Review

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D-dimer: old dogmas, new (COVID-19) tricks

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Abstract: D-dimer is a fibrin degradation product encompassing multiple cross-linked D domains and/or E domains present in the original fibrinogen molecule, whose generation is only theoretically possible when hemostasis and fibrinolysis pathways are concomitantly activated. D-dimer measurement has now become a pillar in the diagnosis/exclusion and prognostication of venous thromboembolism (VTE) and disseminated intravascular coagulation (DIC), when incorporated into validated clinical algorithms and especially using age-adjusted diagnostic thresholds. Although emerging evidence is also supporting its use for predicting the duration of anticoagulant therapy in certain categories of patients, the spectrum of clinical applications is constantly expanding beyond traditional thrombotic pathologies to the diagnosis of acute aortic dissection, acute intestinal ischemia and cerebral venous thrombosis among others, embracing also clinical management of coronavirus disease 2019 (COVID-19). Recent findings attest that D-dimer elevations are commonplace in patients with severe acute respiratory syndrome (SARS-CoV-2) infection (especially in those with thrombosis), its value predicts the clinical severity (up to death) of COVID-19 and remains more frequently increased in COVID-19 patients with post-discharge clinical sequelae. Further, D-dimer-based anticoagulant escalation may be associated with a lower risk of death in patients with severe SARS-CoV-2 infection and, finally, D-dimer elevation post-COVID-19 vaccination mirrors an increased risk of developing vaccine-induced thrombocytopenia and thrombosis (VITT).

Keywords: COVID-19; D-dimer; SARS-CoV-2; thrombosis; venous thromboembolism.

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Hemostasis and D-dimer

The term hemostasis is conventionally referred to as a physiological process where a combined effort of anticoagulant and pro-coagulant forces within the blood vessels cooperate to maintain the fluidity of blood when vessel walls are uninjured or, conversely, promoting generation of blood clots when the architecture of the vasculature may be damaged by a variety of insults, thus preventing excessive blood loss [1]. Despite a comprehensive description of hemostasis being outside the scope of this article, an important reminder is that hemostasis is initiated by platelet activation, which is then followed by a shape change and their aggregation and/or adhesion at the site of vascular injury (i.e., primary hemostasis), and subsequently by activation of blood coagulation (i.e., secondary hemostasis), encompassing several sequential steps where coagulation factors are activated in sequence, with the ultimate aim of generating platelet clumps stabilized by a sufficient amount of fibrin (Figure 1) [1, 2]. Throughout the activation of blood coagulation, molecules of fibrinogen are continuously converted into fibrin monomers, which passively aggregate until, through an enzymatic process catalyzed by the transglutaminase activated factor XIII (FXIIIa), covalent links are created within adjacent fibrin monomers, to ultimately create a stable network of fibrin within which platelets and other blood cells are entrapped (i.e., the "stable" blood clot) (Figure 1) [1, 2]. More specifically, FXIIIa catalyzes the formation of isopeptide bonds between the γ-carboxyamine group of a glutamine and the ε-amino group of a lysine lying on two D fibrinogen domains belonging to two adjacent fibrin monomers (Figure 2) [3].

Although this model of hemostasis activation is finalized to efficiently "fill the holes" in the blood vessels, it is inherently obvious that – once the integrity of the vessel wall has been restored – the clot has ceased is utility and

