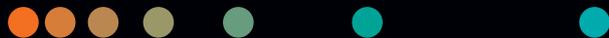


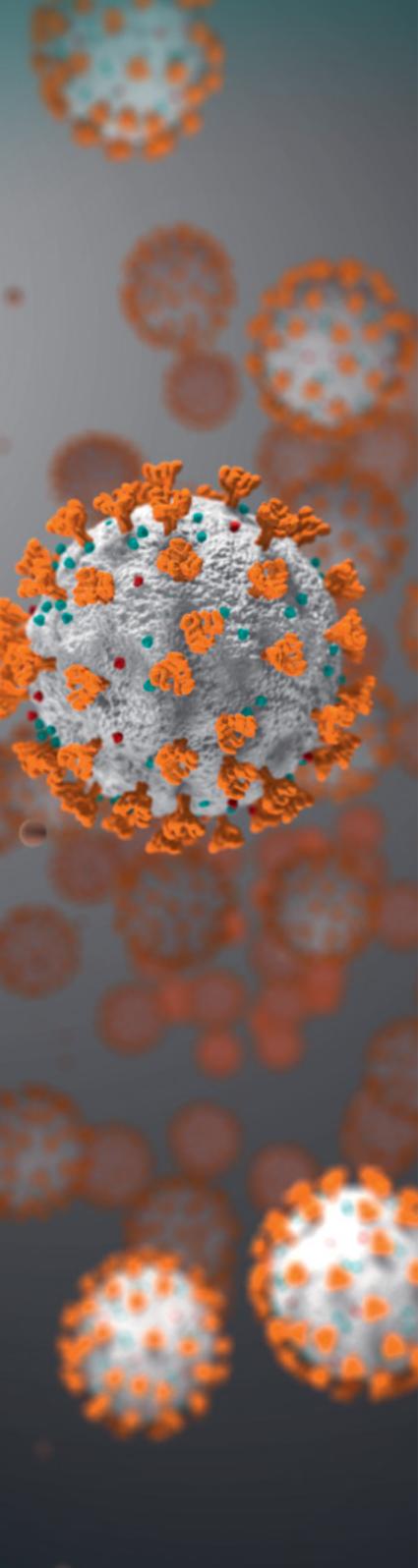


Revisited: Coagulation abnormalities in COVID-19 patients

2022 Edition:
Current testing and
treatment protocols in
acute infection and insights
on long-COVID research

siemens-healthineers.com/covid-19-hemostasis





Siemens Healthineers is supporting labs in the diagnosis, treatment, and management of coagulation abnormalities in COVID-19 patients

For more than 40 years, Siemens Healthineers has been recognized as the global leader in hemostasis testing. We offer the broadest range of scalable hemostasis systems for low-, mid-, and high-volume laboratories. Our comprehensive portfolio of coagulation assays supports physicians in making sound diagnostic and therapeutic decisions.

COVID-19 patients are experiencing serious—and sometimes fatal—thrombosis

While it's not unusual for infections to raise the risk of clotting, the COVID-19 virus is associated with an unprecedented range of clotting-related disorders in affected patients. From benign skin lesions on the feet to life-threatening thrombotic events, the COVID-19 virus has demonstrated a strikingly high prevalence of deadly blood clots. A meta-analysis of venous thromboembolism (VTE) in COVID-19 patients in the intensive care unit (ICU) revealed a prevalence of pulmonary embolism (PE) as high as 32%, and of deep vein thrombosis (DVT) of 27%, and showed that the occurrence of VTE doubled the odds of death.¹ The risk of VTE in COVID-19 patients is much higher compared to non-COVID-19 patients if patients are admitted to the ICU.²

We've increased production of vital coagulation assays for quick, accurate identification and treatment of clotting abnormalities

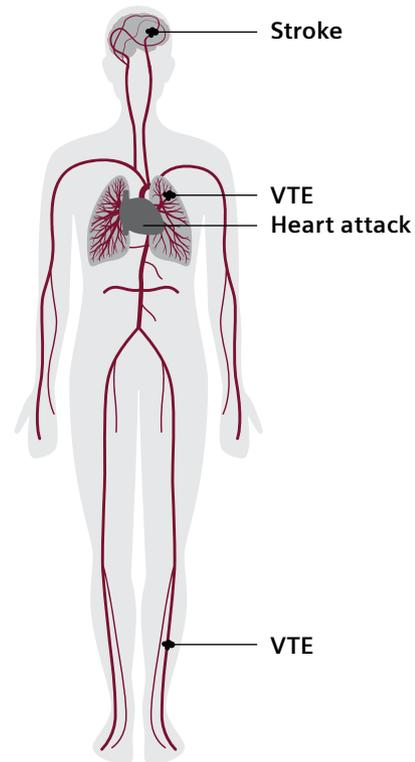
Our coagulation tests are playing an important role in the diagnosis, treatment, and management of coagulation in COVID-19 patients. We've been working diligently to produce these assays at a higher volume than ever before. We've changed our production model to ensure an increased output of reagents while implementing appropriate safety measures to help protect our workers from exposure to COVID-19. We will continue these efforts so that we remain positioned to provide high-quality assays to meet the increased testing demand.

