Review

BIO Integration

Coronavirus Pneumonia and Pulmonary Thromboembolism

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Abstract

In 2019, a novel pneumonia, called coronavirus disease 2019 (COVID-19), spread rapidly throughout the world. This novel global pandemic severely threatened public respiratory health and medical services. To date, except for the common respiratory symptoms, coagulation disorders, especially pulmonary thromboembolism (PTE), has been proven as an important complication in severe COVID-19 patients, and the incidence of PTE causes poor clinical outcome and increased fatality. Therefore, it is important that healthcare providers, including respiratory physicians, emergency medicine specialists, hematologists, cardiologists, infectious disease specialists, and other specialists, recognize that patients with COVID-19 are at increased risk of PTE, and ensure that appropriate prophylaxis is administered to the appropriate patients, and that they effectively manage PTE when it does occur. The mechanism of PTE in patients with coronavirus pneumonia consists of endothelial injury, activated platelet, cytokine storm, and a suppressed fibrinolytic system. Early prophylaxis, antiviral therapy, anticoagulation, and supportive treatment are beneficial to COVID-19 patients. In this review, we summarize the harm that coronavirus pneumonia wreaks and highlight the clinical relationship between PTE and coronavirus infection. The potential mechanism and the prophylaxis and therapeutic measures are also discussed to call for more effort and research to investigate the strategies for PTE in COVID-19.

Keywords

Coronavirus pneumonia, COVID-19, pulmonary thromboembolism.

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The background of coronavirus and pulmonary thromboembolism

Coronaviruses (CoVs) are a group of single-stranded positive-sense RNA viruses, which can infect humans and other species and which have had a great impact on global public health in the recent decades. CoVs can not only destroy the respiratory system of humans, but can also induce coagulation disorders and even pulmonary thromboembolism (PTE) [1]. PTE refers to a blood clot from the venous system or the right side of the heart that obstructs the pulmonary arteries and their branches and it has a poor clinical prognosis [2]. Patients with coronavirus disease 2019 (COVID-19) have an increased risk of thrombotic complications and the incidence of coagulation disorders or PTE can cause the deterioration of a patient's condition and increases the mortality rate [3]. Therefore, this review will elaborate the mechanisms of the occurrence of coagulation disorders and PTE in patients with coronavirus pneumonia and introduces prophylatic and therapeutic measures.

The detrimental effect of coronaviruses and pulmonary thromboembolism

Coronaviruses belong to the Coronaviriane subfamily of the Coronaviridae family and they can be divided into four genera: alpha CoVs, beta CoVs, gamma CoVs, and delta CoVs. To date, a total of seven coronaviruses that can infect human have been found, including HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, SARS-CoV, MERS-CoV, and SARS-CoV-2 (2019-nCOV) and these CoVs can lead to respiratory or digestive symptoms in humans. HCoV-229E and HCoV-NL63 are alpha CoVs while HCoV-OC43, HCoV-HKU1, SARS-CoV, MERS-CoV, and SARS-CoV-2 are the members of beta coronoaviruses [4].

SARS-CoV, MERS-CoV, and SARS-CoV-2 can result in a life-threatening pneumonia and all of them have caused global pandemics in the 21st century. At the end of 2002, the first case of severe acute respiratory syndrome (SARS) was reported in Guangdong Province, China. The disease

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then spread to mainland China and Hong Kong as well as other 27 countries due to international travel and trade and it ultimately caused 8096 reported cases with 774 deaths. Middle East respiratory syndrome (MERS) was first reported in Saudi Arabia in 2012 and continued to spread from the Middle Eastern area to the rest of the world. MERS-CoV finally infected 1728 people with 624 deaths in 27 countries [5]. Currently, a novel coronavirus strain disease, defined as COVID-19 by the World Health Organization (WHO), is spreading worldwide, involving nearly 200 countries. It has caused a global pandemic and is infecting countless people with, at the time of writing, more than ten million cases and it has caused hundreds of thousands of deaths [1].

