

# Common Coagulopathies Associated With COVID-19 Patients

Received 01/16/2023  
Review began 04/07/2023  
Review ended 04/19/2023  
Published 04/24/2023

© Copyright 2023

Gupta et al. This is an open access article distributed under the terms of the Creative Commons Attribution License CC-BY 4.0., which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Vinish Gupta<sup>1</sup>, Sourya Acharya<sup>1</sup>, Akshunna Keerti<sup>1</sup>

1. Department of Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Wardha, IND

Corresponding author: Akshunna Keerti, akshunnakeerti@gmail.com

## Abstract

The coronavirus disease 2019 (COVID-19) outbreak, which first appeared in the Chinese province of Hubei city of Wuhan, has been spreading internationally since December 2019. The World Health Organization (WHO) declared the coronavirus illness from 2019 to be a pandemic on March 11, 2020. Patients hospitalised with severe coronavirus or comorbid conditions (like cardiovascular disease and obesity) are linked to a worse prognosis. The rise in D-dimer and its relationship to prognosis are the most often documented aberrations in coagulation/fibrinolysis in COVID-19. However, the D-dimer assessment's utility is not limitless. Since the coagulation/fibrinolytic state might occasionally change over a short period of time, routine exams are also advantageous in understanding the relevance of the inquiry. Both thrombotic and hemorrhagic diseases should be taken into consideration, despite the fact that the pathophysiology of disseminated intravascular coagulation (DIC) linked with coronavirus disease 19 differs significantly from that of septic disseminated intravascular coagulation. Coagulation as well as fibrinolysis indicators are used to make the diagnosis of COVID-19 thrombosis, which encompasses both macro- and micro-thrombosis. Compared to bacterial-sepsis-associated coagulopathy/DIC, COVID-19 has a lower prevalence of prolonged prothrombin time, activated partial thromboplastin time, and decreased antithrombin activity. However, the causes of coagulopathy remain poorly understood. Hypoxia, endothelial injury, dysregulated immunological responses mediated by inflammatory cytokines, and lymphocyte cell death are thought to be implicated. While blood loss tends to be rare, it is uncertain if COVID-19 suffers from thrombosis or whether the current recommendations for regular venous thromboembolic dose are appropriate. It is important to decide on the COVID-19 therapy phases. Antiviral therapy, cytokine storm therapy, and thrombosis therapy are the steps. Future advancements are predicted, such as a therapy that combines heparin and nafamostat.

**Categories:** Internal Medicine, Medical Education, Epidemiology/Public Health

**Keywords:** disseminated intravascular coagulation, thrombosis, thrombocytopenia, d-dimer, coagulopathy, sars-cov-2

## Introduction And Background

Coronavirus disease 2019 (COVID-19), a syndrome brought on by severe acute coronavirus syndrome 2 (SARS-CoV-2), causes severe acute respiratory symptoms. 80% of persons with the condition are asymptomatic or exhibit only very mild symptoms, compared to 20% who develop significant illness and 2% to 5% who die [1]. The geriatric group and patients with comorbidities (including cardiovascular disease, hypertension, diabetes mellitus, and obesity) are more prone to getting more serious diseases. Males are known to contract infections more frequently than females. But even in young people and healthy individuals, serious illness can arise, and many aspects of what affects the outcomes are still unclear [2]. There can also be some inherited variables at play. Individuals with the O blood group have a relatively lower chance of acquiring COVID-19 as compared to non-O group individuals, and there have been reports of gender differences in the immune responses to this virus [3].

The primary cause of mortality is respiratory failure. Multiple organ failure, thrombosis, disseminated intravascular coagulation (DIC), activation of the coagulation system in association with excessive immune/inflammatory reactions (representing the so-called cytokine storm), and more are other issues [4]. Particularly, thrombosis and DIC have the potential to significantly exacerbate the disease.

In addition to mild thrombocytopenia and coagulation problems, patients with COVID-19 pneumonia commonly have elevated levels of fibrinogen and D-dimer. Elevated D-dimer levels have been associated with a higher death rate [5]. In a subgroup of COVID-19 people, prothrombin time/international normalised ratio (PT/INR) and activated partial thromboplastin clotting time (aPTT) might be abnormally short [6]. The shorter aPTT is usually linked to increased Factor VIII as an acute-phase response (FVIII) [6]. In more severely ill individuals, a syndrome that resembles DIC with relatively mild PT and aPTT prolongation (although fibrinogen tends to stay normal/elevated) may develop [7].

