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REVIEWS

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D-dimer as a biomarker for COVID-19-associated pulmonary thromboembolism: a narrative review from molecular pathways to the imaging findings

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Abstract

Background The coronavirus disease 2019, also known as COVID-19, imposed various challenges to healthcare and became a pandemic accompanied by a high rate of mortality. This infection has many manifestations and affects nearly all body systems. The circulatory and coagulation systems also seem to be affected. Studies show elevated rates of thrombotic events within COVID-19 patients such as disseminated intravascular coagulation (DIC), deep vein thrombosis (DVT), and pulmonary embolism (PE). Incidences of such coagulopathies were correlated to poor patient prognosis and mortality. Given the importance, complication, and mortality caused by thrombotic events (TEs) in COVID-19 patients, the goals of this study are to collect and analyze data on coagulopathy in COVID-19 patients and the pathophysiology and molecular events behind it. We also aim to bring attention to the role of D-dimer in COVID-19 infection by presenting the most recent information available from research studies evaluating D-dimer as a potential biomarker for disease severity, as well as mortality in COVID-19 patients.

Main body Various mechanisms are described for COVID-19 coagulopathies such as endothelial cell dysfunction, fibrinolysis inhibitor overexpression, immuno-thrombosis, and imbalance between pro- and anticoagulants, to name a few. D-dimer which is a degradation product of fibrin is a helpful diagnostic tool for the assessment of clots and thrombosis. Given the pro-thrombotic nature of COVID-19 infection, within the current narrative review, we studied the diagnostic value of D-dimer for PE prediction. Several studies utilized D-dimer as a predictive tool for detecting PE, and the results were varied. Different cutoff points are proposed ranging from 0.5 up to over 4 mg/L with varying sensitivity and specificity. Although CT pulmonary angiography (CTPA) is the standard model for the prediction of PE, radiation exposure, contrast nephropathy, higher cost, and lack of adequate access can shift our diagnosis into models based on D-dimer.

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Short conclusion In summary, various coagulopathies have been associated with COVID-19 infection, and a safe and early diagnosis is needed. D-dimer showed various successes in PE prediction and can be a good candidate for further research and diagnostic model and algorithm development.

Keywords COVID-19, D-dimer, CTPA, Coagulopathy, Thrombosis

Introduction

Acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which is a part of the coronavirus family and is known as the cause of the coronavirus disease 2019 (COVID-19) infection, characterized by a highly contagious respiratory infection rapidly spread across countries and in March 2020, was announced as a worldwide viral pandemic by the World Health Organization (WHO) [1–4]. COVID-19 patients presented with a host of symptoms including fatigue, dyspnea, anosmia, cough, arthralgia, fever, chest pain, sore throats, and gastrointestinal symptoms [5, 6]. Respiratory failure, acute respiratory distress syndrome (ARDS), super-infection, acute hepatic, renal and cardiac damage, shock, fatal multi-organ dysfunction, and hypoxic encephalopathy are among the complications of severe COVID-19 infection [7–9].

Given the hypoxemic, ischemic, and inflammatory nature of COVID-19, many different systems can be affected by the infection such as the nervous [10], endocrine [11], gastrointestinal [12], immune [13], renal [14], and cardiovascular systems [15]. Cardiovascular damages including myocarditis, cardiac arrhythmias, endothelial cell damage, myocardial interstitial fibrosis, and thrombotic events (TE) are observed and reported within some of the COVID-19 patients [16]. The coagulation and the hemostatic pathways—as a part of the cardiovascular system—are not immune to COVID-19 damage, with many reports of coagulopathy being described in COVID-19 patients [17]. Increased levels of D-dimer and factor VIII in COVID-19 patients are described in studies as a sign of abnormal thrombotic parameters and display hemostatic system dysfunction [17].

