 and 51–60 years (18.18%).

Table 2 shows the frequency distribution of the patients with confirmed COVID-19 with and without clinical symptoms according to sex and age. The analysis according to sex showed that the proportion of patients without clinical symptoms was higher among the female patients than among the male patients. In contrast, the analysis according to age revealed that the majority of the patients were adults (90.79%).

**Table 2: Frequency distribution of patients with confirmed COVID-19 with and without clinical symptoms according to sex and age**

| Category | Severe-to-critical clinical symptoms | | Mild-to-moderate clinical symptoms | | No clinical symptoms | | Chi-square test | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | Value | Sig. |
| Sex | | | | | | | | |
| Male | 50 | 68.49 | 34 | 41.46 | 28 | 36.84 | 17.444 | 0.001 |
| Female | 23 | 31.51 | 48 | 58.54 | 48 | 63.16 | | |
| Age group | | | | | | | | |
| Infant | 1 | 1.37 | 1 | 1.22 | 1 | 1.32 | 31.530 | 0.001 |
| Child | 1 | 1.37 | 2 | 2.44 | 2 | 2.63 | | |
| Teenager | 1 | 1.37 | 4 | 4.88 | 2 | 2.63 | | |
| Adult | 43 | 59.91 | 62 | 75.6 | 69 | 90.79 | | |
| Elderly | 27 | 36.98 | 13 | 15.86 | 2 | 2.63 | | |

In the analysis according to sex, mild-to-moderate clinical symptoms were noted in 48 (58.54%) women. In the analysis according to age, the symptoms were most commonly observed in the adult patients, followed by the elderly patients.

The analysis according to both sex and age demonstrated that severe-to-critical clinical symptoms were found in 50 (68.49%) men. Meanwhile, the analysis according to age indicated that these symptoms were more common in the adult and elderly patients.

In the Chi-squared test according to sex, the p-value was 17.444, with a significance value of 0.001. The test statistical value was >5.991; the $\alpha$ value was 5%; and the p-value was 0.05. Thus, sex was related to the clinical symptoms on CT of the patients with confirmed COVID-19. In the Chi-squared test according to age, the p-value was 31.530, with a significance value of 0.001. The test statistical value was >15.507; the $\alpha$ value was 5%; and the p-value was 0.05. Thus, age was associated with the clinical symptoms on CT of the patients with confirmed COVID-19.

Table 3 shows the frequency distribution of the chief complaints of the patients with confirmed COVID-19 with clinical symptoms. In the patients with mild-to-moderate clinical symptoms, the most common chief complaint was cough, followed by shortness of breath and fever. In those with severe-to-critical clinical symptoms, the most frequent chief complaint was shortness of breath, followed by cough and fever.

**Table 3: Frequency distribution of the chief complaints of patients with confirmed COVID-19 with clinical symptoms.**

| Chief complaints | Clinical symptoms | | | |
|---|---|---|---|---|
| | Severe-to-critical | | Mild-to-moderate | |
| | n | % | n | % |
| Fever | 30 | 41.1 | 14 | 17.07 |
| Shortness of breath | 60 | 82.19 | 23 | 28.04 |
| Cough | 49 | 67.12 | 53 | 64.63 |
| Cephalgia | 0 | 0 | 1 | 1.219 |
| Pneumonia (radiology) | 0 | 0 | 6 | 7.317 |
| Swallowing pain | 0 | 0 | 2 | 2.439 |
| Cephalgia | 0 | 0 | 1 | 1.219 |
| Diarrhea | 0 | 0 | 3 | 3.658 |
| Heartburn | 1 | 1.37 | 1 | 1.219 |
| Weakness | 2 | 2.74 | 4 | 4.878 |
| Vomiting | 0 | 0 | 1 | 1.219 |
| Hyposmia | 1 | 1.37 | 2 | 2.439 |
| Nausea | 4 | 5.48 | 0 | 0 |

To analyze the relationship between pulmonary vascular dilatation and clinical symptoms on chest CT, we performed a bivariate analysis using the Chi-squared test. A significant relationship was considered when the statistical value in the Chi-squared test was 5991 or when the $\alpha$ value was 5%. Table 4 shows the frequency distribution of vascular dilatation in the patients with confirmed COVID-19 with clinical symptoms.

In the patients without vascular dilatation, 76 (100%) were asymptomatic; 51 (62.2%) had mild-to-moderate symptoms; and 22 (30.2%) had severe-to-critical symptoms. Pulmonary vascular dilatation was more commonly observed in the patients with severe clinical symptoms (n = 51; 69.8%) than in those with mild-to-moderate clinical symptoms (n = 31; 37.8%) and without clinical symptoms (n = 0; 0%). In the Chi-squared test, the p-value was 79.668, with a significance value of 0.001. The test statistical value was >5.991; the $\alpha$ value was 5%; and the p-value was 0.05. Thus, pulmonary vascular dilatation was related to the clinical symptoms on CT of the patients with confirmed COVID-19.