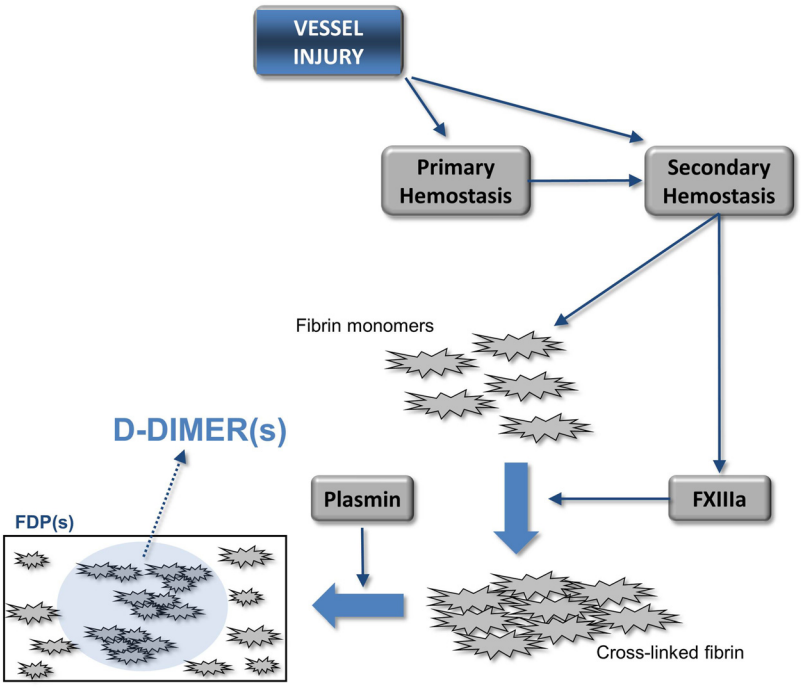

Figure 1: Hemostasis and fibrinolysis concur in D-dimer generation. FXIIIa, activated factor XIII; FDP, fibrin/fibrinogen degradation products.

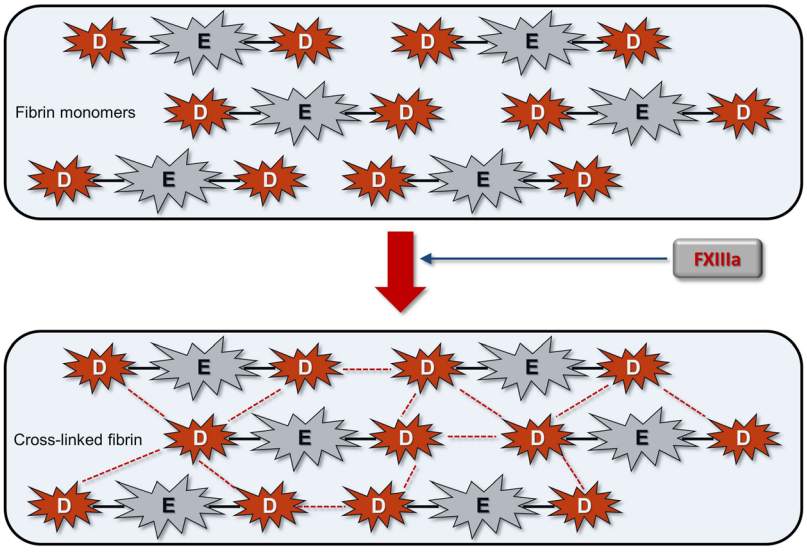

Figure 2: Cross-linking of fibrin monomers catalyzed by activated factor XIII (FXIIIa). FXIIIa, activated factor XIII.

needs to be removed [1]. The process of blood clots dissolution is conventionally known as fibrinolysis, and entails the degradation of stabilized fibrin by the enzyme plasmin, which can be activated from its precursor plasminogen by a number of endogenous (e.g., urokinase, tissue Plasminogen Activator; tPA) or exogenous (e.g., recombinant tPA) enzymes. Stabilized fibrin degradation results in the generation of a heterogeneous mixture of so-called "fibrin degradation products" (FDPs), differing mostly in size and composition (Figures 1 and 2) [1, 2]. Some enzymes may also breakdown fibrinogen to create fibrinogen degradation products. However, D-dimer generation only occurs through the breakdown of stabilized fibrin, thus making it a highly specific biomarker of fibrin degradation. The basic structure of "D-dimer" is a 180 kDa fragment containing only two D domains, but the architecture of the cross-linked FDPs can be highly convoluted, encompassing multiple cross-linked D domains and/or E domains of the original fibrinogen molecule (Figure 1). Irrespective of their final structure and size, all these molecules are classified under the name of D-dimer and, ideally, can be measured using

immunoassays containing monoclonal antibodies that can specifically bind to the isopeptide bonds between two linked D domain [1, 2].