By the standards of the International Society of Thrombosis and Haemostasis (ISTH) [7], DIC is still regarded as having abnormal D-dimer levels even though D-dimer parameters are markedly increased to any anomalies detected in the PT/INR [8], aPTT, fibrinogen, or platelet. In contrast to the typical pattern of DIC

### How to cite this article

Gupta V, Acharya S, Keerti A (April 24, 2023) Common Coagulopathies Associated With COVID-19 Patients. Cureus 15(4): e38067. DOI 10.7759/cureus.38067

brought on by bacterial sepsis or trauma, coronavirus exhibits minor aPTT and/or PT prolongation, mild thrombocytopenia (a platelet count of 100-150 10<sup>9</sup>/L), sporadic hypofibrinogenemia, as well as sporadic laboratory evidence of hyperfibrinolysis [9]. The term "COVID-19-associated coagulopathy" refers to this spectrum of coagulation disorders [10]. The literature has identified three stages of coronavirus-related coagulopathy: stage 1, which is characterised by elevated D-dimer; stage 2, which is characterised by elevated D-dimer as well as a mild increase in PT/INR and aPTT as well as mild thrombocytopenia; and stage 3, which is characterised by critical illness and laboratory findings that progress towards classic disseminated intravascular coagulation. [11].

Review

Methodology

Google Scholar, Science Direct, PubMed, and Google Search were all employed in the comprehensive electronic literature search for this review. The terms "SARS-CoV-2," "Coagulopathy," "D-dimer," "Thrombocytopenia," "Thrombosis," and "Disseminated intravascular coagulation" were used both individually and together. All relevant studies, including reviews, meta-analyses, organisational submissions, and original research, were carefully arranged. Even though highly regarded earlier studies were regularly mentioned, the most recent study was given preference. The flow diagram for PRISMA is shown in Figure 1 below.