Thrombotic events have been reported to be common in COVID-19 patients, especially in critically ill patients admitted to the intensive care unit (ICU), despite receiving prophylactic anticoagulants. Acute pulmonary embolism (PE), ischemic stroke, and deep vein thrombosis (DVT) are among common coagulopathies in COVID-19 patients, affecting about one-third of the ICU patients, and are attributed to poor patient prognosis [18–24]. Systematic studies report a 74% increase in mortality in patients experiencing thrombotic event (TE) in the forms of DVT, PE, and arterial TE during the active COVID-19 infection [25].

Given the importance, complication, and mortality caused by TEs in COVID-19 patients, the goals of this study are to collect and analyze data on coagulopathy in COVID-19 patients and the pathophysiology and molecular events behind it. We also aim to bring attention to the role of D-dimer in COVID-19 infection by presenting the most recent information available from research studies evaluating D-dimer as a potential biomarker for disease severity, as well as mortality in COVID-19 patients.

Main text

COVID-19's pathogenesis

The initial wave of COVID-19 studies emphasized the cellular and molecular basis of phenotypes and virus-body interactions using omics technologies. The results did provide us with valuable information on pathways and mechanisms focused on certain cell types. Studies then aimed to highlight the innate immunological responses and mechanisms which govern protection and disease in COVID-19 [26, 27].

In the healthy alveoli of the lung, epithelial cells which are divided into type I and II pneumocytes are parts of the blood-alveolar barrier where gas exchange takes place, and a substance called surfactant is secreted to reduce local surface tension. Innate immune responses in the lungs are provided by alveolar macrophages (AM), and they are responsible for the maintenance of immune surveillance and responses through phagocytosis and antigen presentation [28].

Following the attachment of the viral spike to the cellular membrane receptor-angiotensin-converting enzyme 2 (ACE2), cleavage and membrane fusion takes place. Viral mRNA is expressed, and following maturation, viruses are released from the cells [29]. Subsequent to pathogen infection, monocytes, neutrophils, and natural killer (NK) cells are recruited to provide an early innate immune reaction in response to inflammatory cytokines released by infected local epithelial and immune cells. Innate immune cells then phagocyte infected cells, release further inflammatory cytokine, and activate adaptive immune response via antigen processing [30].

COVID-19 has been shown to be a state of neutrophilia [31]. Neutrophils are recruited to interstitial spaces upon chemokine gradient. Alongside their phagocytic abilities and removal of infected cells, they appear to exert a particular process called NETosis, in which they produce extracellular traps within the

inflammatory vessels of the lung and are believed to restrict further viral release. The NETosis process can also cause further endothelial damage and increased capillary permeability which can result in pulmonary edema [32, 33]. While AMs and inflammatory monocytes help viral clearance via Fc receptor cellular phagocytosis, M1 macrophages which are derived from monocyte during inflammation can also cause pulmonary damage by secreting increased levels of IL-6, nitric oxide synthase, tumor necrosis factor (TNF), and matrix metallopeptidases [21].

Infected epithelial cells were also shown to produce enhanced levels of IL-8 and Il-6 during active COVID-19 infection. Il-8 is a chemoattractant for both neutrophils and T cells. The activated cytotoxic T cells are important for fighting the infection, nonetheless can cause lung injury in the case of severe types of COVID-19 infection. In addition, T cells face exhaustion and have decreased functional diversity which is another contributing factor to the disease's poor prognosis and pathophysiology [29]. Another characteristic of COVID-19 infection, particularly in those infected with severe forms, is the increased plasma concentrations of pro-inflammatory cytokines. The most involved and studied cytokines in COVID-19 pathogenesis include IL-6, IL-8, IL-17, IL-1β, and TNF. Excessive cytokine release could result in a hyper-inflammatory state called cytokine release syndrome (CRS). CRS can result in lethal pneumonia, multiple organ failure, and ARDS and is usually derived from viral damage or hyper-filtration and hyper-function of granulocyte within infected tissue [29, 34].