Physiology of D-dimer

Although it is almost undeniable that D-dimer can only be generated by concomitant activation of hemostasis and fibrinolysis, as a result of a stable blood clot dissolution process (as summarized in Figure 1), a certain amount of cross-linked FDP is normally produced under physiological conditions, and such amount progressively increases with ageing [1, 2]. This explains why a level of D-dimer can be measured in all of us and thus, like many other diagnostic biomarkers, a numeric value is always used to define the upper limit of normal (ULN) of D-dimer concentrations, and is typically set at around 500 μg/L (or 0.5 mg/dL) FEU (fibrinogen equivalent unit; 1 μg/L FEU roughly equals 0.5 μg/L D-dimer units [DDU]), but conventionally increasing after the age of 50 years according to the age-adjusted formula: [age (in years)] × [10] (e.g., 600 μg/L FEU in a 60-year old patient). This is mainly due to the fact that a physiological conversion of nearly 2–3% of fibrinogen into fibrin also occurs in healthy subjects, a process that is known to gradually increase as people age [4]. Interestingly, additional strategies have been proposed, e.g., using different D-dimer cut-offs according to the clinical pretest probability. In a recent study, for example, Kearon and colleagues found that a diagnostic strategy based on low clinical probability and D-dimer value <1,000 μg/L combined with moderate clinical probability and D-dimer value of <500 μg/L was safe and effective to rule out pulmonary embolism (PE) [5].

Although no definitive evidence has been provided in health and disease, the conventional half-life of D-dimer is around 6–8 h, thus meaning that it may take several days (or even weeks) to return to "normal" levels when the reference range has been overcome by 1 or 2 orders of magnitude [4, 6]. Another aspect that may need to be clearly acknowledged, is that any increase of D-dimer does not necessarily mirror the presence of macroscopic blood clot(s), in that D-dimer concentration may be increased by a number of physiological conditions (e.g., pregnancy, physical activity) and pathological states (cancer, inflammation, infection, hypertension and so forth) not necessarily associated with the presence of an ongoing macroscopic thrombotic process [4, 7]. Last but not least, besides the concept that D-dimer elevation is not always a direct consequence of a thrombotic process, normal D-dimer values can also be found in patients with clinically significant thrombotic episodes, either because the blood clot is small (and, therefore, the amount of D-dimer generated by fibrinolysis remains below the diagnostic threshold), old (and thus no longer digestable by fibrinolytic enzymes) or due to the effect of ongoing antithrombotic treatments [4].

Old dogmas (Table 1)

Diagnosis of venous thromboembolism and prediction of recurrence

Owing to its remarkably high negative predictive value, close to 100% using high-sensitive techniques in patients with major symptomatic venous thromboembolism (VTE), D-dimer measurement has been endorsed by a multitude of national and international organizations within multiple cost-effective strategies for triage of patients with suspected VTE. The most remarkable examples of including D-dimer assessment within multidisciplinary diagnostic algorithms for diagnosis/exclusion of VTE are summarized in Table 2. Briefly, the Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis (SSC-ISTH) endorses routine D-dimer measurement in patients with suspected VTE and low or unlikely pretest probability, as well as in those with equivocal imaging findings [8]. The most recent guidelines of the European Society of Cardiology (ESC) also endorse the routine assessment of D-dimer in patients with low or intermediate clinical probability of VTE, preferably using a highly sensitive immunoassay [9]. Likewise to these indications, the American Society of Hematology (ASH) also endorses the measurement of D-dimer in patients at low (unlikely) VTE risk in its 2018 guidelines, since using D-dimer as initial test may be a cost-effective strategy to limit the number of other imaging diagnostic tests [10]. Some limitations in D-dimer measurement have been highlighted by the Clinical Guidelines Committee of the American College of Physicians (ACP), which endorsed its

Table 1: Consolidated clinical applications of D-dimer testing.

– Venous thromboembolism (VTE)
– Diagnosis (within validated algorithm, entailing pre-test probability assessment)
– Predicting duration of anticoagulant therapy, especially in patients with previous episodes of (unprovoked) thrombosis
– Disseminated intravascular coagulation (DIC)
– Diagnosis (within a validated scoring system)
– Monitoring of disease progression

Table 2: Current indications and recommendations for using D-dimer testing in diagnosis/exclusion of venous thromboembolism.

Society/ Organization	D-dimer assessment	Measurement strategy
ISTH (8)	Yes	In patients with low or unlikely pretest probability or equivocal imaging findings
ESC (9)	Yes	In patients with low or intermediate clinical probability
ASH (10)	Yes	In patients with low (unlikely) clinical probability
ACP (11)	Yes	In patients with intermediate or low pretest probability not meeting predefined PE rule-out criteria
ACCP (12)	Yes	In patients with low pretest clinical probability
NICE (13)	Yes	In patients with unlikely clinical probability
CISMEL/SIBioC/ AcEMC (14)	Yes	In all patients admitted to the emergency department, followed by estimation of clinical probability