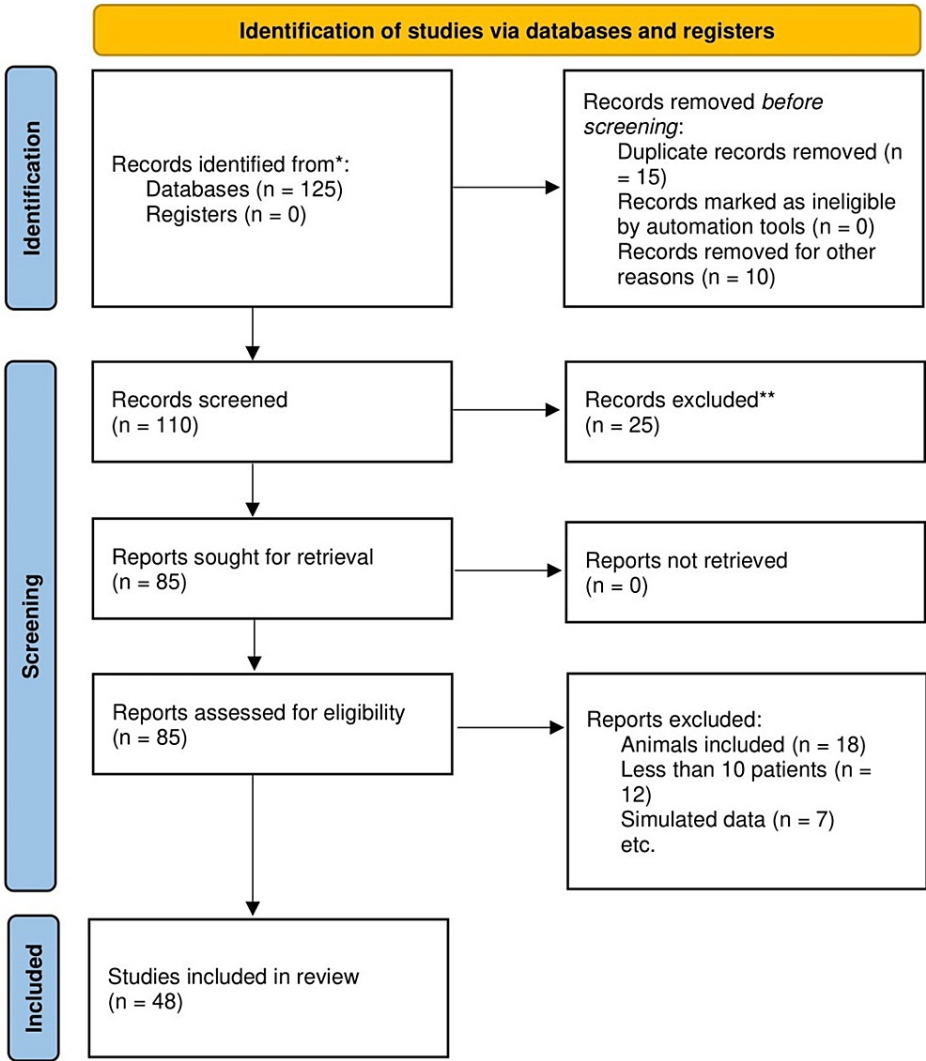


FIGURE 1: PRISMA flow diagram

15 records were removed due to duplication.

25 records were excluded due to a lack of correlation between coagulopathy and COVID-19

COVID-19 associated coagulopathy

A coagulation profile, which includes the measurements of D-dimer, partial thromboplastin, partial thromboplastin time, and platelet count, should be carried out in hospitalised patients with suspected or confirmed COVID-19 [12]. These indicators may change 4-10 days after admission to the hospital or 7-11 days after the onset of symptoms. D-dimer, prothrombin time, and platelet count should all be repeated in patients with severe COVID-19 at least once every two to three days.

A prolonged PT, thrombocytopenia, and a high D-dimer are all signs of DIC [13]; however, the disease does not present the same way as sepsis, where the thrombocytopenia is much more severe and the elevation in the D-dimer does not approach the levels seen in patients with coronavirus disease 2019 [14]. In the majority of individuals with severe illness, low-grade DIC and pulmonary thrombotic microangiopathy-which are thought to be related to COVID-19-are likely to result in serious organ failure.

One feature of the severe coronavirus 2019 sickness is the emergence of coagulopathy as a part of the systemic inflammatory response syndrome. Hematologic abnormalities in coagulation tests, such as increased D-dimer, prolonged PT, thrombocytopenia, and decreased fibrinogen levels, were seen in 20-50% of COVID-19 patients who were hospitalised [15]. This syndrome is characterised by thrombotic episodes instead of haemorrhagic occurrences (venous thromboembolism [VTE]). In COVID-19 deaths, fibrin and thrombin deposition, mainly in the pulmonary microvasculature, is the primary cause of acute respiratory distress syndrome, coagulopathy, the thrombosis of central lines and catheters, and vascular occlusive events (cerebrovascular events, limb ischemia, etc.) [16]. Furthermore, the hypoxia that develops in severe COVID-19 may exacerbate thrombosis by thickening the blood and initiating a signalling cascade that depends on hypoxia-inducible transcription factors [17].

The pathophysiology of the microcirculatory changes brought on by SARS-CoV-2 infection involves a specific kind of endotheliopathy. The sepsis-induced coagulopathy (SIC), which includes impaired fibrinolysis and elevated thrombin generation, is analogous to this endotheliopathy. The angiotensin-converting enzyme-2 (ACE-2) receptor on endothelial cells serves as the viral adhesion receptor, and viral replication results in inflammatory cell infiltration, endothelial death, and microvascular prothrombotic events [18]. Mononuclear and polymorphonuclear cell infiltration, viral inclusions inside endothelial cells, and signs of endothelial mortality have all been found during post-mortem investigation of SARS-Cov-2 infection. The clinical effects that COVID-19 patients experience as a result of microcirculatory dysfunction are therefore important. Additional anomalies that may be applicable in coagulopathy include low fibrinogen, increased Lactate dehydrogenase (LDH), and, in certain cases, substantially raised blood ferritin values.

The procoagulant response during the acute phase of COVID-19 infection is another crucial aspect of the disease. Acute phase reactants such Factor VIII, von Willebrand factor (vWF), and fibrinogen are linked to a higher risk of thrombosis and have an impact on fibrinogen levels. Inflammatory cytokines that are produced in greater amounts during the latter stages of the disease include tumour necrosis factor and interleukins, notably interleukin-1 (IL-1) and interleukin-6 (IL-6) [18]. Thrombin is produced by macrophages, and IL-6-induced tissue factor expression causes coagulation to start [19]. The main mediators of the endogenous coagulation cascade's inhibition are tumour necrosis factor and IL-1. A cytokine storm with high proinflammatory cytokines and chemokines levels may occur in a group of very ill individuals, victims of COVID-19 [20].