PTE is defined as a thrombus that blocks the pulmonary circulation and it can lead to acute rises of pulmonary vascular resistance and the afterload of the right ventricle which will finally induce right heart failure and obstructive shock. PTE and deep venous thrombosis (DVT) are collectively referred to as venous thromboembolisms (VTEs) and they are considered as the different clinical manifestation of VTEs in different time and at different locations [2]. The majority of pulmonary embolisms (PEs) are derived from DVTs of the lower extremities while nearly 50% of DVTs can induce silent PEs [6]. VTEs not only cause deaths in 5–10% of hospitalized patients, but also aggravate the burden of medical resources, with a $2 billion to $10 billion cost per year [7]. The incidence of VTE is about 350,000 to 600,000 in the United States annually and at least 100,000 deaths have been considered to be related to PTE and DVT [8]. The incidence of VTEs is associated with gender and age. Heit and his colleagues suggested that men had a higher occurrence and recurrence rate of VTEs than women [9]. A recent study by Heit et al. found that the risk of VTEs increased with age and those aged more than 40 years of age had a higher risk of VTEs than younger people [10]. Besides, VTE has also been associated with many non-infectious factors, such as surgery, pregnancy, and immobilization [2]. However, many recent studies have found that infectious diseases can result in the incidence of PTE, especially coronavirus pneumonia.

Coronavirus-associated pulmonary thromboembolism

SARS and PTE

There was an outbreak of SARS in Toronto, Canada between March and July, 2003 that resulted in 375 infected cases. Forty-four patients died of SARS; post-mortem examinations were performed on 20 of them in order to understand the progression of SARS. Researchers found, using Martius scarlet blue staining, that endothelial injury of pulmonary small vessels and intravascular fibrin deposition were evident in all the cases of those who died. Fibrin thrombi (85%, 17/20) and pulmonary infracts (60%, 12/20) were also commonly found in those who died [11]. Furthermore, Lee et al. reported SARS patients usually had some concomitant coagulation disorders, such as thrombocytopenia (44.8%), prolonged activated partial-thromboplastin time (42.8%), and elevated D-dimer (45.0%) [12] and a retrospective analysis demonstrated that the incidence rate of thrombotic events in severe SARS patients would be much higher [13].

MERS and PTE

Li et al. found that microthrombi in pulmonary vasculature could present in the histopathologic examination of transgenic mice expressing the human dipeptidyl peptidase 4 (hDPP4) with the infection of MERS-CoV [14]. Moreover, Assiri and his colleagues found that thrombocytopenia was a common clinical feature of MERS patients [15]. Hwang et al. also reported that MERS patients tend to have a relatively lower platelet count [16]. These studies indicate that the poor prognosis of MERS patients may be associated with coagulation disorders and PTE.

COVID-19 and PTE

A recent single institutional study performed by Zhang et al. showed that out of 143 patients hospitalized with COVID-19, 66 patients developed lower extremity DVTs (46.1%, 66/143) and 43 of the patients developed DVTs in their distal veins (65.2%, 43/66), while the other 23 patients developed DVTs in their proximal veins (34.8%, 23/66) [17]. Kaminetzky et al. found 23 patients (37.1%) had positive computed tomography pulmonary angiography (CTPA) results for PE in a cohort of 62 COVID-19 patients who underwent CTPA [18]. Klok et al. also studied 184 COVID-19 patients in ICUs and found that the incidence rate of thrombotic events was as high as 31%, of which 27% were diagnosed as VTE and 3.7% were found to be arterial thrombi in the body circulation and this research indicated that COVID-19 may result in coagulation disorders in both the venous and arterial systems [19]. Bilaloglu et al. found that 533 out of 3334 hospitalized COVID-19 patients (16.0%), most of whom received low-dose anticoagulation for prophylaxis, had thrombotic events (patients could have more than one thromboembolism) and venous thromboembolism occurred in 207 (6.2%), while arterial thromboembolism occurred in 365 (11.1%) [20]. In Germany, Wichmann and his colleagues performed autopsies for 12 COVID-19-positive deaths and the autopsies showed that seven of 12 patients (58%) had DVTs. These venous thromboembolism events were not detected by clinical doctors and PE was the direct lethal factor in four patients while the other three patients had fresh venous thrombosis in their lower extremities. Fresh thrombosis was also found in the prostatic venous plexus in six male patients. And the histopathologic results of lungs revealed diffuse alveolar damage, microvascular thromboemboli, capillary congestion, and protein-enriched interstitial edema were the main pathological manifestations [21].