The information in this document is accurate as of posting time. However, as the situation surrounding COVID-19 continues to evolve, it's possible that some data will have changed since publication. While Siemens Healthineers is trying to keep COVID-19 content as up to date as possible, we encourage readers to stay informed on news and recommendations by referencing guidelines published by the ISTH, AACC, CDC, and WHO and consulting with local healthcare authorities.

COVID-19 and thrombosis: an overview

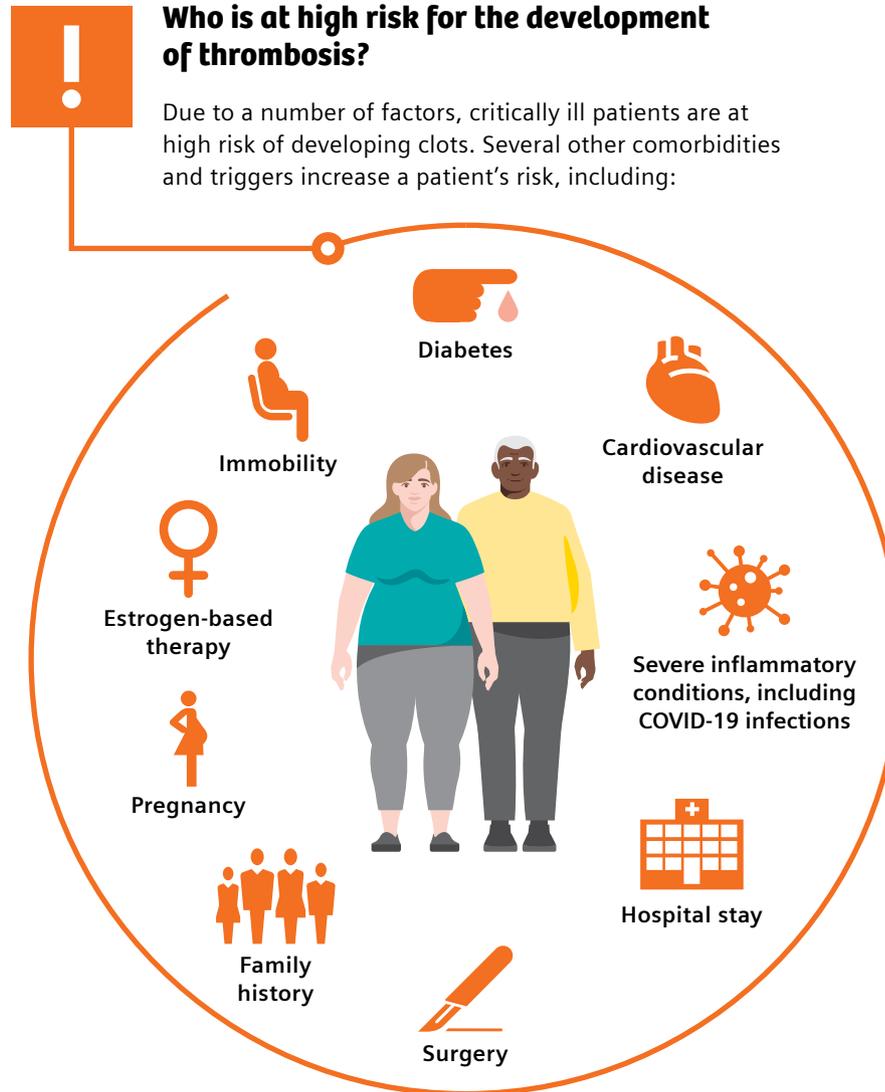
What is thrombosis?

Thrombosis is a blood clot that forms in an artery or vein. It is the one disorder that causes the world's top three cardiovascular killers: **heart attack, stroke, and venous thromboembolism (VTE)**, a blood clot found mostly in the leg and lungs.



Who is at high risk for the development of thrombosis?

