# RADIOLOGICAL ASSESSMENT OF THE VASCULAR COMPLICATIONS OF COVID-19 IN CORRELATION WITH D-DIMER LEVEL

Mohamed M. Abdel Aziz, Mohamed Yosry and Ahmed Elshimy

#### **ABSTRACT**:

Radiology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt **Corresponding author**: Ahmed Elshimy Mobile: +201224466755. E-mail: <u>ahmedchimi@hotmail.com</u>,

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**Background**: The COVID-19 pandemic causes primarily respiratory disease as well as non-respiratory complications such as thromboembolic complications with D-dimer elevation, which lead to multisystem organ dysfunction and respiratory failure.

Aim of the work: To determine the value of radiological assessment of vascular complications in COVID-19 infections and its relation to D-dimer levels as important tools for early diagnosis and proper management of these patients.

**Patients & Methods:** The study included 100 patients diagnosed as COVID-19 positive with embolic manifestations depending on their symptoms, signs, and laboratory assessment, which included D-dimer levels. They underwent radiological assessment of their vascular complications, including CT, MRI, and CT angiography.

**Results:** Among 100 COVID-positive patients with thromboembolic symptoms, 55 had evidence of pulmonary embolism, 13 had strokes, 4 had mesenteric arterial occlusion and 28 patients had no radiological evidence of vascular manifestations. D-dimer levels were increased (0.50 mcg/mL or greater) in 70 percent of positive COVID patients, including 89% of those with pulmonary embolism, 84% of those with stroke, 75% of mesenteric thrombosis cases, and in 7 patients (25% of those with symptoms suggestive of vascular thrombosis without radiological imaging of thromboembolic manifestations), with a sensitivity of 88.6%, specificity of 75%, positive predictive value of 90.9%, and negative predictive value of 70%.

**Conclusion:** This study confirmed that D-dimer elevation in COVID-positive patients is highly suggestive of thromboembolic complications, especially pulmonary, cranial, and abdominal embolisms, and that confirmation by proper radiological evaluation is mandatory for the diagnosis of these findings and proper management of their complications.

Keywords: COVID 19, vascular complications, D-dimer.

#### **INTRODUCTION:**

Since the emergence of the worldwide pandemic coronavirus disease (COVID-19), which causes respiratory tract infection as well as multisystem affection, venous thromboembolism has been identified as one of the disease's most serious complications<sup>[1&2]</sup>. The COVID-19-related thromboembolic complications were a significant factor in these patients' admission to intensive care <sup>[3]</sup>.

A variety of potential risk factors for venous thromboembolism exist in COVID-19 patients, especially those who are severely and critically ill. These include infection, immobilization, respiratory failure. mechanical ventilation, and central venous catheter use <sup>[4]</sup>. Furthermore, the virus was discovered to affect coagulation factors, resulting in a cascade of coagulation profile alteration with elevation of the D-dimer, which in turn led to multisystem organ dysfunction and increased respiratory failure<sup>[5]</sup>. Moreover, several theories for thromboembolic mechanisms associated with COVID-19 exit, include direct effect through several illnesses, severe inflammatory response, or hypoxia<sup>[6]</sup>.

The outcomes of these thromboembolic events include mainly acute pulmonary embolism (PE): however. other coagulopathies such as deep-vein thrombosis ischemic (DVT). stroke. mvocardial infarction, or systemic arterial embolism have also been reported<sup>[3]</sup>. These complications are usually associated with poorer prognoses and high mortality rates<sup>[7]</sup>, with increased risk when severe lymphopenia and elevations of D-dimer greater than 2.0 mg/ml are also noted [2].

For diagnosis, the chest x-ray is considered the primary modality for assessment of COVID-19<sup>[8]</sup>. However, chest computed tomography (CT) plays an important role in the diagnosis of COVID eliminating pneumonia and alternate diagnoses or added pathologies, particularly for acute pulmonary embolism. However, in patients with severe clinical features of COVID-19 or elevated D-dimer who may have associated acute pulmonary emboli, the use of contrast-enhanced CT (pulmonary CT angiography) rather than routine non-contrast CT may be considered for these patients<sup>[9&10]</sup>.</sup>

## AIM OF THE WORK:

So, the aim of this study was to determine the value of radiological assessment of vascular complications in COVID-19 infections and its relation to Ddimer levels as important tools for early diagnosis and proper management of these patients.