## Discussion

The increased number of male patients with severe-to-critical clinical symptoms may be attributed to

**Table 4: Relationship between pulmonary vascular dilatation and clinical symptoms on chest computed tomography in patients with confirmed COVID-19**

| | Severe-to-critical clinical symptoms | | Mild-to-moderate clinical symptoms | | No clinical symptoms | | Chi-square test | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | Value | Sig. |
| With pulmonary vascular dilatation | 51 | 69.8 | 31 | 37.8 | 0 | 0 | 79.668 | 0.0001 |
| Without pulmonary vascular dilatation | 22 | 30.2 | 51 | 62.2 | 76 | 100 | | |

male lifestyles and habits, such as smoking. In addition, the susceptibility to COVID-19 differs according to sex through hormone regulation of ACE2 and TMPRSS2 in SARS-CoV-2 infection. ACE2 expression is increased in female patients either through estrogen activation or constitutively through X chromosome inactivation or methylation reduction, providing a greater reservoir of ACE2 to maintain the fundamental balance of the RAS regulatory axis after viral infection at the multi-organ level. Meanwhile, low androgen levels in women may maintain low levels of TMPRSS2 expression, which is a further protective factor against the development of COVID-19. Both mechanisms have consistently demonstrated the role of sex hormones and chromosomes in the different severities of SARS-CoV-2 infection between the sexes, suggesting the cause of the increased susceptibility to COVID-19 in men [13].

Any individual at any age can be infected with COVID-19, although middle-aged and elderly adults are more commonly infected, and older people are more likely to experience clinical deterioration. The high infection rate of COVID-19 in adults is attributed to their daily activities and high mobility; these intensify the potential to encounter patients infected with COVID-19, thereby increasing the risk of infection. Meanwhile, elderly people experience clinical worsening of COVID-19 because they tend to have inherited diseases, such as metabolic and cardiovascular diseases. Similar trends were found in the study by Revzin *et al*. [14].

Initial epidemiological studies conducted in China by Zhou *et al*. [15] and subsequent reports on the spread of COVID-19 worldwide showed that COVID-19 had various clinical manifestations, with the most common being cough, fever, and shortness of breath. In this study, the patients with confirmed COVID-19 with clinical symptoms had a chief complaint of cough (65.8%), shortness of breath (53.5%), and fever (28.4%), which are in line with the clinical manifestations of lower respiratory tract infection. Other clinical symptoms, including nausea, weakness, diarrhea, swallowing pain, hyposmia, vomiting, heartburn, cephalgia, and dizziness, were experienced by approximately 1–5% of the patients.

In the patients with mild-to-moderate clinical symptoms, the most common chief complaint was cough (n = 53; 64.63%); in those with severe-to-critical clinical symptoms, the most common complaint was shortness of breath (n = 60; 82.19%). This is consistent with the occurrence of a decrease in the $SpO_2$ level, which results in shortness of breath as a sign of worsening clinical symptoms that require assistance with respiratory modalities. In general, there are differences in the initial clinical symptoms between COVID-19 and other viral and bacterial infections. In COVID-19, cough, fever, and diarrhea are the chief complaints; in other viral infections, high fever, cough, and pharyngitis; and in other bacterial infections, runny nose and nasal congestion [16]. Compared with SARS-CoV-2 infection manifestations, dyspnea, fever, cough, and headache are generally non-specific. The severity of infection can vary from asymptomatic to fatally severe [17], [18]. Initially, the disease is characterized by a triad of fever, cough, and shortness of breath. The US Centers for Disease Control and Prevention later added chills, muscle ache, headache, sore throat, and loss of the sense of taste or smell to this list (neurological manifestations).

Cough was the most common manifestation found in this study (65.8%), which is directly related to viral transmission through respiratory droplets. The cough reflex increases the release of secretions and particles from the airways because of irritating mechanisms, such as accumulation of secretions, postnasal drip, and pathogens, in addition to the inflammatory process. In some conditions, it can be excessive and potentially harmful to the airway mucosa. Additional symptoms in the upper respiratory tract, including sneezing, nasal congestion, and sore throat, have also been observed [19].

Shortness of breath was the second most common complaint and was found in 53.5% of the patients with clinical symptoms. In general, this symptom is related to the severity of the condition; there are many cases of confirmed COVID-19 with severe-to-critical clinical symptoms that require assisted breathing modalities. During physical examination, patients usually appear to show serious manifestations following shortness of breath, such as increased respiratory rate, speech tremor, weakened breath sounds, and diminished lung percussion. Pulmonary vascular dilatation may be a significant cause of hypoxemia in patients with COVID-19 respiratory failure. Hypoxemia in patients with acute respiratory distress syndrome (ARDS) is largely due to systemic venous blood flowing into the lung area with collapsed and/or fluid-filled alveoli that are deprived of oxygen as it passes through the lungs [20].

