UDC 616.24-002-06:[616.98:578.834COV]:616-005.6-092
DOI: 10.15587/2519-4798.2025.329831

MAIN MECHANISMS OF THROMBOTIC COMPLICATIONS AMONG PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA COMBINED WITH CORONAVIRUS INFECTION

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The review article is devoted to the pathogenesis of complications in patients with community-acquired pneumonia associated with coronavirus infection. The current understanding of the pathogenetic mechanisms of SARS-CoV-2 and the progression of COVID-19 indicates complex changes in the neurohumoral status. Understanding the pathogenetic mechanisms of complications in patients with COVID-19 makes it possible to select biomarkers for risk stratification and understand the clinical context of the disease.

***The aim of the study**: to determine the main mechanisms of thrombotic complications in patients with community-acquired pneumonia associated with coronavirus infection.*

***Materials and methods:** using the Internet resources of scientometric databases PubMed, Web of Science, and SCOPUS, a retrospective analysis of the literature on this topic for the period 2020-2024 was carried out.*

***Results:** A persistent inflammatory state in severe and critically ill patients with COVID-19 is an important trigger of the coagulation cascade. It is important to remember that thrombotic complications are a sign of severe COVID-19 disease and are associated with multiple organ failure and increased mortality. Therefore, the literature review identified the main pathogenetic mechanisms of complications in patients with COVID-19, which allowed us to select the appropriate laboratory tests necessary to predict the course of the disease. An understanding of the pathophysiology of COVID-19 in terms of immune-mediated inflammation and endothelial dysfunction makes it possible to include more appropriate adjunctive treatments in the patient management regimen.*

***Conclusion.** Understanding the underlying mechanisms of complications in patients with community-acquired pneumonia in combination with coronavirus infection allows the selection of biomarkers to predict disease progression. Thrombotic complications are markers of severe COVID-19, and information on the pathogenetic mechanisms of their occurrence facilitates understanding of the clinical picture of the disease. An understanding of the pathophysiology of COVID-19 makes it possible to incorporate more appropriate adjunctive therapy into patient management protocols*

***Keywords:** COVID-19, SARS-CoV-2, community-acquired pneumonia, mechanisms of complications, inflammation, thrombotic complications, endothelial dysfunction*

How to cite:
Skorokhodova, N., Yatsenko, O., Karaban, A. (2025). Main mechanisms of thrombotic complications among patients with community-acquired pneumonia combined with coronavirus infection. ScienceRise: Medical Science, 1 (62),14–19. http://doi.org/10.15587/2519-4798.2025.329831

1. Introduction

The pathogen, called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), causes a pathogenic condition called coronavirus disease 2019 (COVID-19). COVID-19 was first reported in late December 2019 in Wuhan, China. Accumulating clinical evidence suggests that SARS-CoV-2 infection can lead to a variety of clinical conditions, ranging from asymptomatic to life-threatening cases [1, 2].

Pneumonia and pulmonary dysfunction usually dominate the clinical picture, but it is now clear that COVID-19 significantly involves other organs and systems of the body, including the heart, intestines, kidneys, and brain. The current understanding of the pathogenic mechanisms of SARS-CoV-2 infection and COVID-19 progression emphasizes complex changes in neurohumoral status. The key role of an overreaction of the immune system is now emphasized, characterized by widespread endothelial damage, complement-induced coagulation, and systemic microangiopathy [3, 4].

SARS-CoV-2 infection is mainly combined with cytokine production, inflammation, and cell death, which are pathophysiological processes also associated with oxidative stress.

Evidence suggests that oxidative stress contributes to the pathogenesis of COVID-19 by increasing the production of reactive oxygen species (ROS) and causing an imbalance in the antioxidant system. In addition, respira-

tory hypoxia combined with COVID-19 infection can cause a hypoxic state in the brain and thus induce oxidative stress. According to studies, hypoxia induces ROS production, which is involved in inflammation and immune response [5, 6].

Knowledge of the pathogenic mechanisms of complications may help identify new or existing therapeutic interventions to limit disease progression and treat severe cases. Further in-depth research into the pathogenesis of COVID-19 is essential to develop new and improve existing treatment strategies. As our knowledge of pathogenesis improves, so do our treatment approaches. Understanding the pathogenetic mechanisms of complications that occur in patients with COVID-19 opens up opportunities to select biomarkers for risk stratification and understand the clinical picture of the disease, which determined the purpose of this research [7, 8].

Objective. To determine the main mechanisms of thrombotic complications among patients with community-acquired pneumonia combined with coronavirus infection.

2. Materials and methods

Using the Internet resources of the scientometric databases PubMed, Web of science, SCOPUS, a retrospective analysis of the literature on this topic for the period 2020–2024 was conducted.