## **PATIENTS & METHODS:**

## Patients:

This pilot study was designed as a crosscontrol blinded study. A total of 100 patients diagnosed as COVID-19 positive by PCR testing, presented with embolic manifestations depending on their symptoms, signs, and laboratory assessment and were referred to the Radiology Department of our institute during a period of nine months (from January to September 2022) were included in the study. Unstable or critically ill patients and those with a history of renal impairment, allergy, or hypersensitivity to contrast material were excluded.

Patients were informed about the study design, and a written consent for their participation was obtained. The research protocol was approved by the Radiology Department Scientific Board and fulfilled the ethical guidelines of the institute.

## Clinical and laboratory evaluation:

A revision of the history and initial assessment data of all patients was done, including their ages, sex, body weights, and heights, with calculation of body mass index (BMI). Also, their clinical symptoms and signs, such as respiratory and heart rates, blood pressure, embolic manifestations, and others, were documented. In addition, all available laboratory data, particularly hematologic data, including D-dimer levels and renal functions, were reviewed.

## **Radiologic interventions:**

Patients were arranged in groups according to their clinical presentations and examined by either a 128 slice multi-detector computed tomography (MDCT) scanner with contrast or by magnetic resonance imaging (MRI).

MDCT scanning (GE Optima CT 660 SE 128, Germany) was done in the supine position after fasting for about 4–6 h before the study. The scans were taken from the thorax inlet (the root of the neck, including the proximal aspect of the common carotid and subclavian arteries) to 2 cm below the diaphragm (at the level of the portal vein inferiorly) in a craniocaudal direction in a patient suspected to have a pulmonary embolism, or taken from the lung bases to the level of the symphysis pubis in a patient suspected of having a visceral embolism.

MRI brain stroke protocol using 1.5T scanner (Philips Medical Systems, Acheiva, Netherlands), in cases of suspected stroke, was done. The scans were taken from the skull vault to the skull base in a craniocaudal direction.

A contrast agent (nonionic) was injected into their ante-cubital veins, omnipaque 350 mg Iodine/ml (Iohexol, GE Health Care Ireland, Cork, Ireland), in a dose of 1.5–3 mL/kg followed by a saline chase of 15-20 mL, with an injection rate of 1.5–3 mL/s injected by a dual mechanical power injector. In the case of MRI brain, however, contrast is usually unnecessary.

The region of interest (ROI) is placed at the pulmonary artery in case of suspected pulmonary embolism or the descending aorta in case of visceral embolism, with a trigger threshold set at 150 HU. Repetitive low-dose monitoring examinations (100 kV, 50 mAs, and 0.5 s scanning time) were performed 10 s after contrast medium injection began. When the trigger threshold is reached, the scan starts immediately after the breath-holding command, if possible. The patient was kept under observation for 15–30 minutes after the procedure until recovery from sedation.

The acquired axial images were reconstructed in the sagittal and coronal planes. Furthermore, a variety of high-quality 2D reformatted and 3D reconstructed images were generated. Data were reviewed to obtain all clinically relevant information using a combination of three-dimensional maximum intensity projections (MIP) and multiplanar reconstruction (MPR).

Image analysis was performed in an independent way by two radiologists with at least five years of MDCT or MR imaging experience. If a non-clear finding or observer variability was present, a revision of this variable was done by the two radiologists (in a conjoint form) until an agreement on the finding was reached and no inter-observer variability was present.

# Statistical analysis:

Study results were analyzed by the Statistical Program for Social Science (SPSS) version 24. Quantitative variables were described in the form of range, mean, and standard deviation, while qualitative variables were described as numbers and percent's and compared using the Chi-square (X2) test. The diagnostic parameters sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of D-dimer levels for the detection of vascular complications in COVID-19 were also calculated.