ESC, European Society of Cardiology; ISTH, International Society of Thrombosis and Hemostasis; ASH, American Society of Hematology; ACP, American College of Physicians; ACCP, American College of Chest Physicians; NICE, National Institute for Health Care and Excellence; CISMEL, Italian Committee for Standardization of Hematology and Laboratory Methods; SIBioC, Italian Society of Clinical Biochemistry and Clinical Molecular Biology; AcEMC, Academy of Emergency Medicine and Care.

assessment as initial diagnostic test in patients with intermediate or low pretest probability, who will not meet predefined PE rule-out criteria [11]. These recommendations are hence in line with the historical indications formulated by the American College of Chest Physicians (ACCP), endorsing initial testing with D-dimer in patients with low pretest clinical probability [12]. D-dimer assessment is also endorsed by the UK National Institute for Health Care and Excellence (NICE) guidelines in patients with unlikely clinical probability of VTE [13].

At partial discrepancy with these indications, a joint document of three Italian societies of laboratory medicine and emergency care (Italian Committee for Standardization of Hematology and Laboratory Methods (CISMEL), Italian Society of Clinical Biochemistry and Clinical Molecular Biology (SIBioC) and Academy of Emergency Medicine and Care (AcEMC)) reiterates the recommendation of measuring D-dimer in patients with suspected VTE, but suggesting that it becomes a first-line test (i.e., in all patients), to be then combined with a clinical probability score for determining the cumulative risk of VTE upon emergency department admission [14]. Taken together, therefore, all major guidelines and recommendations definitely include D-dimer as a first-line tests in patients with suspected VTE, preferably in those with low or modest (or unlikely) clinical probability, thus making it an almost inestimable resource in this clinical setting.

As then concerns anticoagulation management of patients with VTE episodes, the 2nd update to the 9th edition of the CHEST Guideline and Expert Panel Report on antithrombotic therapy for VTE disease published at the end of the year 2021 suggests that D-dimer shall be measured one month after stopping anticoagulant treatment, and persistently positive values may then favor choosing to prolong anticoagulation in subjects with unprovoked thrombosis [15]. This conclusion is based on several studies, which revealed that the objective risk of developing recurrent VTE is strongly dependent upon D-dimer values [16, 17], especially using age-, gender- and method-specific diagnostic thresholds [18]. This last aspect is especially important since many clinical decision rules, such as the HERDOO2 (Hyperpigmentation, Edema or Redness; D-dimer; Obesity; Older) [19], the Vienna prediction model [20] or others [21], require accurate identification of assay-dependent cut-points to prevent patient misclassification.

Diagnosis and monitoring of disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) is an almost catastrophic pathology, characterized by diffuse and indiscriminate generation of blood clots within arteries, veins and capillaries, the most unfavorable consequence of which is multiple organ failure, frequently leading to death [22]. Regardless of the pathogenesis, which is multiple and sometimes even multifactorial, the hallmarks of DIC encompass continuous fibrin formation and degradation, which may almost inevitably lead to a remarkable increase in blood concentration of FDPs and D-dimer. Based on this framework, it is hence not surprising that D-dimer has become a cornerstone in the diagnostic approach to DIC [23]. Coincidentally, its measurement is now endorsed by all national and international guidelines for diagnosing DIC [24–26]. The incorporation of D-dimer into diagnostic algorithms for DIC is based on an assumption of excellent negative predictive value, since a “normal” concentration would generally lead to efficiently and safely rule out ongoing DIC. Notably, the clinical performance of the three mostly used scoring systems (ISTH/SSC score, especially used for diagnosing overt DIC; JMHLW (Japanese Ministry of Health, Labor and Welfare)

score, especially used for DIC prognostication; and Japanese Association of Acute Medicine (JAAM) score, mostly useful in patients with sepsis) seems almost overlapping, at least in terms of predicting unfavorable outcomes and/or death [27]. The performance of D-dimer at higher values is suboptimal. As a possible solution, the threshold values of plasma D-dimer could be adjusted based on assay methodology. For example, for DIC diagnosis according to the ISTH definition, the appropriate D-dimer cut-off value for 2 points ranged from 3,500 ng/mL to 6,500 ng/mL, depending on the reagents used [28].

Sequential D-dimer assessment is also recommended in patients with DIC, since it would allow identification of an evolving disease, with greater likelihood of developing severe/critical illness and leading to death. This is also in keeping with the current recommendations of the ISTH, where the use of a validated scoring system for diagnosing DIC is suggested, advocating also sequential laboratory tests repetition (thus including D-dimer) over time for purposes of monitoring progressive changes that may hence guide the clinical and therapeutic management [26].

