

Correlation Between Thrombotic Parameter D-Dimer and Disease Severity in Patients Infected With SARS-CoV-2 in Da Nang City, Vietnam

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Abstract

Background: The COVID-19 pandemic posed a significant healthcare crisis due to the emergence of acute respiratory infections, leading to severe complications such as thrombosis. Meanwhile, the D-dimer index serves as a dependable routine diagnostic marker for thrombosis. Therefore, it is hypothesized that D-dimer could serve as a potential prognostic marker for COVID-19 infection.

Objective: To assess the association between D-dimer levels and the severity of COVID-19 among patients in the Vietnamese central coastal region.

Methods: A retrospective cross-sectional study was conducted at Da Nang Hospital for Pulmonary Diseases and its satellites on patients admitted for COVID-19 from September 2021 to April 2022. Clinical data were analyzed using the chi-square test. The receiver operating characteristic (ROC) curve was used to determine the best cut-off for D-dimer levels that differentiate between mild and severe cases amongst COVID-19 positive patients.

Results: This study comprised of 205 confirmed COVID-19 patients (mean [SD] age, 66.71 [18.80] years). The participants were divided into 2 groups based on their D-dimer levels: those with D-dimer levels greater than 500 µg/L or less than 500 µg/L. The median D-dimer level of each group were 1507.50 µg/L and 302 µg/L, respectively. Patient age and a history of diabetes correlated with D-dimer elevation in COVID-19 patients. The ROC curve indicated that D-dimer of greater than 638 µg/L was associated with severe disease (sensitivity 80%, specificity 90.8%, area under the curve [AUC] = 0.900).

Conclusions: Elevated D-dimer levels was associated with more severe instances of COVID-19 with levels exceeding 638 µg/L demonstrating high sensitivity and specificity.

Keywords: COVID-19 patients, D-dimer, ROC curve, Thrombosis parameter

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Introduction

The SARS-CoV-2 virus and its variants caused a significant healthcare crisis by giving rise to the acute respiratory infection known as COVID-19. Consequently, the World Health Organization (WHO) declared COVID-19 a global pandemic on 11 March 2020.¹ While the majority of COVID-19 patients experienced mild and common symptoms such as fever, cough, nausea, vomiting, and diarrhea, a small proportion of patients continued to suffer from severe symptoms that require intensive care unit (ICU) treatment and invasive mechanical ventilation. These outcomes were possibly due to the occurrence of serious complications like disseminated intravascular coagulation syndrome, septic shock, and

severe acute respiratory syndrome, with high mortality rate.² COVID-19 is an acute viral infection which severe cases lead to various complications. Moreover, due to the hypoxemic, ischemic, and inflammatory characteristics of COVID-19, other multiple organs including the cardiovascular,³ nervous,^{4, 5} endocrine,⁶ immune,⁷ gastrointestinal,⁸ and renal systems⁹ can be affected by the COVID-19 infection.

Cardiovascular complications, such as myocarditis, cardiac arrhythmias, endothelial cell damage, myocardial interstitial fibrosis, and thrombotic events (TE), are well documented in certain individuals with COVID-19.¹⁰ Noticeably, the coagulation process and hemostatic pathways are also adversely affected by COVID-19. Several reports described coagulopathy in COVID-19 patients. Thrombotic events remain prevalent in COVID-19 patients despite prophylactic anticoagulant treatment, especially among those who are critically ill and admitted to the ICU. Acute pulmonary embolism (PE), ischemic stroke, and deep vein thrombosis (DVT) are among the common coagulation disorders in COVID-19 patients with approximately 30% of ICU patients.¹¹⁻¹⁵