# Ethics Approval and Consent to Participate:

This study was approved by the Research Ethics Committee of the Faculty of Medicine, Ain Shams University in Egypt on 29/12/2021; Reference Number of approval: FWA000017585. FMASU R217/2021

# **RESULTS:**

Among the 100 COVID-positive patients with thromboembolic symptoms included in our study, 73 were males and 27 were females. These patients were presented mainly with clinical symptoms and signs of chest pain and dyspnea in cases suspected of pulmonary embolism (75 patients), motor or sensory loss and weakness in cases of suspected stroke (19 patients), and abdominal pain in cases suspected to have mesenteric vascular occlusions (6 patients), as shown in Table 1.

According to their imaging and radiological basis, 55 out of 75 patients (73.3%) had evidence of pulmonary embolism, 13 out of 19 had stroke (68.4%), 4 out of 6 had mesenteric arterial occlusion (66.9%), and the remaining 28 had no radiological evidence of vascular thromboembolic manifestations (table 2).

Furthermore, among 55 patients with pulmonary embolism, 29 had main right or left pulmonary artery embolism (52.7%) and 23 had peripheral pulmonary embolism (47.3%). In addition, of 13 patients with MRI-diagnosed stroke, 9 had basal ganglionic infarction (69.2%), 3 had middle cerebral artery (MCA) thrombosis (23.1%), and one had superior sagittal thrombosis (7.7%). On the other hand, 3 out of 4 mesenteric vascular occlusion patients were found to have main superior mesenteric and celiac trunk thrombosis (75%), and the fourth patient showed portal vein thrombosis (25%). (Figure 1,2,3)

D-dimer levels were increased (0.50 mcg/mL or greater) in 70 percent of our positive COVID patients, including 49 of 55 (89%) patients with pulmonary embolism, 11 of 13 (84%) patients with stroke, 3 of 4 (75%) patients with mesenteric thrombosis, and 7 of 28 (25%) patients with symptoms suggestive of vascular thrombosis without radiological imaging of thromboembolic manifestations (table 3).



Figure 1a



Figure 1b



Figure 1c



Figure 1d

Figure (1): MDCT pulmonary angiography with contrast and thin axial and coronal cuts of known case of COVID19 with bilateral pulmonary embolism, (1a, 1b and 1c) show multiple filling defects in both main pulmonary branches, MDCT chest pulmonary window (1d) in the same case shows mainly peripheral oriented ground glass density and small consolidation patch.



Figure 2a



Figure 2b



Figure 2c



Figure 2d



Figure 2e

Figure (2): MDCT mesenteric angiography with contrast and thin axial and sagittal cuts of known case of COVID19 with mesenteric artery embolism, (2a, 2b, 2c and 2d) show filling defects in mesenteric artery, MDCT chest pulmonary window (2e) in the same case shows mainly peripheral oriented extensive ground glass density.



Figure 3a





Figure 3c



Figure 3d

Figure (3): MDCT cerebral angiography MIP and 3D with contrast of known case of COVID19 with left middle cerebral artery embolism, (3a, 3b), axial T2WI (3c) shows area of cortical and subcortical area of infarction in the territory of left MCA with small hemorrhagic area, MDCT chest pulmonary window (4d) in the same case shows mainly peripheral oriented ground glass density.

On studying the relation of D-dimer to the occurrence of embolic disease in these patients, false-positive cases (high D dimer with no evidence of embolism) were found in 7 cases, false-negative cases (low D dimer with evidence of embolism) in 9 cases, true positive cases (high D dimer with evidence of embolism) in 63 cases, and true negative cases (low D dimer with no evidence of embolism) in 21 cases, representing a sensitivity of 87.5% (63 from 72), specificity of 75% (21 from 28), positive predictive value of 90% and negative predictive value of 70%, giving an accuracy for the test of 84% (table 4).