New tricks (coronavirus disease 2019; COVID-19)

Venous thrombosis in COVID-19

It is now universally recognized that the risk of developing symptomatic thrombosis is magnified in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and grows in parallel with illness severity. A recent meta-analysis published by Liu et al., encompassing 18 retrospective, 6 prospective and 2 cross-sectional studies and totaling 4,382 coronavirus disease 2019 (COVID-19) hospitalized patients [29], concluded that the cumulative incidence of VTE was 28.3% (95% CI, 21.6–35.4%), being more than double (38.0%; 95% CI, 29.1–47.4%) in patients with severe illness compared to those with milder disease (17.2%; 95% CI, 11.4–23.8%). Unsurprisingly, COVID-19 patients with VTE had an over twofold higher risk of death compared to those who did not (odds ratio, 2.02; 95% CI, 1.15–3.53). These results were confirmed in several other studies, most of which were summarized in the meta-analysis of Xiao et al. (based on 25 studies, totaling 332,915 patients) [30], also concluding that VTE was associated with both COVID-19-related critical illness (odds ratio, 2.9; 95% CI, 1.6–5.24) and mortality (odds ratio, 2.61 (95% CI, 1.91–3.55), respectively. Even in younger individuals the risk of VTE may be magnified by SARS-CoV-2 infection. As shown in the recent meta-analysis of Vitaliti et al. [31], in children and adolescent with COVID-19 the risk of VTE is as high as 7.35%. Taking these figures as established, the identification and measurement of diagnostic and predictive biomarkers become vital in COVID-19, among which D-dimer would theoretically play a major role.

D-dimer elevations in acute COVID-19

Several lines of evidence now support the clinical usage of D-dimer, for a variety of purposes, in patients with SARS-CoV-2 infection, that will be briefly reviewed in the following paragraphs.

Early at the beginning of this pandemic, we published a brief meta-analysis which showed that D-dimer elevations are commonplace in patients with SARS-CoV-2 infection and, even more importantly, that the relative increase of this biomarker was larger in patients with unfavorable clinical outcomes [32]. Several other critical literature reviews and meta-analyses then confirmed our initial finding. For example, Varikasuvu et al. pooled the results of 68 unadjusted and 39 adjusted clinical studies (including 42,613 patients) [33], and also reported that admission D-dimer values were strongly associated with enhanced risk of disease progression (adjusted odds ratio, 1.64; 95% CI, 1.29–2.09), encompassing severe/critical illness (adjusted odds ratio, 2.00; 95% CI, 1.65–2.14) and death (adjusted odds ratio, 1.36; 95% CI, 1.20–1.54). Such remarkable increase of D-dimer values found in patients with SARS-CoV-2 infection, especially those with severe/critical illness is due to both extra-vascular (i.e., typically within the lung tissue) and vascular generation, in spite of the fact that several studied reported a suboptimal fibrinolytic response in patients with COVID-19, mostly sustained by enhanced levels of plasminogen activator inhibitor 1 (PAI-1), that leads to reduced plasmin generation and attenuated clot lysis [34].

The important role of D-dimer for predicting the risk of PE in COVID-19 has also been confirmed in many clinical studies. A French multicenter investigation, for example, reported that the area under the curve (i.e., 0.829) and the odds ratio (18.5; 95% CI, 6.4–61.5) of highly increased D-dimer levels (i.e., >3,000 μg/L) for predicting PE are both significantly better than those of other important COVID-19 biomarkers such as ferritin, prothrombin time and leukocyte count [35]. In a subsequent study, D-dimer was confirmed as having the highest predictive value for VTE among a multitude of demographical, clinical and laboratory parameters, displaying overall diagnostic accuracy as high as 80% [36]. Interestingly, in another study

published by Maatman and colleagues, not only an increased D-dimer value at admission (i.e., 728 μg/L) efficiently predicted the risk of VTE (area under the curve, 0.735), but its peak value during hospital stay (i.e., 2,600 μg/L) displayed even better accuracy (area under the curve, 0.760) for predicting VTE [37]. Interesting evidence on the kinetics of D-dimer values has then been provided in a large retrospective study carried out by Naymagon et al. [38], showing that COVID-19 hospitalized patients with progressively increasing D-dimer values had nearly 80% and 70% higher risk of needing mechanical ventilation or dying compared to those with a virtually stable D-dimer concentration.