To retrieve information on the thrombotic complications among patients with community-acquired pneumonia and coronavirus infection, various combinations of keywords were used: "COVID-19", "SARS-CoV-2", "community-acquired pneumonia", "mechanisms of complications", "inflammation", "complications". When evaluating the sources identified during the search, the most relevant sources were selected. After analyzing the abstracts of the articles and reading the full text, 45 sources were selected. Based on the data obtained, an in-depth analysis of the original articles on the main pathogenesis of complications among patients with community-acquired pneumonia combined with coronavirus infection was performed.

3. Results and Discussion

The SARS-CoV-2 virus, like other members of the Coronaviridae family, has an enveloped, non-segmented single-stranded ribonucleic acid (RNA) genome. Studies have shown that SARS-CoV-2, as well as other coronaviruses, can use the protein angiotensin-converting enzyme-2 (ACE-2) to enter cells. The ACE-2 is known to be a type I integral membrane protein that performs many important physiological functions. It is expressed in the alveolar cells of the lungs, providing the main pathway for virus entry into the human body. The ACE-2 protein also plays a role in lung protection, so virus binding to this receptor disrupts lung barriers, which contributes to viral pathogenicity [9, 10].

The virus's tropism for upper respiratory tract tissues may explain the continued release and spread of SARS-CoV-2 through the throat when symptoms remain mild and confined to the upper respiratory tract. In the late stages of COVID-19 disease, secondary virulence develops, followed by a widespread attack on target organs expressing ACE-2, such as the heart, kidneys, gastrointestinal tract, and vascular system. This viral spread is associated with clinical deterioration, which occurs primarily around the second week after disease onset [11, 12].

The two main pathological changes that occur in vital organs during COVID-19 are believed to be directly attributed to the cytopathic effect of SARS-CoV-2 and indirectly to the deleterious immune response, but the contribution of each remains to be further investigated. Currently, there is evidence that an aberrant immune response (rather than direct viral cytopathic effects) plays a more important role in the development of COVID-19 complications. The COVID-19 patients have been observed to have the highest viral load in the early stages of the disease. However, the association between clinical worsening, viral load reduction, and immune response (meaning significantly elevated cytokine levels) is primarily immunopathological in nature [13, 14].

The late-stage disease is explained not only by direct viral damage but also by immune-mediated damage caused by SARS-CoV-2. It should be noted that two distinctive features have been observed in severe and critical patients with COVID-19: a progressive increase in inflammation and an unusual tendency to hypercoagulability [15, 16].

Immunocompetent patients without significant risk factors (such as advanced age, comorbid cardiovascular disease, etc.) can generate sufficient immune responses to suppress the virus without excessive immune responses. However, immunocompromised patients may be at higher risk for severe or critical illness and have a higher mortality rate [17, 18].

At the same time, inflammatory markers were significantly elevated, including C-reactive protein, ferritin, interleukin-6, tumour necrosis factor-α, etc. Multiple studies have reported that decreased lymphocyte counts and elevated levels of ferritin, IL-6, and D-dimer are combined with increased mortality from COVID-19 [19, 20].

During the COVID-19 pandemic, the incidence of intravascular coagulation, deep vein thrombophlebitis, pulmonary embolism, myocardial infarction, or stroke was unexpectedly high. It is believed that the imbalance between coagulation and inflammation leads to a hypercoagulable state. Immune-induced thrombosis can limit the spread of SARS-CoV-2, but abnormal activation of this system may lead to endothelial dysfunction, resulting in dysregulated fibrinolysis and thrombosis [21, 22].

Several factors may contribute to coagulation disorders in patients with COVID-19. The persistent inflammatory status in severe and critical patients with COVID-19 acts as an important trigger for the coagulation cascade. Certain cytokines, including IL-6, can activate the coagulation system and inhibit the fibrinolytic system. In the context of COVID-19, lung and peripheral endothelial damage due to direct viral attack may be an equally important inducer of hypercoagulability [23, 24].

The close relationship between inflammation and coagulation is of evolutionary origin. The invasion of pathogens into the bloodstream poses a fatal threat to the host. Effective host defence requires both effective inflammatory immune responses and coagulation reactions to prevent the spread of pathogens. However,

dysregulation of any component of either of these systems can upset the balance, leading to varying degrees of excessive inflammation and thrombosis. An aggressive immune response can be enhanced by dysfunctional coagulation. This is observed in severe SARS-CoV-2 infection, which is characterized by immunothrombotic dysregulation, leading to multiorgan failure and death [25, 26].

It is important to consider that thrombotic complications are a hallmark of severe progression of COVID-19 and are associated with multi-organ failure and increased mortality. Therefore, coagulation activation and thrombocytopenia have emerged as prognostic markers for COVID-19. The problem of thrombosis in COVID-19 should be considered in three aspects: venous thrombosis, arterial thromboembolism, and microvascular thrombosis [27, 28].