When plasmin breaks down stabilised fibrin polymer [21], which is fibrin crosslinked with factor XIII, D-dimer is produced in the blood. The body produces the thrombus as a result of coagulation activation, which is then broken down by fibrinolytic activation. Several publications have observed the connection between elevated D-dimer levels and severity [22]. However, if a considerable amount of thrombus builds up in the body but is not broken down, the increase in D-dimer may be small (indicating the most severe scenario for the body) [23]. Even in dire situations like death, the increase in D-dimer is only marginally perceptible, particularly in the suppressed-fibrinolytic-type disseminated intravascular coagulation brought on by sepsis [24]. As a result, the degree of the D-dimer increase does not always correlate with the severity of the clinical condition [25].

## Anticoagulation

If there are other diseases present (such as cardiovascular disease, obesity, sepsis-induced coagulopathy score > 4, high D-dimer (>6 times the normal), C-reactive protein (CRP), troponins, and other symptoms of disseminated intravascular coagulation) [26], hospital mortality for patients with severe COVID-19 can increase to 42%. It has been demonstrated that by stopping the growth of microthrombi and the associated pulmonary coagulopathy and decreasing concurrent inflammation, low molecular weight heparin (LMWH) given as the first anticoagulant treatment in this group significantly increases arterial oxygen pressure/inspired fraction of oxygen (PaO<sub>2</sub>/FiO<sub>2</sub>). Mortality was seen to have dropped by 48% and 37% in 7 days and 28 days, respectively [27].

Unless the patient has severe thrombocytopenia (<50,000 mm or active bleeding), anticoagulation should be evaluated for VTE evidence or if the patient is anticoagulated [27]. The drug is selected based on how well the kidneys, liver, platelets, and digestive system are functioning. Parenteral anticoagulation is

recommended for critically ill patients since it can be temporarily stopped and does not interact negatively with any of the drugs being tested to treat COVID-19 [28]. Unfractionated heparin exposure via paraclinical and dose adjustments exposes medical personnel, hence LMWH is recommended in critically ill patients [29]. Direct oral anticoagulants provide a number of benefits, including the simplicity of outpatient care and the absence of ongoing monitoring [30]. However, there are hazards associated with their usage, including clinical deterioration and a shortage of reversal drugs at all sites. In patients who will be discharged, direct oral anticoagulants and LMWH should be chosen over routine INR testing [31].

After 4 to 14 days of heparin medication, a 30-50% decrease in platelet count should be regarded as a symptom of thrombocytopenia brought on by heparin. Suspending this anticoagulant medication is necessary because of the aforementioned factors, some of which may also contribute to the limb ischemia seen by COVID-19 patients [32]. In addition to heparins, the synthetic serine protease inhibitor nafamostat mesylate is thought to be a strong inhibitor of the Middle East respiratory syndrome coronavirus (MERS-CoV) infection and the Ebola virus [33]. It also has anticoagulant effects, such as the inhibition of Factor VIIa. This chemical stops cathepsin B from impeding the viral surface glycoprotein's proteolytic digestion [34].

For patients with a history of bleeding who are receiving cardiopulmonary bypass or continuous renal replacement treatment, nafamostat is also licenced as an anticoagulant medication. It has anticoagulant, antifibrinolytic, and antiplatelet properties. It blocks a number of serine proteases generated during the coagulation cascade and the inflammatory process, including activated Factors VIIa and XIIa, kallikrein, thrombin, elements of the complement system, and trypsin [35]. It also blocks tissue-type and urokinase plasminogen activators. When used to prevent blood coagulation during extracorporeal blood circulation, nafamostat should be continuously given at a dosage of 20 to 50 mg/h. It has been determined that nafamostat is a powerful inhibitor of S-mediated membrane fusion [36]. In severe COVID-19 patients where thrombotic problems are frequent, nafamostat's anticoagulant, antiplatelet, and antifibrinolytic properties may be beneficial in addition to its claimed antiviral efficacy. It has been established that nafamostat is a secure and reliable anticoagulant [37]. To prevent bleeding, one must be aware of possible interactions with other anticoagulant therapies that may be used concurrently.

## Platelets

In 2003, between 20% and 55% of SARS patients had thrombocytopenia. A later rebound thrombocytosis was also noted. Higher rates of morbidity and mortality were seen in patients who had thrombocytopenia throughout the epidemic [38]. The thrombocytopenia was also connected to MERS [39].