Last but not least, and indeed worthwhile mentioning here, an elevated D-dimer value after receiving a COVID-19 adenoviral-based vaccine is one of the most important predictors of vaccine-induced thrombocytopenia and thrombosis (VITT), as comprehensively reviewed elsewhere [39].

D-dimer elevations in post-discharge COVID-19

Not only has D-dimer value been found to have important clinical significance in the acute phase of infection, but emerging evidence seems also to give a relevant, long-term prognostic role to this biomarker, since a considerable number of patients, especially those who suffered from more severe forms of COVID-19, may still have elevated values for long after remission and hospital discharge [40, 41]. Atalay et al. followed-up 222 patients with SARS-CoV-2 for up to 12 months, concluding that increased D-dimer values were associated with a nearly 60% higher risk of 1 year mortality (odds ratio, 1.62; 95% CI, 1.08–2.42) [42]. Important evidence has also been provided by a large prospective study which investigated the kinetics of D-dimer values more than 3 months after hospital discharge in patients who recovered from COVID-19 [43]. Briefly, persistently increased D-dimer values, which likely reflect a residual pro-thrombotic state, could be identified in as many as 15% of these patients, more frequently in those with severe respiratory disease and enhanced inflammation. Li et al. conducted a clinical study including nearly 3,000 adult patients hospitalized with COVID-19 [44], and found that patients with highly increased peak D-dimer level (i.e., >3,000 μg/L) had a nearly fourfold (odds ratio, 3.76; 95% CI, 1.86–7.57) higher risk of developing post-discharge VTE episodes.

To test the potential usefulness of defining the duration of anticoagulant therapy based on D-dimer values, Tassiopoulos et al. carried out a clinical trial with a propensity-matched analysis in COVID-19 patients with respiratory failure needing endotracheal intubation [45], revealing that a protocol encompassing enoxaparin escalation according to individual D-dimer values was associated with significantly lower mortality rate compared to those receiving standard thromboprophylaxis regimen (i.e., 31% vs. 57%). In another retrospective study, including 171 patients hospitalized for COVID-19, Arachchillage et al. reported that thromboprophylaxis adjustment according to an algorithm incorporating weight, renal function and D-dimer values was effective to significantly reduce the risk of thrombosis and ICU admission in patients with COVID-19 [46]. In keeping with these important findings, the updated guidelines from the anticoagulation forum endorse the measurement of D-dimer for deciding to adjust post-hospital thromboprophylaxis in COVID-19 patients who have been discharged [47].

D-dimer cut-off(s) in COVID-19

The most important drawback of D-dimer use for purposes of diagnosing/excluding VTE in patients with SARS-CoV-2 infection or establishing severity and prognosis of COVID-19, is more or less the same as in other pathological and even physiological conditions characterized by frequently increased D-dimer generation irrespective of the presence of macroscopic thrombosis (i.e., pregnancy, malignancy, systemic infections, etc.). The identification of diagnostic cut-offs is hence a challenging enterprise in patients with SARS-CoV-2 infection, in whom values above the conventional 500 μg/L upper range limit are commonplace. In keeping with this concept, García-Cervera et al. studied nearly 10,000 COVID-19 patients, 2.2% of whom diagnosed with VTE, and found that the sensitivity for diagnosing VTE and the in-hospital mortality were proportional to D-dimer elevations [48]. More specifically, the sensitivity for diagnosing VTE decreased in parallel with the augmentation of D-dimer cut-off, being around 60% for values twice the conventional diagnostic threshold (i.e., 1,000 instead of 500 μg/L), but decreased to <30% for D-dimer values as high as 4,700 μg/L. Likewise, the death rate was found to be comprised between 26 and 29% for patients with D-dimer values between 2000 and 3,000 μg/L, but increased to over 31% in those with levels >3,000 μg/L.

Another important and still unsolved issue is the lack of standardization of D-dimer measurement, which may hamper transferability of results of COVID-19 studies and adoption of universal decisional thresholds [49, 50]. As a

feasible solution to overcome such limitation, the findings of a large Spanish multicentre study using multiple D-dimer immunoassays are worth mentioning [51]. Briefly, the results of D-dimer testing in COVID-19 patients were harmonized using a model encompassing the transformation of assay-specific regressions to a reference regression line. This approach enabled to identify a universal cut-off of 945 μg/L FEU for predicting increased risk of in-hospital death, achieving fairly good diagnostic performance across the multiple participating centers (area under the curve, 0.66).