The inflammatory cytokines, especially IL-6, mediate signals that increase capillary permeability and leakage, which are responsible for lung failure and hypotension in ARDS patients. Also, it has been shown that pulmonary fibrosis is a pathology caused by cytokines such as IL-6 and transforming growth factor (TGF-β) and also M2 macrophages during pulmonary infections [35, 36]. Upregulation of IL-6 and TNF-α within SARS-CoV-2 infection can also activate nuclear factor-κB (NF-κB) through pattern-recognition receptors (PRR). NF-κB is capable of inducing IL-6 amplifier which results in further pro-inflammatory cytokine and chemokine production, including IL-8, IL-6, vascular endothelial growth factor (VEGF), and monocyte chemoattractant protein 1 (MCP-1) [37]. STAT3 is also another transcription factor increased within COVID-19 via IL-6 and angiotensin II and can reduce lymphopoiesis, expression of E-cadherin, and antiviral responses which include interferon-mediated signaling, the activity of NK cells and helper T and cytotoxic CD8 cells. Thus, activation of STAT3 causes hyper-inflammation, viral persistence, vascular leak, and lung fibrosis [35].

In summary, COVID-19 pathophysiology is complex and mostly immune-based. Upon viral attachment and fusion via angiotensin receptors, the innate immune response is initiated via local and humoral granulocytes. Thereafter, various cytokines produced by infected and immune cells cause a hyper-inflammatory state, which then results in pulmonary edema, tissue injury, and finally lung fibrosis.

Thrombosis and D-dimer

Rudolph Virchow was the first to explain the relationship between three critical components that lead to the development of thrombosis in the nineteenth century. These include endothelial injury, stasis of blood flow, and hypercoagulability. However, the pathophysiology is beyond the imbalance between platelets, coagulation factors, endogenous anticoagulants, and the fibrinolytic system. Thrombosis can be divided into venous and arterial types. Arterial thrombi can cause myocardial infarction, and venous thrombi may lead to pulmonary embolism and venous thromboembolism. In arterial thrombosis, platelet-rich thrombi are developed around atherosclerotic plaques which are ruptured and injured epithelium under intense pressure whereas venous thrombi are formed in areas with intact endothelium walls and lower pressure and flow. These clots are rich in fibrin and withhold activated platelets and erythrocytes [38].

D-dimer is a product of soluble fibrin that results from the decomposition and degradation of vascular clots through fibrinolysis. This molecule which is made up of two fragments of fibrin exhibits distinctive properties as a biomarker of hemostatic abnormalities as well as an indicator of intravascular thrombosis namely VTE, PE, DVT, and DIC [39, 40]. The D-dimer level is increased whenever a thrombosis or a DIC takes place due to activation of the coagulation system and is an indicator of destroyed fibrin being present in the bloodstream [40, 41].

Active malignancy causes a variable enhancement in D-dimer, which implies a higher risk of thrombosis. Following anticoagulation for a thrombotic episode, an elevated D-dimer implies a higher risk of recurrent thrombosis. There is also a notable increase of D-dimer within infections and sepsis which has been correlated with poor clinical outcomes. An elevated D-dimer associates with an escalated risk for incidental and recurrent VTE and thrombotic-related mortality. Although D-dimer levels can be increased in non-thrombotic pathological conditions, it still remains a sensitive yet specific marker of vascular thrombosis [42]. D-dimer also correlates significantly with the recurrence of VTE among both carriers and non-carriers of thrombophilia [43]. Taken together, thrombosis can lead to various complications and is divided into platelet-rich arterial and

fibrin-rich venous thrombi. D-dimer which is a product resulting from fibrinolysis is elevated in TEs and can be a biomarker for a variety of disorders.

Molecular coagulopathy mechanism in COVID-19 patients

Viral infections have been demonstrated to induce prothrombotic states through modulating several coagulation proteins. SARS-CoV-1 and a bunch of other viral respiratory infections increase intravascular thrombi and fibrin accumulation in the lung [44]. Results of a retrospective study recognized VTE in 35 of 74 ICU patients (11 with PE) in spite of being on thrombosis prophylaxis [45].