One of the laboratory parameters that garner attention among scientists for prognosticating severity of SARS-CoV-2 infection is D-dimer.¹⁶⁻²¹ The D-dimer, a protein fragment that could be found in fibrin degradation products. It is a distinctive indicator of fibrin degradation, resulting from the sequential action of three enzymes: thrombin, factor XIIIa, and plasmin. Initially, thrombin cleaves fibrinogen, generating fibrin monomers that polymerize to form the framework for the formation of factor XIIIa and plasmin. Additionally, thrombin activates plasma factor XIII, leading to production of factor XIIIa and induction of covalent bonds between D-domains within the polymerized fibrin structure. Ultimately, plasmin breaks down the cross-linked fibrin, resulting in the release of fibrin degradation products and the exposure of the D-dimer.²² While the standard level of plasma D-dimer observed in clinical settings is below 500 µg/L, an elevated D-dimer level could indicate the presence of a DVT or PE.²² A study on a Chinese population found that D-dimer index could be elevated in COVID-19 patients compared to healthy individuals. Additionally, D-dimer levels were higher in COVID-19 patients with severe illness or mixed complications compared to those with nonsevere disease. Another study reported that D-dimer levels were higher in patients with acute respiratory distress syndrome (ARDS) compared to those without ARDS; particularly deceased ARDS patients exhibited higher levels of D-dimer compared to those who survived the condition.¹⁶

As of February 2022, Vietnam's Ministry of Health reported over 11 million infections and more than 43 000 deaths.^{23, 24} As a pivotal city in Vietnam, Da Nang city witnessed COVID-19 outbreak in the middle of 2020 with multiple waves of infections. Subsequently, more than 100 000 cases were recorded in this city until 2023 while the case fatality rate in Vietnam was over 400/100 000.²⁵ This research was conducted at Da Nang Hospital for Pulmonary Diseases, a specialized medical facility that not only caters to its own patients but also extends its services to COVID-19 patients referred from other district clinics within the city of Da Nang who reached moderate or severe levels of illness, during the early stage of Vietnamese outbreak when vaccination was not widely available. The primary goal of this study is to assess D-dimer levels in individuals at the time of COVID-19 diagnosis and analyze the correlation between D-dimer and other risk factors. Our aim was to gather additional evidence regarding the shift of the thrombotic parameter D-dimer among patients infected with the SARS-CoV-2 virus within the Vietnamese population.

Methods

Research Ethics Issue and Sample Population

The retrospective research project focused on patients admitted for COVID-19 at Da Nang Hospital for Pulmonary Diseases in Vietnam from September 2021 to April 2022. The study adhered to the guidelines outlined in the Declaration of Helsinki.²⁶ Approval for this research was granted by the Biomedical Ethics Committee of Da Nang University of Medical Technology and Pharmacy, as well as by the Board of Directors of Da Nang Hospital for Pulmonary Diseases, under reference No. 646/BB-HDDD issued on 20 December 2021.

The written informed consent was obtained from patients and/or their family members (legal representatives) to participate in the study. All information was used solely for research purposes. Patients were free to decline or withdraw from the study at any time. Each patient was assigned an identifier, and their names were coded instead of being compiled. According to the research questionnaire, all data was encrypted and kept private. Research data was only accessible to the leader of the research team. This study enrolled all participants who tested positive for COVID-19 via reverse transcription-polymerase chain reaction (RT-PCR), following Vietnamese Ministry of Health guidelines (Decision 2008 QD/BYT, issued on 26 April 2021).²⁷ Pregnant women, individuals under 18, and those with coagulation disorders were excluded from participation.

Data Collection

Classification of Severity of COVID-19

The severity of the disease was categorized into various levels based on the COVID-19 treatment guidelines issued by the Vietnamese Ministry of Health.²⁴ These levels included asymptomatic, mild, moderate, severe, and critical (Table 1).

Clinical Characteristics and Laboratory Measurements

Information on the clinical features of the individuals was collected, encompassing the presence of chronic illnesses (such as diabetes mellitus, hypertension, dyslipidemia, and others including cardiovascular disorder, chronic respiratory conditions, aging, liver and kidney diseases, malignancy, etc). The documented clinical signs included breathlessness, cough, fatigue, elevated body temperature, throat discomfort, cognitive impairments, and altered taste perception. The laboratory parameters included red blood cell (RBC), white blood cell (WBC), platelet count, hemoglobin (Hb), and D-dimer were assessed using the hemostasis testing system (ACL TOP 500 CTS, Werfen, MA, USA) at the time of COVID-19 diagnosis.

Statistical Analysis

We utilized SPSS version 20.0 (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp; 2011) and Medlab software version 12.5 (MedCalc Software Ltd, Ostend, Belgium) for statistical calculations. The chi-square test was employed to compare proportions and for ordinal variables. The levels of significance were set at $P < .05$. The relationships were present as ORs with 95% CIs. The receiving operating characteristic (ROC) curve was utilized to determine the optimal cut-off point for D-dimer concentration to predict the point of transition from mild to severity level of clinical situation, along with its corresponding sensitivity and specificity for predicting the severity of COVID-19 infection in patients.