Zhang et al. suggested that COVID-19 patients with DVT had a lower oxygenation index and higher values of

C-reactive protein and procalcitonin than those without DVT. Besides, COVID-19 patients with DVT had a higher possibility of being found to have pulmonary hypertension and larger right atrial and right ventricular diameters on echocardiograms compared with a non-DVT group. In the same study, researchers revealed that advanced age (>65 years), prolonged bedridden time (>72 h) and high Pauda score (>4) were the risk factors of DVT in COVID-19 patients and the patients with DVT had a worse prognosis and higher mortality [17]. Kaminetzky et al. also found evidence of right heart strain on either an echocardiogram or CTPA in 10 of 23 COVID patients (43.5%) with PEs [18].

Moreover, the increase of d-dimer is the most common abnormal laboratory examination for COVID-19 patients. D-dimer is the product of fibrin degradation and usually increases during the incidence in a thrombotic event so it is used as a reliable marker of fibrinolysis [2]. A large clinical study in China showed 260 of 560 COVID-19 cases (46.4%) had an elevated d-dimer while the proportion was even higher in ICU patients (59.6%) [22]. Another study performed by Goshua et al. also demonstrated that the level of d-dimer of COVID-19 ICU patients was much higher than those in a non-ICU group and among the standard reference range [23]. Kaminetzky et al. suggested that the mean level of d-dimer in COVID-19 patients with PEs was much higher than those without PEs (6432 ng/ml versus 1774 ng/ml, $p < 0.001$) and they identified a value of d-dimer (>1394 ng/ml), which could predict the incidence of PE with a sensitivity of 94.5% and a specificity of 71.4% [18]. A recent study also pointed out that there was a positive correlation between the level of d-dimer and the mortality of COVID-19 patients who did not receive heparin treatment [24] and Zhang and his colleagues found that the level of d-dimer (>2.0 mg/L) could predict the patients' mortality with 92.3% sensitivity of and 83.3% specificity [25].

A meta-analysis by Lippi et al. revealed that thrombocytopenia was a common feature in critically ill COVID-19 patients [weighted mean difference -31×10^9 /L; 95% confidence interval (CI), from -35 to -29×10^9 /L] and the decrease of platelet count was associated with the increased risk of severe disease and deaths in COVID-19 patients [26]. In contrast, some studies have reported that no significant difference of platelet count existed between the severe COVID-19 patients and moderate patients [27–29]. Lastly, a study also showed that the platelet count in COVID-19 patients with DVT was not significantly different from those without DVT [17]. Moreover, Qu et al. found platelet peaks and platelet-to-lymphocyte (PLR) at the platelet peak were associated with the severity and duration of COVID-19 patients [30]. However, some cases reported an elevated platelet count in severe COVID-19 patients and this phenomenon was considered as the over-activation of platelets resulting from the over-production of proinflammatory factors and the formation of a cytokine storm [30, 31]. Therefore, the platelet count can vary with each individual and the specific relation between platelets and COVID-19 needs more research to reveal it.