Depending on the severity of the illness, thrombocytopenia, which is commonly mild (counts are frequently between 100 and 150 10<sup>9</sup>/L), is found in 5.4-41.7% of COVID-19 patients. In 58-95% of COVID-19 severe cases, mild thrombocytopenia was seen; individuals with severe illness frequently had platelet counts 23-31 10<sup>9</sup>/L lower than those with non-severe disease [39]. Average platelet counts are found in patients who are ill and have systemic immunological and coagulation activity, which shows a large compensatory platelet production response. Rarely have reports of significant thrombocytopenia in COVID-19.

For a number of reasons, viral infection and thrombocytopenia can coexist. Increased platelet clearance/destruction frequently facilitates the rapid start of thrombocytopenia in response to viral infections, even while hypo proliferative thrombocytopenia is present in the later stages of viral disease. Platelets that have been activated by viral antigen-antibody complexes or inflammatory reactions from the host are removed from circulation more quickly by the reticuloendothelial system [40]. Viruses can also affect megakaryocytes and reduce platelet production.

Platelets are necessary for the body to react to infections and signal inflammation. Platelets may aid in concentrating haemostasis and immune responses against potential infectious agents to block the microbial invasion by combining thrombotic and immunological recruitment capacities. Platelets directly interact with viruses through a variety of receptors, such as Toll-like receptors [41]. Platelets can agglomerate and absorb diseases, but they cannot kill microorganisms. Platelets and the products they make have been seen to either support or suppress viral infection, depending on the particular infection. Platelets' capacity to attract and activate circulating leukocytes on the surface of the endothelium is thought to be the cause of white blood cell diapedesis. The procoagulant effect of viral infections depends on interactions between leukocytes, platelets, and endothelial cells [42]. In viral infections, thrombocytopenia, platelet secretion, and interactions with leukocytes may have either unfavourable or good immunological effects.

While platelets assist in preserving the basal barrier integrity of the alveolar capillaries, they may also play a role in the onset of a number of pulmonary illnesses and syndromes that cause lung injury. In animal models, platelet-leukocyte aggregates and platelet-endothelial interactions appear to be associated with acute lung injury brought on by physical/chemical damage and influenza infection, respectively [43]. For instance, during dengue infection, platelet-derived IL-1 increases endothelial permeability.

## Antiplatelet agents

Although there is no randomised study to support this, antiplatelet medicines may play a role in COVID-19 disease [44]. Particularly for people with mild thrombocytopenia, such treatment would have an increased risk of bleeding. Treatments for coronavirus, such as lopinavir/ritonavir, remdesivir, bevacizumab, tocilizumab, sarilumab, fingolimod, chloroquine/hydroxychloroquine, interferon, and azithromycin, may interact harmfully with antiplatelets [44].

## Discussion

The indication suggests a combination of localised pulmonary platelet consumption, low-grade disseminated intravascular coagulation (rarely meeting the ISTH DIC criteria), and variably thrombotic microangiopathy as the pathogenesis of coronavirus coagulopathy. In post-mortem studies, higher amounts of vWF and soluble thrombomodulin are indicative of activated or injured endothelium [45]. Ultra-large vWF multimers that interact with platelets and can cause platelet activation, microthrombi, and platelet consumption are expected to be produced by damaged endothelium. Increased activation of the endothelium and/or circulating platelets is suggested by elevated levels of soluble P-selectin and platelet flow cytometric investigations in COVID-19 patients [46]. The SARS-CoV-2 Spike protein directly activates platelets, according to recent studies. There is a link between severe COVID-19 illness and more platelet activation and platelet-monocyte aggregation. Platelets from seriously unwell individuals with COVID-19 can increase monocyte tissue factor (TF) expression (under the control of P-selectin and IIb/3), which may exacerbate inflammation and hypercoagulability in these patients [47].

Findings reveal that severe cases of thrombotic coagulation disorder are very common, despite the fact that our understanding of coagulopathy in COVID-19 is still in its infancy. The prevalence of thrombocytopenia is less common than septic shock, despite the fact that the D-dimer is a more accurate indication of the severity and more sensitive than other coagulation markers [48]. Contrary to thrombotic events, bleeding problems are far less prevalent in COVID-19, hence anticoagulant therapy is not required.

## Conclusions

There are still many ways in which the pathophysiology of COVID-19 has to be fully described. Laboratory haematology research is still being done to better understand pathophysiology. Despite its limitations in determining the reason behind the coagulation anomalies seen by COVID-19, D-dimer is an excellent diagnostic tool. It is anticipated that adding markers like thrombin-antithrombin complex (TAT), plasmin- $\alpha$ 2 plasmin complex (PIC), and soluble fibrin (SF) will make the pathological condition clearer.