Parameter	COVID 19 positive patients
	Mean $\pm$ SD (Range)
A and (Mara)	$52.4 \pm 8.35$
Age (Yrs)	(30 – 66)
Sex (n)	
Male	73
Female	27
$W_{a}:=ht(V_{a})$	$78.44 \pm 14.19$
weight (Kg)	(58 - 115)
Usisht(sm)	$166.55 \pm 7.82$
Height(cm)	(150 - 188)
	$28.16 \pm 4.90$
BMI (kg/m2)	(20.1 - 39.8)
Smoking (n)	40
Hypertension (n)	72
Diabetes (n)	32
S & S  of PE(n)	75
S & S  of  S  troke  (n)	10
S & S  of  MVO(n)	<u> </u>
$\frac{1}{1000} \frac{1}{1000} \frac{1}{1000$	70
mign D-unner ( $\geq 0.50$	70
mcg/mL)	

Table 1: Demographic, clinical and laboratory parameters of our 100 COVID 19 positive patients.

S & S = symptoms & signs, PE= pulmonary embolism, MVO= mesenteric vascular occlusion

Table 2: Radiological findings of vascular complications in different groups suspected of embolism in our 100 COVID 19 positive patients.

Parameter	Cases with suspected	Cases with suspected	Cases with suspected	Total
	PE	stroke	MVO	
Positive findings of	55	13	4	72
embolism				
Negative findings of	20	6	2	28
embolism				
Total	75	19	6	100

The chi-square statistic is 0.2715. The p-value is .873056. The result is not significant at p < .05.

Table 3: Incidence of high D-dimer levels in different groups with and without radiological evidence of embolism in our 100 COVID 19 positive patients.

Parameter	Cases with	Cases with	Cases with	Cases without	Total
	PE	stroke	MVO	embolism	
High D-dimer	49	11	3	7	70
Normal D-dimer	6	2	1	21	30
Total	55	13	4	28	100

The chi-square statistic is 37.9154. The p-value is < 0.00001. The result is significant at p < .01. (Highly significant)

Parameter	Cases with vascular embolism	Cases without vascular embolism	Total
High D-dimer	63	7	70
Normal D-dimer	9	21	30
Total	72	28	100

Table 4: Relation of D-dimer level to occurrence of vascular embolism in our 100 COVID 19 positive patients.

## **DISCUSSION:**

Thromboembolic complications have emerged as significant sequelae since the beginning of the COVID-19 pandemic, resulting in significant morbidity and mortality in these patients. So, early detection of these problems, either clinically or by laboratory and radiological procedures, was considered mandatory to save lives and prevent further morbidities from these complications <sup>[6&11]</sup>.

In the present study, of 100 COVID-19proven patients with different manifestations of thromboembolic events, radiological evidence of pulmonary embolism was detected in 55% of them. In addition, 73.3% of suspected PE cases (having chest pain and dyspnea) were proved by CT angiography examination. The incidence of PE in patients with coronavirus disease (COVID-19) who underwent pulmonary CT angiography was reported to be between 23% and 30% <sup>[9&12]</sup>. Also, Poyiadji et al. (2020) reported a similar rate of 22% <sup>[13]</sup>, while Klok et al. found a 31% cumulative incidence of thrombotic events in ICU patients with COVID-19 infections <sup>[3]</sup>.

The higher incidence of PE in our cases may be attributed to many factors. First, we chose COVID-19 patients who presented with manifestations suggestive of thromboembolic events and not all infected patients. Second, our cases were mostly obese or overweight (BMI ranged from 20.1 to 39.8 with a mean of  $28.16 \pm 4.90$  kg/m<sup>2</sup>), which has been linked to an increased risk of PE in previous studies<sup>[13]</sup>. Thirdly, the presence of a high incidence of smoking (40%) in our cases is a risk factor for the development of thromboembolic events <sup>[14]</sup>, in addition to the controversial roles of high incidences of hypertension and diabetes (72% and 32%, respectively) <sup>[15]</sup>. Lastly, the possible late presentations and lack of resources for diagnosis and management may have a role in this high incidence of embolic complications in our patients.

The location of the embolus on CT scan among our 55 patients with pulmonary embolism was found in the main right or left pulmonary artery in 29 patients (52.7%), while 23 patients showed peripheral pulmonary embolism (47.3%). Leonard-Lorant et al. (2020) found only 22% of the embolization in main pulmonary artery cases, while 34% occurred in the lobar artery, 28% in the segmental artery, and 16% in the sub segmental artery <sup>[12]</sup>.