In a retrospective cohort study of 119 H1N1 cases, nearly 6% of patients had vascular thrombotic events—either within arteries or veins—and the proposed mechanism can be explained through altered pro- and anticoagulant factor ratios, dysfunctional vascular endothelium, immobility stasis, and increased platelet activation [46]. D-dimer is produced within the blood as a result of the degradation and decomposition of stabilized fibrin polymer (fibrin cross-linked with factor XIII) by plasmin. That is, the thrombus or the clot is formed in the body through coagulation activation and is decomposed by fibrinolytic mechanisms. Even though many studies have indicated that elevated levels of D-dimer are attributed to the severity of the thrombosis, if a large amount of thrombi forms in the vessels but is not dissolved, the increase in D-dimer may be mild. Specifically, the increase in D-dimer that represented the suppressed fibrinolytic-type DIC, which is caused by sepsis, is relatively mild even in severe cases that result in death [47, 48].

DIC is another common complication of COVID-19 patients and increases mortality significantly [49]. In patients with viral infections like COVID-19 infection, sepsis-induced DIC is interrelated with organ failure. Microvascular thrombosis of extra-pulmonary organs has also been reported and may explain the acute onset of multi-organ failure [50]. Although DIC is usually characterized by intravascular coagulation and loss of localization, COVID-19–caused DICs seem to differ. Common findings of DIC are increased D-dimer, prolonged coagulation times namely PT, decreased platelet counts, and coagulation inhibitors concentration in the serum. Notwithstanding, COVID-19 patients go through a prothrombotic state without a consumption coagulopathy alongside increased venous thromboembolism [51]. The main characteristic of COVID-19 coagulopathy is a pronounced elevation of D-dimer without platelet reduction or prolongation of coagulation times, which suggests a process of generation of thrombin and a local rather than systemic fibrinolysis [52].

COVID-19-associated coagulopathy (CAC) has emerged as a hallmark of disease severity in ICU patients [53]. Excessive enhancement of D-dimer and mild increase in PT time is commonly seen in COVID-19 patients. Thrombocytopenia is another hemostatic dysfunction in COVID-19 patients, but unlike other severe infections is not significantly related to mortality. Although coagulation factors are normal in COVID-19 patients, fibrinogen plasma concentration can significantly increase owing to acute phase response. Several studies indicated abnormal clotting in COVID-19 patients and enhanced viscoelastic parameters [51].

COVID-19—as discussed previously—is a hyperinflammatory state with upregulation of several inflammatory cytokines including IL-1 and IL-6 and TNF [54]. Inflammation activates endothelial cells, platelets, monocytes, and tissue factors, altering fibrinolytic and endogenous anticoagulant pathways such as thrombomodulin, proteins C and S, and tissue factor pathway inhibitor (TFPI) [55]. Thrombin generation is usually a consequence of factor expression on macrophages and monocyte caused by IL-6 induction. The significant release of plasminogen activators caused by inflammation-driven endothelial cell disturbance can also explain COVID-19 coagulopathy [51]. Generally, an increase in D-dimer is believed to reflect the activation of both fibrinolysis and coagulation in vivo [47, 48]. Oppositely, one report has discussed the D-dimer origin of COVID-19. The paper suggests that D-dimer elevation reflects fibrin byproduct degradation accumulating within the lung parenchyma and the alveoli and thus causing lung damage [56].

Tissue hypoxia—often observed in severe COVID-19—increases thrombosis via inducing transcription factors, namely fibrinolysis inhibitors. For instance, thrombin-activatable fibrinolysis inhibitor (TAFI) and plasminogen activator inhibitor 1 (PAI-1) are among the stimulated transcription factors which can increase the risk of thrombi formation in COVID-19 patients [57].

Another mechanism of microvascular thrombosis in COVID-19 is endothelial activation which is caused by viral penetration of endothelial cells via ACE receptors [58]. microvascular thrombosis has been also reported following ARDS autopsies. Common findings include thickening of the vascular wall and lumen stenosis and also the formation of platelet-rich microthrombi, especially within the lungs which could be accompanied by hemorrhage or granulocyte accumulation [51].