The COVID-19 pandemic may have a variety of effects on thrombotic or thromboembolic disease prevention and therapy. First, think about how the cytokine storm that produces COVID-19 could be impacted directly or indirectly. According to the most recent national and international recommendations, each institution should adhere to the protocols for thromboprophylaxis, anticoagulation, and other considerations for managing coagulopathy and bleeding.

## Additional Information

### Disclosures

**Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

## References

- Asakura H, Ogawa H: COVID-19-associated coagulopathy and disseminated intravascular coagulation. *Int J Hematol.* 2021, 113:45-57. [10.1007/s12185-020-03029-y](https://doi.org/10.1007/s12185-020-03029-y)
- Gómez-Mesa JE, Galindo-Coral S, Montes MC, Muñoz Martín AJ: Thrombosis and coagulopathy in COVID-19. *Curr Probl Cardiol.* 2021, 46:100742. [10.1016/j.cpcardiol.2020.100742](https://doi.org/10.1016/j.cpcardiol.2020.100742)
- Wool GD, Miller JL: The impact of COVID-19 disease on platelets and coagulation. *Pathobiology.* 2021, 88:15-27. [10.1159/000512007](https://doi.org/10.1159/000512007)
- Perico L, Benigni A, Casiraghi F, Ng LF, Renia L, Remuzzi G: Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. *Nat Rev Nephrol.* 2021, 17:46-64. [10.1038/s41581-020-00357-4](https://doi.org/10.1038/s41581-020-00357-4)
- Iba T, Levy JH, Levi M, Thachil J: Coagulopathy in COVID-19. *J Thromb Haemost.* 2020, 18:2103-9. [10.1111/jth.14975](https://doi.org/10.1111/jth.14975)
- Miesbach W, Makris M: COVID-19: coagulopathy, risk of thrombosis, and the rationale for anticoagulation. *Clin Appl Thromb Hemost.* 2020, 26:1076029620938149. [10.1177/1076029620938149](https://doi.org/10.1177/1076029620938149)
- Huang C, Wang Y, Li X, et al.: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020, 395:497-506. [10.1016/S0140-6736\(20\)30183-5](https://doi.org/10.1016/S0140-6736(20)30183-5)
- Zhou F, Yu T, Du R, et al.: Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020, 395:1054-62. [10.1016/S0140-6736\(20\)30566-3](https://doi.org/10.1016/S0140-6736(20)30566-3)
- Eastin C, Eastin T: Clinical characteristics of coronavirus disease 2019 in China: Guan W, Ni Z, Hu Y, et al. N

