Received: 15 December 2021 | Revised: 31 March 2022 | Accepted: 15 April 2022

DOI: 10.1002/rth2.12730

rpth research & practice in thrombosis & haemostasis

FORUM

D-dimer testing in clinical practice in the era of COVID-19

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Funding information
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Handling Editor: Dr Cihan Ay

Abstract

D-dimer is a fragment of crosslinked fibrin resulting from plasmin cleavage of fibrin clots and hence an indirect biomarker of the hemostatic system activation. Early in the coronavirus disease 2019 (COVID-19) pandemic, several studies described coagulation disorders in affected patients, including high D-dimer levels. Consequently, D-dimer has been widely used in not-yet-approved indications. Ruling out pulmonary embolism and deep vein thrombosis in patients with low or intermediate clinical suspicion is the main application of D-dimer. D-dimer is also used to estimate the risk of venous thromboembolism recurrence and is included in the ISTH algorithm for the diagnosis of disseminated intravascular coagulation. Finally, numerous studies identified high D-dimer levels as a biomarker of poor prognosis in hospitalized patients with COVID-19. This report focuses on validated applications of D-dimer testing in patients with and without COVID-19.

KEYWORDS
anticoagulant, biomarker, COVID-19, COVID-19 vaccines, D-dimer, disseminated intravascular coagulation, fibrin, fibrin fragment D, fibrinogen degradation products, predictive value of tests, prognosis, pulmonary embolism, venous thromboembolism

Essentials

- D-dimer is an indirect biomarker of the hemostatic system activation.
- D-dimer is a sensitive but not specific biomarker of venous thromboembolism.
- D-dimer has been widely used in new indications since the beginning of the coronavirus disease 2019 pandemic.
- D-dimer testing prescription should be strictly limited to approved applications.

The coagulation process results in an insoluble clot of crosslinked fibrin. Subsequently, the fibrinolytic system activates to limit the clot size. Finally, plasmin degrades crosslinked fibrin into different soluble fragments including D-dimer. D-dimer assays were initially based on ELISA technology. Nevertheless, this method tends to be replaced by more rapid and cost-effective techniques relying on immunofluorescence, latex-enhanced immunoturbidimetry or chemiluminescence.

During the coronavirus disease 2019 (COVID-19) pandemic, early studies described coagulation disorders in patients with COVID-19, including high D-dimer levels.[1,2] COVID-19 is associated with endotheliopathy,[3] which is probably at the origin of the coagulopathy[4] and the high incidence of venous thromboembolism (VTE)[5] that have been observed in this condition. Since the beginning of the pandemic, D-dimer testing has been widely used in not-yet-approved indications. The interpretation of the results is therefore often challenging. The objective of the present report is to sum up evidence-based applications of D-dimer and key points for the interpretation of the results in patients both with and without COVID-19 (Figure 1).

1 | PULMONARY EMBOLISM AND DEEP VEIN THROMBOSIS EXCLUSION

When the diagnosis of pulmonary embolism (PE) is suspected, clinical pretest probability must be evaluated through validated clinical tools such as the simplified revised Geneva score or the 2-level Wells score.[6] This first evaluation enables to identify patients with low or intermediate clinical probability of PE. In this population, PE prevalence is low, and negative D-dimer can safely exclude PE with a high negative predictive value. Consequently, computed tomography pulmonary angiography (CTPA) is not required in this situation, avoiding radiation exposure and risk of contrast medium–induced nephropathy.[6,7] Positivity threshold was first established at 500 μg/L for most available commercial assays. Nevertheless, several studies showed that D-dimer levels increase with age, therefore reducing its clinical usefulness in elderly patients. As a consequence, an age-adjusted D-dimer threshold has been prospectively validated and is widely used to exclude PE[8]: 500 μg/L in patients aged <50 years old or age ×10 μg/L in patients aged ≥50 years.

Many conditions and diseases may increase D-dimer levels, such as pregnancy or inflammatory diseases. D-dimer remains interpretable in these conditions: a negative D-dimer safely excludes PE.[9] A pregnancy-adapted algorithm including D-dimer testing was prospectively validated based on the YEARS algorithm.[10]

However, D-dimer cannot be used in patients with therapeutic anticoagulation to exclude PE or DVT, as D-dimer levels can be underestimated and lead to a false-negative result. Consequently, a negative result does not exclude PE nor DVT in these patients.

D-dimer is also used in clinical practice to exclude lower- and upper-limb DVT; nevertheless, age-adjusted positivity thresholds were not confirmed with prospective studies in this indication yet (ADJUST DVT; NCT 02384135).