Table 1. Severity Classification of COVID-19 Infection

Severity Classification	Description
Asymptomatic	Patients could exhibit positive test with COVID-19 but no symptoms.
Mild	Patients could exhibit nonspecific upper respiratory symptoms such as fever, dry cough, sore throat, stuffy nose, fatigue, headache, and muscle aches.
Moderate	Patients could develop pneumonia with symptoms such as fever, cough, difficulty breathing, rapid breathing, SpO ₂ level of at least 93% in room air conditions
Severity	Patients could present pneumonia symptoms and one or more of the following signs: a respiratory rate exceeding 30 breaths per minute, severe shortness of breath or respiratory difficulty, the use of accessory respiratory muscles to breathe, and an SpO ₂ level below 93% in room air conditions. These patients may also exhibit tachycardia, bradycardia, abnormal blood pressure, agitation, fatigue, or lethargy. Chest x-rays and/or chest CT scans may reveal lung damage with infiltrates exceeding 50%.
Critical	Patients could present conditions such as ARDS, sepsis, infection shock, and other complications. They exhibit critical abnormalities in respiratory rate (≥ 30 or ≤ 10 breaths per minute), acute respiratory failure, respiratory acidosis, increased effort to breathe, abnormal respiration patterns, and require high-flow nasal cannula therapy or ventilators. These patients could also experience decreased consciousness or be comatose. Their pulse rate may be either fast or slow, accompanied by low blood pressure, decreased urine output (oliguria), or absence of urine output (anuria). Chest x-rays and chest CT scans may reveal lung damage with infiltrates exceeding 50%. Lung ultrasonography may also show the presence of multiple B-lines. Additionally, the PaO ₂ /FiO ₂ index ≤ 300 indicated critical conditions in patients.

Abbreviations: ARDS, acute respiratory distress syndrome; CT, computed tomography; FiO₂, fraction of inspiratory oxygen concentration; PaO₂, partial pressure of oxygen in arterial blood; SpO₂, oxygen saturation level.

Results

A total of 205 individuals were included in this research study, with mean (SD) age of 66.71 (18.80) years (range, 18-16 years). Individuals aged over 60 years accounted for 67.3% of the population. The gender distribution was nearly equal, and comprised of 50.7% females and 49.3% males. The most common clinical manifestations in the study population were dyspnea (51.7%), and cough (48.8%). While the least reported symptom was loss of taste (10.7%). In terms of the medical history of chronic illnesses, hypertension was the most prevalent (47.8%), followed by diabetes in 31.2% of the patients. Regarding the severity of the disease, most patients (42.4%) were classified as having severe COVID-19 while "no symptoms" and "critical" classification were the lowest at 7.3% each. The mean (SD) duration of hospitalization was 8.6 (5.60) days (Table 2).

The assessed values of D-dimer concentrations were divided into 2 groups, those with D-dimer levels below 500 µg/L and those with the levels above 500 µg/L, showing the medians of 302 µg/L and 1507.50 µg/L respectively. Within the population of individuals diagnosed with COVID-19, the group with elevated D-dimer levels accounted for 73.2% of patients. Laboratory findings also showed a broad range of D-dimer values, spanning from 8 µg/L to 58 416 µg/L (Table 3).

A significant relationship was found between elevated D-dimer and patient age, with those over 60 years old showing a higher rate of elevated D-dimer ($P < .05$). Additionally, a statistically significant association was observed between elevated D-dimer levels and diabetes ($P < .05$), but not with other documented diseases. Furthermore, there was a significant correlation between increased D-dimer values and severity classification ($P < .05$) (Table 4). Significant correlations ($P < .05$) were found between D-dimer levels and other parameters including WBC, RBC, and Hb (Table 5). Additionally, an increase in D-dimer levels was associated with the severity of COVID-19 infection (Table 6).