Finally, immune thrombosis is also described in COVID-19 patients as coagulopathy caused by immune cells such as neutrophils [59]. As previously discussed, infections such as COVID-19 can induce neutrophils to produce NETs via inflammatory mediators, Toll-like receptors, or immunoglobulin production. NETs contain platelets, coagulation factors, and endothelial cells which

are needed for coagulation. Also, two key components of NETs, namely citrullinated histone H3 and genomic DNA, are believed to induce coagulation and thrombin production. Histone and enzymes released by NETs can induce endothelial apoptosis and dysfunction which can contribute to thrombi formation [60].

In summary, various coagulopathies have been demonstrated within COVID-19 patents. Increased TEs are often characterized by increased D-dimer, thrombocytopenia, and increased PT time. Various mechanisms are involved including endothelial dysfunction, pro- and anticoagulant imbalance, enhanced platelet activation, inflammation-caused thrombosis, and immune thrombosis (Fig. 1).

Pulmonary CT angiography for pulmonary thromboembolism

The standard criteria for COVID-19 confirmation are based on microbiological tests including reverse transcription polymerase chain reaction (RT-PCR) and sequencing. However, in urgent care, these tests may be unavailable [61]. Since one of the main clinical presentations and manifestations of COVID-19 is coagulopathy and PE, laboratory confirmation and imaging are needed for confirmation, immediate care, and anti-coagulant treatment initiation [62, 63].

There are several imaging techniques available to assess acute PE. Chest radiography, CTPA, CT venography (CTV), magnetic resonance pulmonary angiography (MRPA), nuclear medicine ventilation/perfusion scan, venous ultrasonography, echocardiography, and catheter pulmonary angiography are among the utilized imaging modalities [64–66].

The precise role of CT imaging within COVID-19 management is still debated; nonetheless, current guidelines recommend using non-contrast chest CT for diagnosis, assessment of severity, and monitorization of COVID-19 [67]. Chest CT scan plays an essential role in optimizing the management of COVID-19 patients, excluding alternative diagnoses and additional pathologies, especially by acute PE [68].

The preferred imaging modality for PE evaluation in suspected patients is CTPA, which is also a key component widely used in clinical diagnostic algorithms. The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) II trial indicated a high accuracy of CTPA, with a sensitivity of 83% and a specificity of 96%. When clinical data were included, the positive predictive value even increased to 96% [64]. In CTPA, acute PE is shown as low-density defects within vessel perfusion, which can be surrounded by opacified blood flow or a totally filling defect with unspecified blood flow. Other findings can include vascular remodeling, oligemia, plate-like atelectasis, pleural effusion, and parenchymal infarction [69]. The result of a retrospective observational study in Madrid indicated that pulmonary angiography with multi-detector computed tomography (MDCT), as well as iodine mapping, can demonstrate PTE and hypo-perfusion in COVID-19 patients. Several visual properties were described in the study to help PTE