2 | RISK PREDICTION MODEL IDENTIFYING PATIENTS AT LOW RISK OF VTE RECURRENCE AFTER A FIRST UNPROVOKED EVENT

Persistent D-dimer increase in patients treated with therapeutic anticoagulation for several months has been associated with a higher incidence of recurrent VTE events. Hence, D-dimer testing is integrated in three risk prediction models for VTE recurrence: the HERDOO2 rule, Vienna prediction model, and DASH score. Currently, the HERDOO2 rule is the only prediction model prospectively validated in a clinical management study. This study identified women at low risk of VTE recurrence after a first unprovoked event. Women with low HERDOO2 risk safely discontinued therapeutic anticoagulation (mostly vitamin K antagonists) after 6 months of treatment. Interestingly, the positive predictive value of D-dimer is used in this situation: positive D-dimer helps to identify patients who are not at low risk of recurrence. The positivity threshold was adjusted to 250 μg/L in patients treated with therapeutic anticoagulation using the Vidas D-dimer reagent on the Vidas instrument.[11] Rodger et al[12] showed that D-dimer assays other than the Vidas D-dimer should not be used in the HERDOO2 rule due to poor concordance and unacceptable misclassification of women at high and low risk of recurrent VTE.[12] Of note, decision making on anticoagulation discontinuation can be challenging and should preferably be made in a center of expertise.

3 | DISSEMINATED INTRAVASCULAR COAGULATION DIAGNOSIS

Disseminated intravascular coagulation (DIC) is characterized by systemic activation of coagulation, which can either lead to thrombosis (small- and midsize-vessel thrombosis, contributing to organ failure), or to bleeding (platelet and coagulation factor consumption). DIC is secondary to another condition, such as severe infections, cancer, trauma, or obstetric complications. The ISTH established a scoring algorithm for the diagnosis of DIC. This score relies on platelet count, level of fibrin markers (including D-dimer), prolonged prothrombin time, and fibrinogen level.[13] Nevertheless, D-dimer is not a specific biomarker (eg, also increased in sepsis) and must be interpreted along with clinical features and other laboratory assays. Fibrin monomer quantification could be a better option.[14]

4 | D-DIMER TESTING IN PATIENTS WITH COVID-19

Early in the pandemic, elevated D-dimer increase in patients with COVID-19 has been associated to poor prognosis in several studies. Hence, high D-dimer levels at admission were associated with worsening, intensive care unit (ICU) referral and higher in-hospital

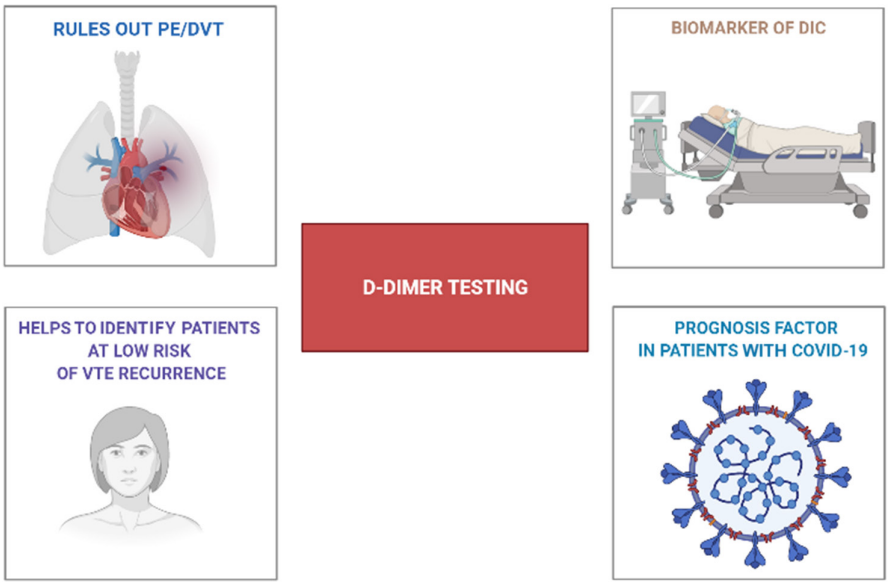

FIGURE 1 Summary of D-dimer testing applications. COVID-19, coronavirus disease 2019; DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism

mortality[1,2] and regardless of VTE occurrence.[15] Consequently, high D-dimer levels help to identify hospitalized patients at high risk of severe COVID-19. Moreover, several data have been published about dynamic changes of D-dimer levels in hospitalized patients with COVID-19 and their potential suitability for the same outcomes.[1,16,17] Early in the pandemic, the interim guidance by the ISTH[18] suggested relying on D-dimer solely at admission to decide whether hospitalized patients with COVID-19 were at risk of worsening and probably need more aggressive critical care support. As critically discussed by Akima et al,[19] D-dimer testing has to be interpreted along with a whole clinical assessment.