Table 2. General Characteristics of the Study Subjects

Characteristic	No. (%)
Age, y	
≤ 60	67 (32.7)
> 60	138 (67.3)
Sex	
Male	101 (49.3)
Female	104 (50.7)
Clinical symptom	
Dyspnea	106 (51.7)
Cough	100 (48.8)
Fatigue	63 (30.7)
Fever	55 (26.8)
Chest tightness	51 (24.9)
Sore throat	49 (23.9)
Cognitive disorders	37 (18.0)
Loss of taste	22 (10.7)
Medical history - chronic illnesses	
Hypertension	98 (47.8)
Diabetes	64 (31.2)
Dyslipidemia	23 (11.2)
Other diseases	93 (45.4)
Classification of disease severity	
No symptoms	15 (7.3)
Mild	55 (26.8)
Moderate	33 (16.1)
Severity	87 (42.4)
Critical	15 (7.3)

Table 3. The D-Dimer Alteration and Relationship Between Increased D-Dimer With Age and Medical History

Characteristic	No. (%)			OR (95% CI)	P Value
	D-Dimer				
	< 500 µg/L (n = 55)	≥ 500 µg/L (n = 150)	All (N = 205)		
D-dimer value, µg/L					
Median (IQR)	302.00 (199.00)	1507.50 (1748.50)	1008.0 (1488.0)	NA	NA
Mean (range)	305.41 (7.68-492)	3503.27 (501-58 416)	2645.31 (7.68 -58 416)	NA	NA
Age, y					
≤ 60	25 (37.3)	42 (62.7)	67 (32.7)	2.14 (1.13-4.06)	.03
> 60	30 (21.7)	108 (78.3)	138 (67.3)		
Diabetes					
Yes	10 (15.6)	54 (84.4)	64 (31.2)	2.53 (1.18-5.42)	.01
No	45 (31.9)	96 (68.1)	141 (68.8)		
Dyslipidemia					
Yes	5 (3.9)	18 (96.1)	23 (11.2)	NA	0.63
No	50 (27.5)	132 (72.5)	182 (88.8)		
Hypertension					
Yes	23 (23.4)	75 (76.6)	98 (47.8)	NA	0.43
No	32 (29.9)	75 (70.1)	107 (52.2)		
Other diseases					
Yes	8 (8.6)	85 (91.4)	93 (45.4)	NA	0.44
No	47 (41.9)	65 (58.1)	112 (54.6)		

Abbreviations: IQR, interquartile range; NA, not applicable.

Table 4. The Blood Counting Indexes of Groups

Blood Counting Index	Mean (SD) [95% CI]	
	D-Dimer	
	< 500 µg/L (n = 55)	≥ 500 µg/L (n = 150)
RBC, ×10 ¹² /L	4.43 (0.57) [4.13-5.44]	4.05 (0.76) [3.92-4.16]
WBC, ×10 ⁹ /L	17.92 (74.3) [2.15-37.99]	10.86 (6.78) [9.76-11.95]
Hb, g/L	134.98 (20.26) [129.50-140.45]	122.05 (22.97) [118.26-125.6]
Hct, L/L	0.41 (0.05) [0.33-0.63]	0.37 (0.07) [0.36-0.39]
PLT, ×10 ⁹ /L	199.73 (66.33) [181.79-217.65]	210.64 (92.42) [195.73-225.55]

Abbreviations: Hb, hemoglobin; Hct, hematocrit; PLT, platelet; RBC, red blood cell; WBC, white blood cell.

Table 5. The Relationship Between D-Dimer Groups and Blood Counting Indexes

Blood Counting Index	No. (%)			OR (95% CI)	P Value
	D-Dimer				
	< 500 µg/L (n = 55)	≥ 500 µg/L (n = 150)	All (N = 205)		
WBC, ×10 ⁹ /L					
4-10	45 (34.9)	84 (65.1)	129 (62.9)	3.54 (1.66-7.54)	.002
> 10	10 (13.2)	66 (86.8)	76 (38.5)		
RBC, ×10 ¹² /L					
< 3.8	5 (9.1)	50 (90.9)	55 (26.8)	5.00 (1.88-13.3)	< .001
3.8-5.5	50 (33.3)	100 (66.7)	150 (73.2)		
Hb, g/L					
< 120	10 (14.1)	61 (85.9)	71 (34.6)	3.08 (1.44-6.56)	.003
120-180	45 (33.6)	89 (66.4)	134 (65.4)		
PLT, ×10 ⁹ /L					
< 150	11 (20.8)	42 (79.2)	53 (25.9)	NA	.284
150-450	44 (28.9)	108 (71.1)	152 (71.1)		

Abbreviations: Hb, hemoglobin; Hct, hematocrit; NA, not applicable ; PLT, platelet; RBC, red blood cell; WBC, white blood cell.