- Engl J Med. 2020 Feb 28 [Online ahead of print] DOI: 10.1056/NEJMoa2002032. J Emerg Med. 2020, 58:711-2. [10.1016/j.jemermed.2020.04.004](https://doi.org/10.1016/j.jemermed.2020.04.004)
10. Takahashi T, Ellingson MK, Wong P, et al.: Sex differences in immune responses that underlie COVID-19 disease outcomes. *Nature*. 2020, 588:315-20. [10.1038/s41586-020-2700-3](https://doi.org/10.1038/s41586-020-2700-3)
  11. Zhao J, Yang Y, Huang H, et al.: Relationship between the ABO blood group and the coronavirus disease 2019 (COVID-19) susceptibility. *Clin Infect Dis*. 2021, 73:328-31. [10.1093/cid/ciaa1150](https://doi.org/10.1093/cid/ciaa1150)
  12. Tang N, Li D, Wang X, Sun Z: Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020, 18:844-7. [10.1111/jth.14768](https://doi.org/10.1111/jth.14768)
  13. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ: COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020, 395:1033-4. [10.1016/S0140-6736\(20\)30628-0](https://doi.org/10.1016/S0140-6736(20)30628-0)
  14. Jose RJ, Manuel A: COVID-19 cytokine storm: the interplay between inflammation and coagulation. *Lancet Respir Med*. 2020, 8:e46-7. [10.1016/S2213-2600\(20\)30216-2](https://doi.org/10.1016/S2213-2600(20)30216-2)
  15. Wright DJ: Prevention of the cytokine storm in COVID-19. *Lancet Infect Dis*. 2021, 21:25-6. [10.1016/S1473-3099\(20\)30376-5](https://doi.org/10.1016/S1473-3099(20)30376-5)
  16. Iba T, Levy JH, Levi M, Connors JM, Thachil J: Coagulopathy of coronavirus disease 2019. *Crit Care Med*. 2020, 48:1358-64. [10.1097/CCM.0000000000004458](https://doi.org/10.1097/CCM.0000000000004458)
  17. Cummings MJ, Baldwin MR, Abrams D, et al.: Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet*. 2020, 395:1763-70. [10.1016/S0140-6736\(20\)31189-2](https://doi.org/10.1016/S0140-6736(20)31189-2)
  18. Wu C, Chen X, Cai Y, et al.: Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020, 180:934-43. [10.1001/jamainternmed.2020.0994](https://doi.org/10.1001/jamainternmed.2020.0994)
  19. Liao D, Zhou F, Luo L, et al.: Haematological characteristics and risk factors in the classification and prognosis evaluation of COVID-19: a retrospective cohort study. *Lancet Haematol*. 2020, 7:e671-8. [10.1016/S2352-3026\(20\)30217-9](https://doi.org/10.1016/S2352-3026(20)30217-9)
  20. Asakura H: [Classifying types of DIC: clinical features and animal models]. *Rinsho Ketsueki*. 2016, 57:397-404. [10.11406/rinketsu.57.397](https://doi.org/10.11406/rinketsu.57.397)
  21. Helms J, Tacquard C, Severac F, et al.: High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med*. 2020, 46:1089-98. [10.1007/s00134-020-06062-x](https://doi.org/10.1007/s00134-020-06062-x)
  22. Fox SE, Akmatbekov A, Harbert JL, Li G, Quincy Brown J, Vander Heide RS: Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. *Lancet Respir Med*. 2020, 8:681-6. [10.1016/S2213-2600\(20\)30243-5](https://doi.org/10.1016/S2213-2600(20)30243-5)
  23. Harzallah I, Deblieux A, Drénou B: Lupus anticoagulant is frequent in patients with Covid-19: Response to reply. *J Thromb Haemost*. 2020, 18:E3-4. [10.1111/jth.14980](https://doi.org/10.1111/jth.14980)
  24. Bikdeli B, Madhavan MV, Jimenez D, et al.: COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. *J Am Coll Cardiol*. 2020, 75:2950-73. [10.1016/j.jacc.2020.04.031](https://doi.org/10.1016/j.jacc.2020.04.031)
  25. Boccia M, Aronne L, Celia B, et al.: COVID-19 and coagulative axis: review of emerging aspects in a novel disease. *Monaldi Arch Chest Dis*. 2020, 90: [10.4081/monaldi.2020.1300](https://doi.org/10.4081/monaldi.2020.1300)
  26. Liu Y, Sun W, Guo Y, et al.: Association between platelet parameters and mortality in coronavirus disease 2019: Retrospective cohort study. *Platelets*. 2020, 31:490-6. [10.1080/09537104.2020.1754383](https://doi.org/10.1080/09537104.2020.1754383)
  27. Klok FA, Kruip MJ, van der Meer NJ, et al.: Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. 2020, 191:145-7. [10.1016/j.thromres.2020.04.013](https://doi.org/10.1016/j.thromres.2020.04.013)
  28. Marietta M, Ageno W, Artoni A, et al.: COVID-19 and haemostasis: a position paper from Italian Society on Thrombosis and Haemostasis (SISET). *Blood Transfus*. 2020, 18:167-9. [10.2450/2020.0083-20](https://doi.org/10.2450/2020.0083-20)
  29. Letko M, Marzi A, Munster V: Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. *Nat Microbiol*. 2020, 5:562-9. [10.1038/s41564-020-0688-y](https://doi.org/10.1038/s41564-020-0688-y)
  30. Vaduganathan M, Vardeny O, Michel T, McMurray JJ, Pfeffer MA, Solomon SD: Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. *N Engl J Med*. 2020, 382:1653-9. [10.1056/NEJMs2005760](https://doi.org/10.1056/NEJMs2005760)
  31. Wrapp D, Wang N, Corbett KS, et al.: Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science*. 2020, 367:1260-3. [10.1126/science.abb2507](https://doi.org/10.1126/science.abb2507)
  32. McGonagle D, O'Donnell JS, Sharif K, Emery P, Bridgewood C: Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *Lancet Rheumatol*. 2020, 2:e437-45. [10.1016/S2665-9913\(20\)30121-1](https://doi.org/10.1016/S2665-9913(20)30121-1)
  33. Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF: The proximal origin of SARS-CoV-2. *Nat Med*. 2020, 26:450-2. [10.1038/s41591-020-0820-9](https://doi.org/10.1038/s41591-020-0820-9)
  34. Zhou P, Yang XL, Wang XG, et al.: A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020, 579:270-3. [10.1038/s41586-020-2012-7](https://doi.org/10.1038/s41586-020-2012-7)
  35. Shi J, Wen Z, Zhong G, et al.: Susceptibility of ferrets, cats, dogs, and other domesticated animals to SARS-coronavirus 2. *Science*. 2020, 368:1016-20. [10.1126/science.abb7015](https://doi.org/10.1126/science.abb7015)
  36. Zhang YZ, Holmes EC: A genomic perspective on the origin and emergence of SARS-CoV-2. *Cell*. 2020, 181:223-7. [10.1016/j.cell.2020.03.035](https://doi.org/10.1016/j.cell.2020.03.035)
  37. Zhou H, Chen X, Hu T, et al.: A novel bat coronavirus closely related to SARS-CoV-2 contains natural insertions at the S1/S2 cleavage site of the spike protein. *Curr Biol*. 2020, 30:2196-2203.e3. [10.1016/j.cub.2020.05.023](https://doi.org/10.1016/j.cub.2020.05.023)
  38. Zhou Y, Hou Y, Shen J, Huang Y, Martin W, Cheng F: Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. *Cell Discov*. 2020, 6:14. [10.1038/s41421-020-0153-3](https://doi.org/10.1038/s41421-020-0153-3)
  39. Schnitzler HJ, Feldmann H: Viral hemorrhagic fever - a vascular disease? . *Thromb Haemost*. 2003, 89:967-72. [10.1055/s-0037-1613397](https://doi.org/10.1055/s-0037-1613397)
  40. Paessler S, Walker DH: Pathogenesis of the viral hemorrhagic fevers. *Annu Rev Pathol*. 2013, 8:411-40. [10.1146/annurev-pathol-020712-164041](https://doi.org/10.1146/annurev-pathol-020712-164041)
  41. Falasca L, Agrati C, Petrosillo N, Di Caro A, Capobianchi MR, Ippolito G, Piacentini M: Molecular