Due to a number of factors, critically ill patients are at high risk of developing clots. Several other comorbidities and triggers increase a patient's risk, including:

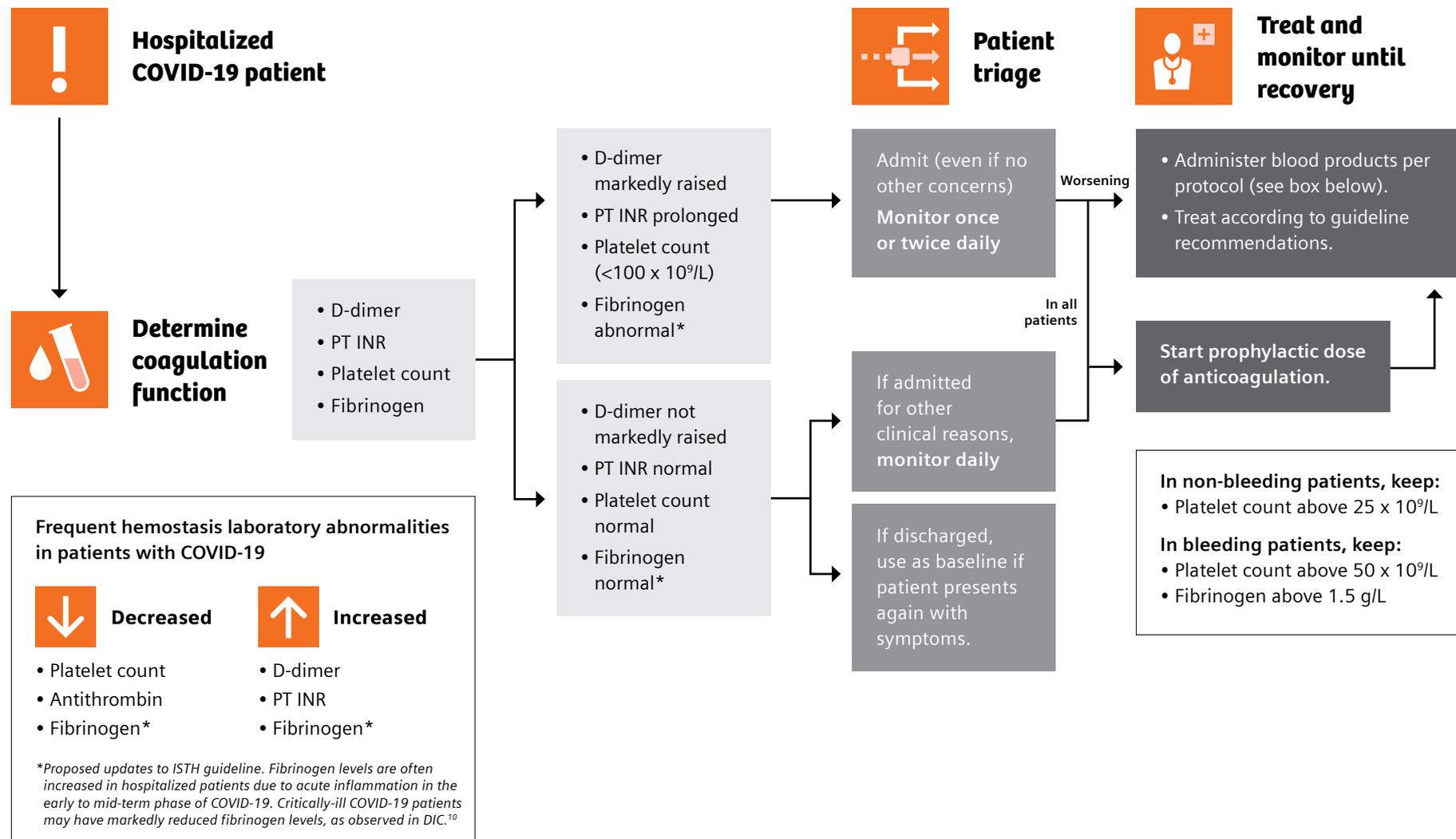


What is the relationship between COVID-19 and thrombosis?