In our 100 COVID-19 positive patients, 13% had radiological evidence of cerebral infarction by MRI, accounting for 68.4% of those 19 patients with motor or sensory loss and weakness (suspected stroke). These thromboembolic events included basal ganglionic infarction (69.2%), middle cerebral artery (MCA) thrombosis (23.1%), and superior sagittal thrombosis in the remaining 7.7%. Qureshi et al. (2021) found acute ischemic stroke in 1.3% of their patients, especially in those with other cardiovascular risk factors such as hypertension, diabetes, hyperlipidemia, atrial fibrillation, and congestive heart failure <sup>[16]</sup>. The higher incidence of stroke in our patients may be attributed to the presence of many risk factors, such as smoking, hypertension, and diabetes, as mentioned before.

On the other hand, 3 of 4 mesenteric vascular occlusion patients (representing 4%

of our 100 COVID patients) were found to have main superior mesenteric and celiac trunk thrombosis (75%), and the fourth patient had portal vein thrombosis (25%). Although the true prevalence of GI symptoms among COVID-19 positive patients is unknown, with estimates ranging from less than 10% to 70% <sup>[17]</sup>, acute mesenteric ischemia is rare and usually fatal, with an overall incidence of less than 1%, which is consistent with our findings.

As the prothrombotic nature of severe acute respiratory syndrome caused by coronavirus disease in the 2019 pandemic has been well established, infection with this virus has been increasingly associated with coagulopathy and thrombotic complications such as PE and others, which are associated with a higher progressive increase in D-dimer levels <sup>[5&18]</sup>. Patients with elevated levels of D-dimer and fibrin degradation products had a higher risk of death, according to Tang et al. in 2020<sup>[19]</sup>.

In the present study, D-dimer levels were increased (0.50 mcg/mL or greater) in 70% of positive COVID patients, who included 89% of pulmonary embolism cases, 84% of stroke cases, and 75% of patients with mesenteric thrombosis. However, only 25% of patients with symptoms suggestive of vascular thrombosis without radiological imaging of thromboembolic manifestations have higher levels of D-dimer. The D-dimer test had a sensitivity of 87.5%, specificity of 75%, a positive predictive value (PPV) of 90% and a negative predictive value (NPV) of 70%, giving an accuracy of 84% for predicting the occurrence of thromboembolic events.

In previous studies, patients with higher levels of D-dimer were found to be at a higher risk of developing PE <sup>[5&13],</sup> which supports our results. Even so, an association between the severity of the disease and the levels of Ddimer was postulated by many others <sup>[19,20&21]</sup>. So, anticoagulant treatment has been found to be associated with decreasing mortality in severe COVID-19-infected patients<sup>[22]</sup>.

Poyiadji et al. (2020) found a D-dimer test sensitivity of 78% and specificity of 81% for the development of PE <sup>[13]</sup>. In the study done by Cui et al. <sup>[23]</sup>, the prevalence of venous thromboembolism (VTE) was 25%, with a sensitivity, specificity, and negative predictive value of the D-dimer cut-off value of 1.5  $\mu$ g/mL of 85, 88.5, and 94.7%, respectively, which supported our findings. More recently, Lin et al. (2023) found that the standard D-Dimer threshold of 500 ng/mL had a sensitivity of 97.8%, a specificity of 40.9%, and a negative predictive value of 99.8% for the diagnosis of PE <sup>[24]</sup>.

Lastly, although our study proved the importance of D-dimer in detecting thromboembolic events in COVID cases, some limitations in this study were present, as follow-up of the test during the course of the thromboembolism was not done (as it was a cross-sectional study), and in addition, we limited our test to patients who presented with manifestations suggestive of vascular events and not all cases from the start of the disease. So, further studies are needed to document the baseline of the test at the start of the COVID infection and its progress when complications start, which may be more predictive in detecting the early occurrence of thromboembolic manifestations in this infection.