The mechanism for coronavirus-associated PTE

The risk factors for the incidence of pulmonary thromboembolism consist of genetic factors and acquired factors. Genetic risk factors mean the genetic mutation varies from person to person. The acquired risk factors include age, pregnancy, malignancy, and postoperative status and they can be summarized as the Virchow triad: blood stasis, endothelial injury, and creating a thrombophilic state [2, 32]. With the progression of coronavirus pneumonia, patients are usually asked for rest in bed or receive invasive manipulation and therefore, the risk factors for PTE would gradually cumulate and result in the episode of PTE. Researchers have demonstrated that SARS-CoV-2 interacts with human angiotensin-converting enzyme 2 (hACE2) via the spike (S) glycoprotein for virus entry [33]. SARS-CoV-2 keep replication and proliferation in alveolar epithelial cells and destroy the alveoli, which will cause hyoxemia and the necrosis of pulmonary vessel endothelium [21]. Besides, the activation of adaptive immune response resulting from the infection of SARS-CoV-2 will increase systematic inflammatory activity in humans. The infiltration of neutrophils and monocytes in the pulmonary vessel wall appears and leads to the apoptosis of endothelial cells and the release of tissue factors into the blood. At the same time, the increased expression of various proinflammatory cytokines on immune cells, such as tumor necrosis factor-α, interferon-γ, interleukin (IL)-1β and IL-6, will form a cytokine storm and initiate the extrinsic coagulation pathway with the tissue factors and excessively activate the coagulation cascade [3]. The excessive activation of the coagulation cascade was also found in an *in vitro* human model with SARS infection [34] and it can be demonstrated using a mouse model infected with MERS-CoV [14]. These proinflammatory cytokines can activate plenty of platelets and make them aggregate at the damaged vessel endothelium, which will promote the coagulation cascade and produce microcirculatory dysfunction and thrombus formation in the body [3]. On the other hand, Gralinski et al. reported the expression of urokinase-type plasminogen activator was reduced in severe SARS patients while the over-expression of plasminogen activator inhibitor-1 has been shown [35], which suggested that the suppression of the fibrinolytic system may play a large role in the formation of PTE in coronavirus pneumonia patients. Recently, some literature indicated that the elevated antiphospholipid antibodies resulting from immune dysfunction in COVID-19 patients may be related to the high incidence of thrombotic events of COVID-19 patients [36, 37].

The prophylaxis of PTE in COVID-19 patients

Compared to COVID-19, SARS was controlled rapidly with the help of strong governmental and medical interventions and no human SARS cases have been found since

2004. Similarly, MERS had been brought under good control after its first appearance and there have been few confirmed human MERS cases in recent years [5]. However, COVID-19 has infected over ten million people and severely threaten global public health and it is very urgent for everyone that we find appropriate measures to deal with this novel coronavirus pneumonia. Therefore, this review focuses mainly on the measures of prophylaxis and treatment for PTE in COVID-19 patients to assist clinical doctors to overcome COVID-19 soon.

Due to the high incidence of coagulation disorders and thrombotic events in critically ill COVID-19 patients, the Chinese Medical Doctor Association (CMDA) recommended that clinical doctors should use the Pauda score to evaluate the risk of venous thromboembolism of all the hospitalized COVID-19 patients and prevent the incidence of VTE. The patients whose total score is no less than 4 are considered as a high-risk group with VTE while the patients who have low score (<4) are considered low-risk patients. Hence, the CMDA recommended using a standard prophylaxis dose of low molecular weight heparin (LMWH) or unfractionated heparin (UFH) for the pharmacological prophylaxis of VTE in severe or critically ill patients according to an initial risk assessment. Even though the severe patients have pharmacological contraindications for anticoagulant therapy, they should also receive mechanical prophylaxis measures, such as an intermittent air pressure pump and graded pressure stretch socks [38]. Besides, some Chinese doctors in a consensus statement, also proposed using intensified heparin for VTE prophylaxis in severely or critically ill COVID-19 patients [39]. However, in a recent study, 53 of 143 hospitalized COVID-19 patients were given DVT prophylaxis and researchers found no statistically significant difference between the DVT group and the non-DVT group (33.3%, 22/66 versus 40.6%, 31/77; $p = 0.393$). Nonetheless, the researchers did not clarify the specific prophylaxis measures for the COVID-19 patients and the sample size of this study was limited, therefore, the real effect of VTE prophylaxis requires further investigation [17].