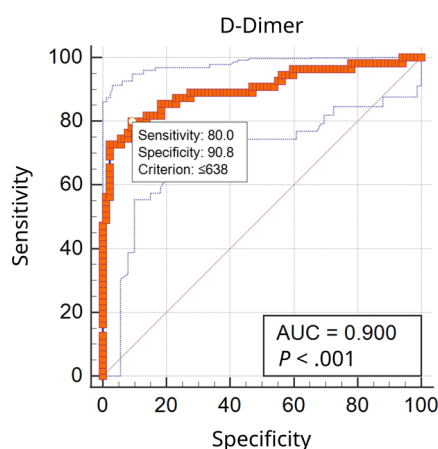
Table 6. The Relationship Between D-Dimer Level and COVID-19 Severity Classification

COVID19 Severity Classification	D-Dimer				P Value
	< 500 µg/L (n = 55)		≥ 500 µg/L (n = 150)		
	No. (%)	Mean (95%CI)	No. (%)	Mean (95%CI)	
No symptoms	10 (66.7)	295 (232.74-357.46)	5 (33.3)	1042.0 (420.41-1663.58)	< .001
Mild	36 (65.5)	293 (251.66-335.73)	19 (34.5)	1654.50 (260.45-3084.55)	
Moderate	7 (21.2)	349.1 (199.18-499.01)	26 (78.8)	2791.16 (1474.12-4108.2)	
Severity	2 (2.3)	415.0 (97.34-732.66)	85 (97.7)	3878.58 (2085-5671.68)	
Critical	0	NA	15 (100)	5848.87 (161.33-11536.4)	

Abbreviation: NA, not applicable.

The Medlab software was utilized to construct the ROC curve to determine the threshold value of D-dimer concentration that can effectively differentiate between mild and severe infection. By considering sensitivity and specificity, the analysis demonstrated an area under the curve (AUC) of 0.9, indicating a robust discriminatory ability with *P* value < .05. The identified cut-off point for D-dimer concentration was determined to be 638 µg/L (Figure 1).

Figure 1. Performance of Model With Receiver Operating Characteristic Curve of D-Dimer Level to Differentiate Between Mild and Severe Infection in COVID-19 Patients



Discussion

The COVID-19 pandemic strained healthcare systems worldwide, with mortality rates being a primary concern. Prompt identification of severe and critical cases is crucial to reduce mortality rates and enhance recovery outcomes. Fatality rates ranging from 4.3% to 15% were reported among hospitalized COVID-19 patients.¹ Thus, it is imperative to identify early predictors of COVID-19 severity to aid clinicians in timely diagnosis and treatment interventions. A study conducted across multiple centers revealed that within the older age group, there was an 18% increase in the risk of mortality.²⁸ The participants in our research ranged in age from 18 years to 106 years (mean [SD], 66.71 [18.80]), consistent with the demographic profile reported from Zhang et al.²⁹ Furthermore, another study demonstrated that chronic health conditions significantly contributed to the poor outcomes associated with the severity of COVID-19.^{29, 30} In terms of medical background, our investigation revealed that several chronic diseases were prevalent among severe cases of COVID-19 patients in Da Nang city, Vietnam. Hypertension was the most common (47.8%), followed by diabetes (31.2%). Other conditions associated with aging, liver and kidney diseases, malignancy, and others accounted for the remaining cases.

The systematic review of D-dimer index values in COVID-19 patients by Rostami et al³¹ found that the median value of D-dimer increased to 1530 $\mu\text{g/L}$. Our study also observed a similar trend with the recorded average value for high-risk group was 1507.50 $\mu\text{g/L}$. We documented the positive correlation between elevated D-dimer levels and the classification of disease severity, consistent to the other reports.^{32, 33}