# **Conclusion:**

In conclusion, this study emphasized the importance of proper radiological detection of vascular thromboembolic complications in COVID-19 infections, such as pulmonary, cranial, and abdominal embolism, especially in patients with elevated D-dimer levels, as a prompt tool for early diagnosis, and thus proper management of these patients.

# **Consent for publication:**

All patients approved and gave written informed consent for their participation in the study.

## Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## **Competing interests:**

We have no competing interests to declare.

## **Funding:**

This study had no funding from any resource.

## Acknowledgements:

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#### List of Abbreviations

CT:	Computed tomography
DVT:	Deep-vein thrombosis
MCA:	Middle cerebral artery
MDCT:	Multi-detector computed
	tomography.
MRI:	Magnetic resonance imaging
MVO:	Mesenteric vascular occlusion
NPV:	Negative predictive value
PE:	Pulmonary embolism
PPV:	Positive predictive value
VTE:	Venous thromboembolism

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#### Mohamed M. Abdel Aziz, et al.,

التقييم الإشعاعي للمضاعفات الوعائية لفيروس كورونا ومدى ارتباطه مع مستوى دي دايمر

#### محمد ممدوح عبد العزيز ومحمد يسري واحمد الشيمي

قسم الأشعة التشخيصيه – كلية الطب جامعة عين شمس

**الخلفية:** تتسبب جائحة كورونا في أمراض الجهاز التنفسي بشكل أساسي بالإضافة إلى مضاعفات غير تنفسية مثل مضاعفات الانسداد التجلطي مع ارتفاع ال د دايمر ، مما يؤدي إلى خلل متعدد للاجهزة وفشل في الجهاز التنفسي.

هدف العمل: تحديد قيمة التقييم الإشعاعي لمضاعفات الأوعية الدموية في عدوى فيروس كورونا وعلاقتها بمستويات ال د دايمر كأدوات مهمة للتشخيص المبكر والإدارة السليمة لهؤلاء المرضى.

**المرضى وطرق الدراسة:** اشتملت الدراسة على ١٠٠ مريض تم تشخيصهم على أنهم مصابون بفيروس كورونا مع ظهور مظاهر الجلطات اعتمادًا على أعراضهم وعلاماتهم وتقييمهم تحاليلهم ، والذي تضمن مستويات ال د دايمر. خضعوا لتقييم إشعاعي لمضاعفات الأوعية الدموية ، بما في ذلك التصوير المقطعي والتصوير بالرنين المغناطيسي وتصوير المقطعي بالصبغه للأوعية.

النتائج: من بين ١٠٠ مريض مصاب بفيروس كورونا يعانون من أعراض الانسداد التجلطى ، كان لدى ٥٥ مريضًا دليلًا على الجلطه الرئوي ، و ١٣ مصابًا بالسكتات الدماغية ، و ٤ مصابين بانسداد الشرايين بالبطن ، ولم يكن لدى ٢٨ مريضًا أي دليل إشعاعي على مظاهر تجلطات الأوعية الدموية. تمت زيادة مستويات ال د دايمر (٥٠,٠ ميكرو غرام / مل أو أكثر) في ٢٠ في المائة من مرضى الكورونا الإيجابي ، بما في ذلك ٨٩ ٪ من المصابين بالانسداد الرئوي ، و ٨٢ ٪ من المصابين بالسكتة الدماغية ، و ٢٥ ٪ من حالات تجلط الدم في شرايين البطن ، وفي ٧ مرضى (٢٠ ٪ من المصابين بأعراض توحي بتجلط الأوعية الدموية دون تصوير إشعاعي لمظاهر الانسداد التجلطى) ، مع حساسية ٦٢ ، ونوعية ٢٥٪ ،

**الخلاصة:** أكدت هذه الدراسة أن ارتفاع ال د دايمر في المرضى المصابين بفيروس كورونا يوحي بشدة بمضاعفات الانسداد التجلطي ، وخاصة الجلطات الرئوية والمخيه واوعيه البطن ، وأن التأكيد من خلال التقييم الإشعاعي المناسب إلزامي لتشخيص هذه النتائج والإدارة السليمة لهذه النتائج ومضاعفاتها.