The therapeutic measures of PTE in COVID-19 patients

Nowadays, research about COVID-19 mainly focuses on three aspects: epidemiology, medical therapeutics, and virology; and interdisciplinary integration would help scientists to summarize the most appropriate methods in pathogen identification, virus screening, vaccine development, and therapeutics. For example, the integration of data collection and medical resources can help governments to track and administer to COVID-19 patients. The use of artificial intelligence (AI) and omics technology provides a new way for screening for the virus. What is more, the integration of data science, clinical medicine, and molecular biology can achieve effective personalized medicine for COVID-19 patients [40]. PTE has been found to be a common but life-threatening coagulation disorder for COVID-19 patients in this article. However, because of the short period of time it has been around and the quick infectious speed of COVID-19, there is no specific medicine available so far for COVID-19. Therefore, a multiple disciplinary team (MDT) is essential to look after COVID-19 patients with coagulation dysfunction, which can remedy limitations in thinking, reduce misdiagnosis, and make an effective protocol [41].

Antiviral treatment

Antivirals are likely to be the most foundational and important treatment of the coronavirus pneumonia. Remdesivir, an adenosine analog, can stop normal virus replication by incorporating it into the nascent SARS-CoV-2 RNA chain and it has shown a strong inhibitory effect to SARS-CoV-2 in *in vitro* experiments [42]. Another study of a cohort of 61 severely ill COVID-19 patients showed that compassionate use of remdesivir effectively promoted the clinical symptoms and condition of patients [43]. Besides, Beigel et al. conducted a randomized placebo-controlled trial in a total of 1063 adult hospitalized COVID-19 patients with evidence of lower respiratory tract involvement and demonstrated that the patients receiving remdesivir had a shorter median time to the disappearance of clinical symptoms (11 days; 95% CI, 9–12) than those who received placebo (15 days; 95% CI, 13–19), and there was evidence of lower respiratory tract infection (rate ratio for recovery, 1.32; 95% CI, 1.12–1.55; $p < 0.001$), which suggests that remdesivir may improve the clinical status of COVID-19 patients [44].

On the other hand, chloroquine was found to inhibit the SARS-CoV-2 in an *in vitro* setting [42]. Chloroquine and its derivatives, such as hydroxychloroquine, have been used to treat COVID-19 patients. Huang et al. found that 10 of 22 COVID-19 patients treated with chloroquine achieved negative SARS-CoV-2 results in a quicker time when evaluated by real-time polymerase chain reaction (RT-PCR) compared with those receiving lopinavir/ritonavir. Besides, the chloroquine group had shorter hospital stays and it took less time for them to achieve lung clearance based on CT imaging [45]. A multicenter prospective observational study by Huang et al. also indicated that chloroquine treatment in COVID-19 patients would shorten the time in achieving an undetectable viral RNA and no severe adverse events were observed during treatment with chloroquine [46]. Another clinical trial performed by Gautret et al. revealed that hydroxychloroquine can effectively clear the viral carriage in COVID-19 patients with the reinforcement of azithromycin [47]. In addition to the direct antiviral effect, chloroquine functions in anticoagulation, antithrombosis and reducing the damage of inflammatory response by inhibiting the release of inflammatory factors and the appearance of a cytokine storm [48], which suggests that chloroquine and hydroxychloroquine may improve the clinical outcome of COVID-19 patients with PTE. However, a randomized controlled trial by Tang et al. suggested that there was no significant difference of the probability

of negative conversion by 28 days between the standard care plus hydroxychloroquine group and the standard care alone group in hospitalized COVID-19 patients (85.4%, 53/70 versus 81.3%, 56/80). In the same study, Tang et al. also found that patients receiving hydroxychloroquine had more adverse events than hydroxychloroquine non-recipients (30%, 21/70 versus 9%, 7/80) [49]. Similarly, another multicenter study by Cavalcanti et al. with a cohort of 667 hospitalized patients with mild-to-moderate COVID-19 indicated that the use of hydroxychloroquine, alone or with azithromycin, had no improvement in clinical status at 15 days as compared with standard care but the prolongation of QT interval and elevation of liver-enzyme levels were more common in hydroxychloroquine recipients [50]. Therefore, the administration of hydroxychloroquine for COVID-19 patients is still being debated and more research is needed to explore its curative effect and safety.