Table 3: Current evidence supporting D-dimer measurement in patients with coronavirus disease 2019 (COVID-19).

- D-dimer is frequently increased in patients with SARS-CoV-2 infection
- D-dimer elevation predicts the clinical severity (up to death) of COVID-19
- D-dimer values are more elevated in COVID-19 patients with VTE compared to those without
- D-dimer elevation remains more frequently increased in COVID-19 patients with post-discharge clinical sequelae
- D-dimer-based anticoagulant escalation may be associated with lower risk of death
- D-dimer elevation post-COVID-19 vaccination might reflect an increased risk of vaccine-induced thrombocytopenia and thrombosis (VITT)

Current indications in COVID-19

Despite that the incorporation of D-dimer within panels of laboratory tests for monitoring COVID-19 has been proposed by us more than 2 years ago [52], and is now supported by multiple evidence [53], the current contents of official recommendations and/or guidelines remains quite heterogeneous.

As concerns the ISTH, the routine screening of VTE using D-dimer is currently discouraged, wherein standard-of-care imaging testing (e.g., angiography, ultrasonography) is preferred in patients with high clinical suspicion [54]. This conclusion is somehow reasonable, supported by the evidence that D-dimer elevations are commonplace in patients with COVID-19, and their identification may foster a justified aggressive diagnostic or therapeutic, at least using the conventional diagnostic thresholds used in patients without SARS-CoV-2 infection. The use of higher D-dimer diagnostic cut-offs (e.g., multiple times the ULN) is also discouraged, because the thresholds may vary largely depending on demographical (age, sex, body mass index), clinical (illness severity, disease duration) and analytical (diagnostic technology, functional sensitivity) factors [28]. In line with these recommendations, the indications of the ASH in patients with unprovoked VTE discourage the use of D-dimer testing to guide the duration of anticoagulation (conditional recommendations, based on very low certainty in the evidence of effects) [55]. A position paper published by the Brazilian Society of Thrombosis and Hemostasis and the Brazilian Association of Hematology, Hemotherapy and Cellular Therapy advises against the use of D-dimer measurement alone for screening VTE in patients hospitalized with COVID-19 [56]. The current UK NICE guidelines advocate that prophylactic dosing of anticoagulants (e.g., heparin) is not based on D-dimer values [57]. Unlike these recommendations, the ESC has recently published (May 2022) clinical indications where it is suggested that serial D-dimer measurement may be helpful in COVID-19, since increased values of this biomarker may help identifying patients with higher risk of having VTE or those needing high-intensity prophylactic anticoagulation [58]. In another recent document, the International COVID-19 Thrombosis Biomarkers Colloquium has endorsed the routine measurement of D-dimer for assessing illness severity, risk of VTE and for predicting the prognosis of SARS-CoV-2 infection, though its assessment for managing anticoagulation has been currently discouraged [59].

Thus, the optimal scenario remains vague, at least on this matter. Despite further studies would be needed to define whether D-dimer measurement may be cost-effective for diagnosis, prognostication, follow-up and anticoagulation management of thrombosis in patients with SARS-CoV-2 infection, preliminary evidence (summarized in Table 3) suggests that these options may be clinically reasonable.

Conclusions

There are now no doubts that D-dimer assessment is a pillar for diagnosing and prognosticating VTE and DIC, though emerging evidence is also supporting its use for predicting the duration of anticoagulant therapy, especially in patients with unprovoked thrombosis and incorporated within validated, assay-specific clinical algorithms (Table 1). Nonetheless, the spectrum of its clinical applications is gradually expanding beyond traditional thrombotic pathologies for diagnosing acute aortic dissection, acute intestinal ischemia and cerebral venous thrombosis among others [60], to embrace also the clinical management of COVID-19. Recent findings attest that D-dimer value is frequently elevated in patients with SARS-CoV-2 infection (especially in those with VTE), predicts clinical severity (up to death) of COVID-19

and remains also more frequently increased in COVID-19 patients with post-discharge clinical sequelae. Then, D-dimer-based anticoagulant escalation may be associated with lower risk of death in patients with severe SARS-CoV-2 infection and, finally, D-dimer elevation post-COVID-19 vaccination reflects an increased risk of developing vaccine-induced thrombocytopenia and thrombosis (VITT) (Table 3).

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