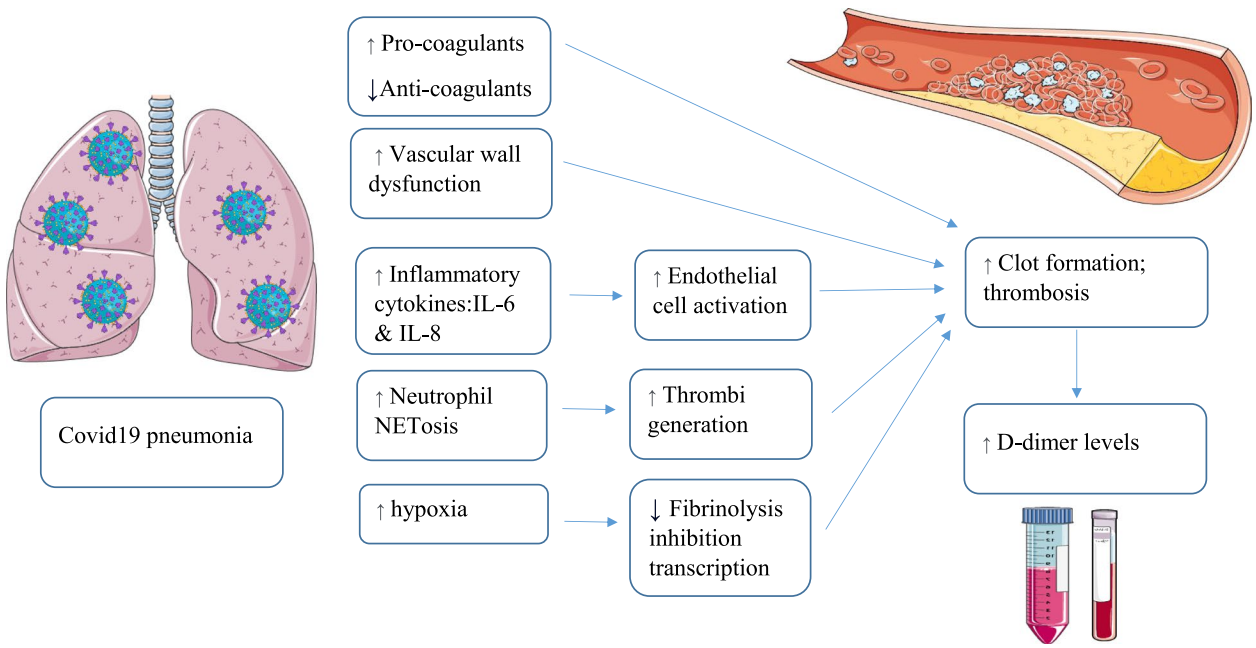

Fig. 1 A summary of the relationship between COVID-19 infection and clot formation

diagnoses such as crazy paving patterns, consolidation, septal thickening, or bronchiectasis [21]. A study by Silva et al. showed that different algorithms for PE detection can increase diagnosis specificity which then results in CTPA use reduction. When they employed the YEARS and PEFeD algorithms which are based on D-dimer levels and clinical variables, a 19% reduction in CPTA utilization was seen [70]. A meta-analysis showed a pooled sensitivity of 97% and specificity of 41% of D-dimer levels for PE diagnosis, whereas CTPA had a sensitivity of 94% and specificity of 98%. It is worth mentioning that such a comparison is made in non-COVID-19 patients, and the results in COVID-19 patients may vary [71]. The study of Ramadan et al. reported that 37% of CTPA were inconclusive for PTE rule out, and there might have been some missed clots. Even without the presence of thromboembolism visualized by CTPA, a large amount of microthrombi still could be present within the patient pulmonary vasculature [72].

Patients with considerably elevated D-dimer levels upon admission (2000–4000 g/mL) or notable D-dimer increases throughout the hospital stay are indicated for a CTPA. Dual-energy CT could help evaluate lung perfusion within COVID-19 patients both in the acute setting and to monitor lung sequelae in subsequent scans [73].

Due to immoderate radiation exposure, viable contrast reactions, and high overall costs, it would be better to prevent CTPA as possible [74]. Considering the mounted studies mentioned in the previous parts, plasma D-dimer levels may be used as an alternative for PE prediction or patient risk assessment prior to or for CTPA.

D-dimer as a biological marker for mortality and disease severity within COVID-19 patients