COVID-19 is characterized by a state of hyper-inflammation with increasing various inflammatory cytokines such as interleukin (IL) 1, IL-6, and tumor necrosis factor (TNF).³⁴ This inflammatory response triggers the activation of endothelial cells, platelets, monocytes, and tissue factors, resulting in the alteration of fibrinolytic and endogenous anticoagulant pathways including thrombomodulin, and proteins (C and S proteins), and tissue factor pathway inhibitor (TFPI). The generation of thrombin is primarily induced by activated innate immune cells including macrophages and monocytes.³⁵ Inflammation-induced

endothelial cell dysfunction leads to a significant release of plasminogen activators, potentially contributing to the observed coagulopathy in COVID-19. Elevated levels of D-dimer are often associated with the activation of both fibrinolysis and coagulation *in vivo*.^{36, 37} Conversely, Hun et al³⁸ proposed an alternative explanation that the increase in D-dimer in COVID-19 was due to the degradation of fibrin byproducts accumulating within the lung parenchyma and alveoli, causing lung damage. Emerging studies were conducted to determine the predictive ability of elevated levels of D-dimer on admission. Marta-Enguita et al³³ with a study on Spanish patients discovered that among the inflammatory parameters measured upon admission, D-dimer was associated with a worse prognosis. Additionally, previous studies reported several cut-off points included values of greater than 1200 ng/mL (sensitivity of 71.43% and specificity of 90.91%),³⁸ of 0.91 µg/mL (sensitivity of 82.2%, specificity of 81.2%),³⁹ and of 0.96 µg/mL (specificity of 77%, sensitivity of 78.1%).⁴⁰ These findings aligned with our own calculations, which determined a cut-off point of 638 µg/L (AUC 0.9) for the patients of Da Nang Hospital for Pulmonary Diseases and its satellite facilities in Da Nang city, Vietnam.

Our investigation revealed a correlation between increased D-dimer levels and other parameters including the age and diabetes. Specifically, patients over the age of 60 exhibited a significantly higher increase in D-dimer levels (OR [95% CI], 2.14 [1.13-4.06]; $P < .05$), consistent with previous studies.⁴¹⁻⁴⁴ In terms of the association between increased D-dimer levels and chronic disease, our study observed a greater increase in the D-dimer index among COVID-19 patients with diabetes compared to those without diabetes. This difference was statistically significant ($P < .05$), with a 2.53-fold higher risk of D-dimer elevation in patients with diabetes. These findings are consistent with previous research.⁴⁵⁻⁴⁸ This phenomenon can be attributed to the impact of diabetes on the blood vessel structure, which increases the risk of atherosclerosis, hypercoagulability and thrombosis. Furthermore, diabetic patients with increased D-dimer levels showed poor prognosis and higher risk of mortality due to association with age, hypertension and obesity. Furthermore, diabetes could enhance susceptibility to cytokine storms and thrombotic complication in COVID-19.⁴⁷ Our finding of the association bolstered the evidence linking the severity of COVID-19 with diabetes, as documented in various research studies.⁴⁹⁻⁵¹ The strengths of the standing work include the clear research questions with the strong theoretical foundation of the COVID-19 infection. Moreover, our data were collected from more than 200 participants from the hospital with comprehensive ethical consideration. Nevertheless, due to challenges in data collection and limited recruitment from a single hospital, this study remains some limitations. Notably, there was no analysis of changes in D-dimer levels amongst the severe cases with chronic respiratory or cardiovascular disease after hospital admission, nor an investigation into the correlation of COVID-19 vaccination with D-dimer levels.

Conclusions

This study determined that increased D-dimer levels are correlated with the severity of COVID-19 cases in patients at Da Nang Hospital for Pulmonary Diseases and its satellite hospitals. Specifically, patients with D-dimer levels above 638 µg/L exhibited more severe symptoms, as indicated by the ROC curve showing sensitivity of 80% and specificity of 90.8%, with an AUC of 0.900. In addition, the age and diabetes in patients were significantly correlated with changes in the D-dimer levels. These findings suggested

D-dimer could be applied as a biomarker to identify patients at risk of more severe symptoms, particularly among the elderly and those with diabetes, who should be monitored for D-dimer as an indicator to predict high risk of complications.

Additional Information

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Ethics Approval: The study adhered to the guidelines outlined in the Declaration of Helsinki. Approval for this research was granted by the Biomedical Ethics Committee of Da Nang University of Medical Technology and Pharmacy, as well as by the Board of Directors of Da Nang Hospital for Pulmonary Diseases under reference (No. 646/BB-HDDD on 20 December 2021).

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