Anti-coagulant therapy

Anticoagulant treatment is essential for all patients with PTE, which can effectively prevent the thrombosis from forming and relapsing and activating the human fibrinolytic system. Tang et al. reported that the use of heparin, mainly LMWH, achieved good clinical outcomes and notably decreased the 28-day mortality in severe COVID-19 patients with coagulation disorders compared with those not receiving heparin treatment (40.0% versus 64.2%, $p = 0.029$) [24]. Moreover, heparin can inhibit the inflammatory response in body and protect the endothelium of the microvessels [51], which suggests that heparin plays an important role in treating COVID-19 patients with PTE in various ways. However, the concrete dose of heparin should be carefully administered by clinical doctors on the basis of specific conditions and the risks of anticoagulation treatment, especially the threat of uncontrolled massive hemorrhage, should be weighed and considered in detail [2].

Symptomatic and supportive treatment

Due to the lack of a specific drug for COVID-19, symptomatic and supportive treatment has become the main and basic therapeutic mode for treating COVID-19 patients. The recent study by Zhang et al. revealed that COVID-19 patients with DVT need more high-flow oxygen (68.2% versus 42.9%, $p = 0.002$) and invasive mechanical ventilation (28.8% versus 5.2%, $p < 0.001$) while they had a higher portion of cardiac or pulmonary dysfunction compared with those without DVT [17]. Therefore, the monitoring of vital signs, electrocardiograms and arterial blood gasses should be provided for all the COVID-19 patients with high risk of or confirmed PTE and the supplemental oxygen and fluid resuscitation may be beneficial to these patients [2]. For patients who present a massive PE based on CTPA and echocardiogram, thrombolytic agents, such as alteplase (tPA), urokinase, and streptokinase, can be used for therapy after obtaining the fully informed consent of patients and the ruling out of related contraindications of thrombolysis, which can decrease the resistance of pulmonary vessels, recover the pulmonary perfusion, and improve the function of the side of the right heart. But the risk of massive hemorrhage or intracranial hemorrhage after thrombolytic therapy requires that doctors take more time to care about the clinical condition of their patients [2, 38].

Conclusion

In conclusion, the infection of CoVs, especially SARS-CoV-2, can frequently induce coagulation disorders and PTE, which will cause the deterioration of the patient, organ failure, and mortality in those with coronavirus pneumonia. The mechanism of PTE in coronavirus pneumonia patients, including pulmonary thromboembolism and the formation of primary thrombosis in pulmonary vessels, consist of four aspects: the damage of the pulmonary vessel endothelium, the production of excessive proinflammatory factors and a cytokine storm, the aggregation and adhesion of platelets, and the suppression of the human fibrinolytic system. Advanced assessment and prophylaxis, including both pharmacological and mechanical prophylaxis, may be beneficial to decrease the occurrence of PTE. For coronavirus pneumonia patients with PTE, antiviral treatment, anticoagulation treatment, and symptomatic and supportive treatment can effectively promote the clinical outcome and reduce the fatality rate. To date, the interdisciplinary communication and integration among academia, industry, government organizations and clinical medicine have been applied in the outbreak of COVID-19 to realize the appropriate methods for diagnosis and therapeutics. With the help of multidisciplinary cooperation and research, scientists can find better strategies for diagnosis, prophylaxis, and therapy for PTE in patients with coronavirus pneumonia.

Conflicts of Interest

The authors declare no conflict of interest.

Acknowledgments

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