Recent studies have shown a significant increase in the incidence of venous thrombosis among patients with COVID-19. Indeed, its cumulative incidence is reported to be between 25 % and 49 % of patients with severe COVID-19, with pulmonary embolism being the most common thrombotic complication [29, 30].

Importantly, even with the use of venous thromboprophylaxis, the risk remains elevated. The study by S.F. Lax et al. aimed to evaluate pathological changes in organ systems and the clinical and pathological basis of severe and fatal outcomes. It was determined that the death of patients may be caused by thrombosis observed in segmental and subsegmental pulmonary arterial vessels, despite the use of prophylactic anticoagulation. In addition, according to the data obtained by D. Wichmann et al. massive pulmonary embolism is a direct cause of death in more than 30 % of patients, which emphasizes the important relationship between COVID-19 and venous thrombosis [31, 32].

In addition to venous thrombosis, researchers have reported that patients with COVID-19 have increased rates of arterial thromboembolism. There are several reports from research groups that have reported the incidence of acute ischemic stroke. From 3 % to 5 % of patients hospitalized with COVID-19 developed an acute ischemic stroke. It should be noted that reports show that these ischemic strokes occurred in young people without traditional cardiovascular risk factors [33, 34].

In addition to macrovascular complications, there is a strong link between COVID-19 and microvascular thrombosis. Pulmonary microvascular thrombosis was previously described during autopsies as a complication of severe acute respiratory distress syndrome, and later reported to complicate the course of diseases caused by coronaviruses, including SARS-CoV and MERS-CoV. In combination with other reported thrombotic events, microvascular thrombotic complications indicate a strong relationship between SARS-CoV-2 and coagulation [35–37].

Pulmonary microvascular thrombosis is more pronounced in severe SARS-CoV-2 infection. According to the data, patients with COVID-19 have a 9-fold increase in the prevalence of alveolar-capillary microthrombi compared to patients with influenza [38].

In this regard, autopsy results showed that, in addition to the expected signs of diffuse alveolar damage found in acute respiratory distress syndrome, platelet-fibrin thrombi are a common microscopic finding. They are found in the small pulmonary vasculature, which occurs in 80-100 % of cases of lungs examined during autopsy [39, 40].

The role of endothelial dysfunction in the pathogenesis of COVID-19 complications has been studied using laboratory and pathological data. There is evidence of unexplained organ damage, such as multifocal organ damage, cardiomyocyte damage, acute renal tubular damage, fibrinous necrosis of small vessels, and pulmonary hemorrhage, which may explain endothelial dysfunction [41, 42].

The evidence available to date supports the concept that the thrombotic manifestations of severe COVID-19 are due to the ability of SARS-CoV-2 to penetrate endothelial cells via ACE-2, which is expressed in endothelial cells. Damage to endothelial cells can also strongly activate the coagulation system through the influence of tissue factor [43, 44].

In patients with COVID-19, abnormal endothelial function is implicated in organ failure during viral infection by inducing microvascular leakage, inflammation, procoagulant status, and organ ischemia. Subsequent endothelial inflammation, complement activation, thrombin formation, and initiation of innate and adaptive immune responses result in immunothrombosis, which ultimately causes thrombotic complications such as deep vein thrombosis, pulmonary embolism, and stroke [45].

Therefore, the identified potential mechanisms of complications in patients with COVID-19 allow for the selection of appropriate laboratory tests to predict disease progression. Understanding the pathophysiology of COVID-19 in terms of immune-mediated inflammation and endothelial dysfunction provides an opportunity to incorporate more appropriate additional treatments into patient management protocols.

Limitations of the study. The limitation of the conducted study was the impact of full-scale military operations on the territory of Ukraine on the collection of information, which significantly limited the sample of patients for the study.

Prospects for further research. Thrombotic complications that occur among patients have complex pathogenetic mechanisms, so therapeutic anticoagulation does not always achieve its goal. Given that thrombotic complications are central to the high mortality rate from COVID-19, strategies to prevent thrombosis are extremely important. It is advisable to continue researching the mechanisms of vascular endothelial damage and evaluating treatment regimens that may reduce the risk of complications.

4. Conclusions

1. Understanding the main mechanisms of complications among patients with community-acquired pneumonia combined with coronavirus infection allows the selection of biomarkers to predict disease progression.

2. Thrombotic complications are markers of severe COVID-19, and information about the pathogenetic mechanisms of their occurrence facilitates understanding of the clinical picture of the disease.

3. Understanding the pathophysiology of COVID-19 provides an opportunity to incorporate more appropriate adjunctive therapies into patient management protocols.

Conflicts of interest

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

Funding

The study was performed without financial support.

Data availability

The manuscript has no associated data.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the current work.

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Received 25.03.2025
Received in revised form 17.04.2025
Accepted 06.05.2025
Published 16.05.2025

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