Fever was the third most common complaint in the patients with confirmed COVID-19 (28.4%). This symptom indicates the organism's response to toxins that affect the temperature-regulating center. Fever can appear throughout the course of various infectious diseases, and although it is a favorable signaling process for the host, it requires a considerable increase in energy metabolism. Research shows that fever is less common in patients with COVID-19 than in those with SARS-CoV (99%) and MERS-CoV infections (98%) [3].

Vascular thickening is thickening of the blood vessels with smooth edges, which may be associated with edema of the vessel walls caused by inflammatory stimulation of the pulmonary artery branches. This symptom can be observed especially in areas of the lung with ARF, which have rigid vascular dilatations and irregular contours; these features may be related to the severity of inflammation and localized fibrotic traction. Inflammation-mediated hyperemia is not the only cause of marked vascular dilatation. The hypothesis made by Qanadli and Rotzinger [21] that upregulation of nitric oxide synthase leads to the activation of physiological arteriovenous anastomoses in the involved parenchyma may explain the development of vascular dilatation especially in the periphery areas. Other vascular injuries such as endothelial and/or distal micro thrombosis may also cause dysregulation of intrapulmonary arteriovenous anastomoses and the resulting shunting effect.

In this study, pulmonary vascular dilatation was observed in 31 (37.8%) of the 82 patients with confirmed COVID-19 with mild-to-moderate clinical symptoms and in 51 (69.8%) of the 73 patients with severe-to-critical clinical symptoms. The incidence of pulmonary vascular dilatation increased in the patients with confirmed COVID-19 with severe-to-critical clinical symptoms. Li and Xia [10] found that 42 (82.4%) of 53 people had pulmonary vascular dilatation; Bai *et al*. [6], 219 (59%) of 129 people; Zhao *et al*. [22], 101 (71.3%) of 72 people; and Wang *et al*. [23], 126 (77.8%) of 98 people.

***Relationship between pulmonary vascular dilatation and clinical symptoms on chest CT in patients with confirmed COVID-19***

COVID-19 with involvement of the upper respiratory tract results in clinical symptoms such as cough and fever. The SARS-CoV-2 can also enter the lower respiratory tract, which contains many ACE2 receptors, reaching the alveoli and vasculature, especially endothelial cells. Direct viral infection of endothelial cells, which highly express ACE2, can result in extensive endothelial dysfunction and associated vascular inflammatory responses. The simultaneous presence of vascular inflammation and coagulopathy explains the high incidence of thromboembolic complications in patients with COVID-19. Direct endothelial infection by SARS-CoV-2 may also explain the large fibrinolytic profile in these patients. The effect of plasmin on metalloproteinases can modify the extracellular matrix, accelerate capillary leakage, and pulmonary edema that cause clinical symptoms of dyspnea, and worsen following the expansion of COVID-19 infection, which is associated with diffuse alveolar damage due to continuous injury caused by cells. Sequestration of inflammatory cells and replication of viruses result in the loss of Type 1 and 2 pneumocytes, which eventually culminates in ARDS. Blood vessel dilatation in patients with COVID-19 was previously thought to be a marker of increased blood flow [24].

Vascular dilatation in the infected lung area may indicate impaired vasoregulation, leading to substantial ventilation-perfusion imbalance. This finding may partially explain the hypoxemia that can occur in patients with COVID-19 pneumonia. Although the previous attention has been paid to the role of endothelial damage and resulting hypoxic vasoconstrictive dysregulation in patients with ARDS, Lang *et al*. [25] hypothesized that abnormal pulmonary vasoregulation may play a major role in COVID-19 infection even before the occurrence of radiological or clinical signs suggesting ARDS; this may be clearer once ARDS occurs. The related worsening of clinical symptoms, especially shortness of breath, will be accompanied by an increase in the incidence of pulmonary vascular dilatation in the form of vascular thickening on radiography. CT is appropriate for most patients undergoing imaging studies for suspected COVID-19 infection. The typical COVID-19-associated pulmonary radiological findings, including the presence of vascular dilatation, which can help differentiate COVID-19 from other diseases, can be detected on non-contrast-enhanced CT [21], [25], [26].

In this study, we found a relationship between pulmonary vascular dilatation and clinical symptoms of the patients with confirmed COVID-19. The incidence of vascular dilatation increased along with worsening of clinical symptoms based on the Chi-squared test results. Meanwhile, the most important limitation of this study was the non-evaluation of the D-dimer level, considering that an increase in the D-dimer level may be linear with vascular thickening caused by microthrombi.

## Conclusions

Clinical symptoms are most frequently observed in adult and elderly patients with confirmed COVID-19. The most common clinical symptoms are cough, shortness of breath, and fever. Pulmonary vascular dilatation is related to clinical symptoms on chest CT in patients with confirmed COVID-19.

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