The incidence of VTE in hospitalized COVID-19 patients is high. A systematic review determined that 22.7% of patients with COVID-19 treated in the ICU suffer from VTE, while 8% of non-ICU hospitalized patients developed VTE.[5] In outpatients with COVID-19, VTE incidence is unknown.[4] Retrospective studies were led to potentially determine D-dimer thresholds assessing VTE risk but lack prospective validation. Current data seem insufficient to support the routine use of isolated high D-dimer levels to guide decisions regarding investigation for VTE. Hence, in patients with COVID-19 as in patients without COVID-19, D-dimer shows a low positive predictive value for VTE diagnosis.[15] Moreover, D-dimer level increase can be observed in the absence of VTE, as part of COVID-19–associated coagulopathy.[4] Pathophysiology of this coagulopathy involves coagulation activation (microthrombi formation in the microvasculature and/or in large vessels), endothelial activation and damage, upregulation of the innate and adaptive immunity, and activation of the complement system.[3]

Cutoff values for VTE exclusion need to be defined in patients with COVID-19.[20] Several studies advocate the use of higher D-dimer thresholds (between 2500 and 2900 μg/L), or adjusted to computed tomography extent of lung damage, despite a lower sensitivity.[21] Conversely, a recent study used the YEARS algorithm with no D-dimer threshold adjustment, and PE was confirmed in 13% of patients who underwent CTPA.[22] Currently, the ISTH committee recommends standard-of-care objective testing in case of clinical suspicion of VTE (CTPA, ventilation/perfusion scan, magnetic resonance imaging, venography, Doppler ultrasonography). Of note, the ISTH guidelines in COVID-19 does not recommend routine screening for VTE using bedside Doppler ultrasonography of the lower extremities or based on elevated D-dimer levels.[23]

National Institutes of Health guidelines recently included D-dimer as a criterion for selecting full-intensity anticoagulation in hospitalized (non-ICU) patients with COVID-19, although with a low level of evidence (CIIa).[24] This rating results from discrepancies among the three randomized controlled trials on which this recommendation is based (ACTIV4a/multiplatform trial, Rapid trial, HEP-COVID).[25] These trials differed in inclusion criteria including "high D-dimer" threshold, adherence to protocol-assigned anticoagulation, and outcomes. Moreover, <20% of screened patients were included only; consequently, this recommendation may not be generalizable to all hospitalized patients with COVID-19. Further studies may be needed to strengthen this recommendation and define a "high D-dimer levels" threshold. Of note, use of therapeutic anticoagulation in patients with COVID-19 is debated, depending on the severity of the disease.[26]

Furthermore, blood count or D-dimer testing follow-up after anti–COVID-19 vaccination is not recommended, except in case of clinical suspicion of vaccine-induced thrombotic thrombocytopenia. This is an extremely rare severe adverse effect of the ChAdOx1 nCoV-19 COVID-19 vaccine (Oxford/AstraZeneca), and the Janssen Ad26.COV2.S COVID-19 vaccine is associated with unusual thrombosis (mostly cerebral vein or splanchnic vein thrombosis).[27,28] A study focused on global hemostasis parameters following BNT162b2 Pfizer-BioNTech vaccination in healthy volunteers and showed no significant changes at the different time points evaluated before and after vaccination.[27]

To conclude, physicians must keep in mind that D-dimer assays have low specificity for VTE. For instance, high D-dimer levels can be observed in acute or chronic inflammatory syndrome, recent

surgery, trauma, pregnancy, liver diseases, or active malignancy regardless of VTE occurrence. Consequently, D-dimer testing prescription must be strictly limited to the validated indications listed above, and the interpretation will depend on this indication. New applications of D-dimer testing are being investigated. For example, Pabinger et al[28] had validated prospectively in two cohorts a clinical prediction model using D-dimer testing to identify ambulatory patients with solid cancer at high risk of VTE. Further prospective studies should evaluate the efficacy and safety of thromboprophylaxis in ambulatory patients with cancer who were initiating chemotherapy and classified as high to very high risk for VTE according to this clinical prediction model. This review is intended to present the current clinical practice for D-dimer testing, which may evolve in future years according to the results of future investigations.

AUTHOR CONTRIBUTIONS

All authors wrote and reviewed the manuscript.

ACKNOWLEDGMENTS

Figure 1 was created with BioRender.com.

RELATIONSHIP DISCLOSURE

All authors declare no conflicts of interest.

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How to cite this article: Auditeau C, Khider L, Planquette B, Sanchez O, Smadja DM, Gendron N. D-dimer testing in clinical practice in the era of COVID-19. *Res Pract Thromb Haemost*. 2022;6:e12730. doi:10.1002/rth2.12730