- mechanisms of Ebola virus pathogenesis: focus on cell death. *Cell Death Differ.* 2015, 22:1250-9. [10.1038/cdd.2015.67](https://doi.org/10.1038/cdd.2015.67)
42. Wong RS, Wu A, To KF, et al.: Haematological manifestations in patients with severe acute respiratory syndrome: retrospective analysis. *BMJ.* 2003, 326:1358-62. [10.1136/bmj.326.7403.1358](https://doi.org/10.1136/bmj.326.7403.1358)
  43. Lee N, Hui D, Wu A, et al.: A major outbreak of severe acute respiratory syndrome in Hong Kong. *N Engl J Med.* 2003, 348:1986-94. [10.1056/NEJMoa030685](https://doi.org/10.1056/NEJMoa030685)
  44. Chong PY, Chui P, Ling AE, et al.: Analysis of deaths during the severe acute respiratory syndrome (SARS) epidemic in Singapore: challenges in determining a SARS diagnosis. *Arch Pathol Lab Med.* 2004, 128:195-204. [10.5858/2004-128-195-AODDTS](https://doi.org/10.5858/2004-128-195-AODDTS)
  45. de Wit E, van Doremalen N, Falzarano D, Munster VJ: SARS and MERS: recent insights into emerging coronaviruses. *Nat Rev Microbiol.* 2016, 14:523-34. [10.1038/nrmicro.2016.81](https://doi.org/10.1038/nrmicro.2016.81)
  46. Hilgenfeld R, Peiris M: From SARS to MERS: 10 years of research on highly pathogenic human coronaviruses. *Antiviral Res.* 2013, 100:286-95. [10.1016/j.antiviral.2013.08.015](https://doi.org/10.1016/j.antiviral.2013.08.015)
  47. Tang YW, Schmitz JE, Persing DH, Stratton CW: Laboratory diagnosis of COVID-19: current issues and challenges. *J Clin Microbiol.* 2020, 58: [10.1128/JCM.00512-20](https://doi.org/10.1128/JCM.00512-20)
  48. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS: Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. *Intensive Care Med.* 2020, 46:586-90. [10.1007/s00134-020-05985-9](https://doi.org/10.1007/s00134-020-05985-9)