While the connection between COVID-19 and thrombosis is still not fully understood, many studies and publications have reported thrombosis and thromboembolism as a leading cause of death in COVID-19 patients.¹⁻⁷ Elevated D-dimer levels were soon found to be a crucial laboratory marker indicating thrombotic risk in COVID-19 patients.^{6,8,9} High D-dimer levels (>4 times the upper limit) and the behavior of the D-dimer level following anticoagulation remain the most reliable coagulation parameters to predict thrombotic risk and mortality in hospitalized COVID-19 patients.¹⁰⁻¹² D-dimer is also a key parameter to detect vaccine-induced thrombotic thrombocytopenia (VITT), a very rare but fatal side effect of vaccination.¹³ In addition to D-dimer as a marker for thrombosis, high levels of von Willebrand factor (VWF) are also common in COVID-19 patients, indicating endothelial dysfunction^{14,15} and, in conjunction with low levels of VWF's physiological counterpart ADAMTS-13, creating a prothrombotic environment in blood vessels.¹⁶

Laboratory testing in the identification of coagulation abnormalities in COVID-19 patients



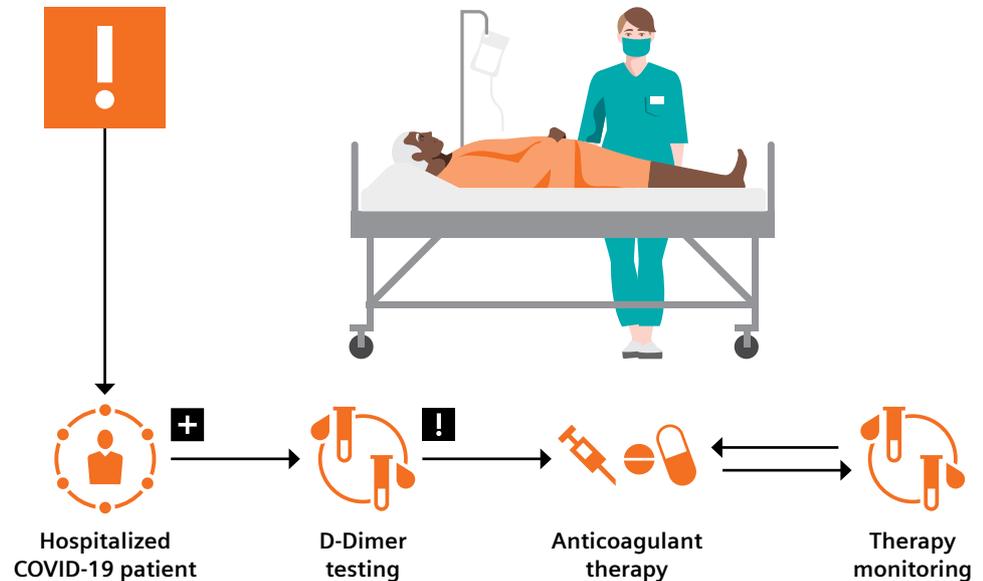
Thromboprophylaxis in COVID-19 patients

Anticoagulant treatment has become the standard of care for hospitalized COVID-19 patients

Prior to the availability of vaccination and the appearance of the Omicron variant of SARS-CoV-2, with its milder course of the disease and significantly lower hospitalization rate, approximately 5–10% of COVID-19 patients developed a severe condition requiring hospitalization. While vaccination significantly reduced infections, the likelihood of severe COVID-19, long-COVID, and mortality,^{17,18} hemostasis testing, therapy, and monitoring continue to play an important role in COVID-19 patient management.¹⁹⁻²¹ Depending on the patient's condition and disease severity, anticoagulation treatment with prophylactic doses has become the standard of care for hospitalized COVID-19 patients²² and is recommended for patients with COVID-19–related critical or acute illness who do not have confirmed or suspected VTE.^{20,23,25}

Thromboprophylaxis is currently not recommended for patients with COVID-19 who are discharged from the hospital and do not have suspected or confirmed VTE or another indication for anticoagulation.²⁵ However, newer studies indicate an advantage for therapeutic heparin dosing over prophylactic dosing in non-critically ill COVID-19 patients.^{21,26} Guiding anticoagulant therapy with an anti-Xa assay is very much recommended.^{20,27,28}

Although prophylactic anticoagulation is a well-established clinical practice in COVID-19 patients, a WHO recommendation is still pending.



Dedicated COVID-19 therapies

Although prophylactic anticoagulation treatment is a well-established clinical practice in COVID-19 patients, a WHO recommendation is still pending. However, the WHO has approved the following drugs for the treatment of COVID-19 (BMJ. 2020;370:m3379.):

- Corticosteroids (dexamethasone, hydrocortisone, methylprednisolone, prednisone), interleukin-6 (IL-6) receptor blockers (tocilizumab, sarilumab), and Janus kinase (JAK) inhibitors (baricitinib) for severely and critically ill COVID-19 patients
- Monoclonal antibody drugs (sotrovimab, casirivimab-imdevimab) for non-severely, severely, and critically ill COVID-19 patients

Role of coagulation in long-COVID, the heavy burden of the pandemic

Post-COVID symptoms: long-term effects after recovery from the infection

After recovery from a SARS-CoV-2 infection, many individuals will continue to suffer from what is known as long-COVID or post-COVID syndrome. The most common persistent symptoms 12 or more weeks following a COVID-19 infection are fatigue, cough, chest tightness, breathlessness, palpitations, myalgia, and difficulty focusing.²⁹

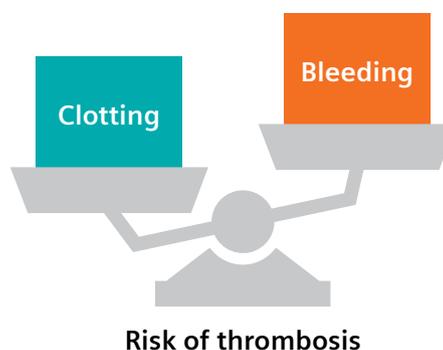
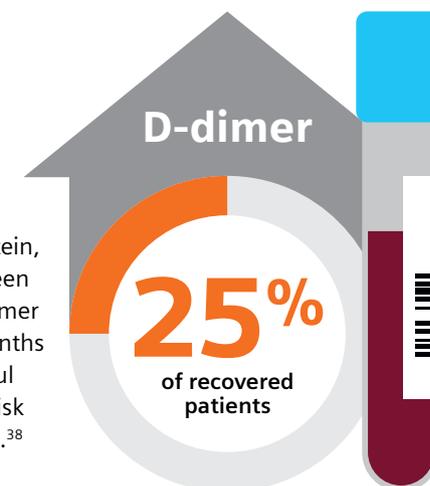


As many as 1 in 3 individuals experienced fatigue or, to a slightly lesser extent, cognitive decline 12 or more weeks following COVID-19 diagnosis.^{30,31} In a large study from Sweden including 1,057,174 people tested positive for SARS-CoV-2, the risks of deep vein thrombosis, pulmonary embolism, and bleeding were found to be significantly increased 70 days after the infection.³²

No treatment or therapeutic strategy has yet been recommended, but initial studies suggest personalized rehabilitation training or application of therapeutic drugs used for similar conditions, such as myalgic encephalomyelitis or chronic fatigue syndrome.³³ Future research will reveal new or confirm existing biomarkers for long-COVID/post-COVID syndrome and might soon yield effective therapies to treat the diverse symptoms of those who continue to suffer after SARS-CoV-2 infection.

Persistent coagulation parameter abnormalities in long-COVID patients

Elevated levels of D-dimer, inflammation markers (C-reactive protein, serum amyloid A, etc.), and decreased lymphocyte count have been reported in patients suffering from long-COVID.³³⁻³⁵ Elevated D-dimer levels are found in up to 25% of recovered COVID-19 patients months post-infection.^{36,37} Thus, measuring D-dimer levels might be useful in convalescent COVID-19 patients to identify those with a high risk of thrombosis who might benefit from sustained anticoagulation.³⁸



Another coagulation parameter frequently found to be elevated and modified post-COVID-19 is von Willebrand factor,^{39,40} indicating a prothrombotic milieu and endothelial dysfunction. Interestingly, elevated levels of α 2-antiplasmin, a strong inhibitor of fibrinolysis, the counterpart of thrombosis, were also reported in long-COVID patients.⁴¹ Circulating microclots rendered resistant to fibrinolysis by the influence of the SARS-CoV-2 spike protein have been suggested as a potential key driver and therapeutic target for the persistent hypercoagulability observed in COVID-19 and long-COVID.^{42,43}

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Our portfolio, spanning from in-vitro and in-vivo diagnostics to image-guided therapy and innovative cancer care, is crucial for clinical decision-making and treatment pathways. With our strengths in patient twinning, precision therapy, as well as digital, data, and artificial intelligence (AI), we are well positioned to take on the biggest challenges in healthcare. We will continue to build on these strengths to help fight the world's most threatening diseases, improving the quality of outcomes, and enabling access to care.

We are a team of 66,000 highly dedicated employees across more than 70 countries passionately pushing the boundaries of what's possible in healthcare to help improve people's lives around the world.

Siemens Healthineers Headquarters

Siemens Healthcare GmbH
Henkestr. 127
91052 Erlangen, Germany
Phone: +49 9131 84-0
siemens-healthineers.com

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Siemens Healthcare Diagnostics Inc.
Laboratory Diagnostics
511 Benedict Avenue
Tarrytown, NY 10591-5005
USA
Phone: +1 914-631-8000