D-dimer, a degradation product of fibrin, is a small protein particle that is present in the blood after the thrombus is broken down by fibrinolysis. Measurement of circulating D-dimer levels is a sensitive tool in clinical settings for the diagnosis of PE and DIC [75]. In addition, underlying disorders such as cancer, stroke, diabetes, and pregnancy can cause elevated D-dimer levels in patients with COVID-19 [40]. Therefore, elevated D-dimer levels in COVID-19 patients rapidly identify patients with high disease severity, pulmonary complications, and risk of thromboembolism within veins as part of a pro-thrombotic condition. An original study in Spain reported that a higher threshold (2903 ng/mL) for D-dimer may predict the risk of PE in COVID-19 patients with a sensitivity of 81% [76]. Another retrospective study in Spain analyzed the value of D-dimer to assess CTPA for diagnosis of PE in COVID-19 patients. They concluded that D-dimer levels higher than 2.00 mg/L could be a sensitive cutoff point for ruling out PE within hospitalized COVID-19 patients. D-dimer increase of 4.00 mg/L since patient admission is useful for the detection of PE [77]. A meta-analysis study in 2021 evaluated the diagnostic value and accuracy of D-dimer within COVID-19. The results showed a pooled sensitivity of 77% of D-dimer for disease severity (95% CI: 73–80%), 75% for mortality (95% CI: 65–82%), and 90% for DVT prediction (95% CI: 90–90%). The specificity was found to be 71% (95% CI: 64–77%), 83% (95% CI: 77–87%), and 60% (95% CI: 60–60%), respectively [78].

Another Spanish study screened patients with D-dimer above 1 mg/L for asymptomatic DVT using Doppler ultrasound. Their results showed higher D-dimer levels within DVT patients (4.527 vs 2050 mg/L). They concluded a cutoff point of approximately 1.5 mg/L had a sensitivity and specificity of 95.7% and 29.3%, respectively. Positive predictive value (PPV) and negative predictive value (NPV) were reported to be 19% and 97.5%, respectively [79]. A study conducted by Cui et al. showed that when a D-dimer cutoff point of 1.5 mg/L is employed, VTE prediction is obtained with 85% sensitivity, 88.5% specificity, and 94.7 NPV [80].

Another retrospective study performed on 697 COVID-19 patients aimed to asses PTE, D-dimer, and CTPA. About a third of admitted patients experienced PTE and had significantly and notably higher D-dimer levels. Their results indicated a D-dimer cutoff of 0.5 mg/L has a specificity of 5.7% and sensitivity of 98.2% for the presence of PTE [81]. Artifoni et al. investigated the diagnostic value of D-dimer for VTE and PE within 79 COVID-19 patients. Lower limb duplex ultrasound and CTPA were used for confirmation of VTE and PE, respectively. They showed a significant increase in D-dimer within DVT patients. D-dimer cutoff point at 1 mg/L had an NPV of 90% and 98% for VTE and PE, respectively. The PPV for VTE was 44% which increased up to 67% if the cutoff is considered at 3 mg/L [82]. Leonard-Loranat et al. also investigated a study with the same purpose. The confirmation was done by a CT angiography. Their findings support that a D-dimer level above 2.6 mg/L is highly suggestive of PE with a sensitivity of 100% and specificity of 67% [83]. The cutoff point of 2.6 mg/L in another study had a sensitivity of 89.7% and a specificity of 59.5% [84]. Lastly, a study performed by Ventuora-Diaz et al. revealed that a cutoff of 2.903 was optimal for PE detection with sensitivity and specificity of 81% and 59%, respectively [76].

A few other studies on D-dimer and PE prediction are worth mentioning. Tuck et al.'s study showed a sensitivity of 81% and a specificity of 70% when a 1.5 mg/L cutoff is employed. When the cutoff was increased to 2 mg/L, sensitivity was reduced by 1% but specificity increased by 6%, which made authors recommend higher D-dimer thresholds for PE exclusion [85]. Another study on 3583

COVID-19 patients and a cohort of 13,091 patients using 2 mg/L cutoff revealed a sensitivity of 70.3% and 70.5%, specificity of 82.4% and 67.8%, and NPV of 98.5% and 99.5%, respectively. However, when the cutoff was reduced to 0.5 mg/L, sensitivity increased to 99.3% and 92% and NPV increased to 99.9% and 99.5%, but specificity dropped to 34.3% and 17%, respectively [86]. Ten percent of CTPAs could have been avoided as a result of two studies with D-dimer lower than 0.5 mg/L, with 98.3% and 98.2% sensitivity, 10.8% and 5.7% specificity, 98.7% and 87.1% NPV, and 8.4% and 33.3% PPV [81, 87]. Other studies showed a 100% and 72% sensitivity and 90.62% and 74% specificity with 2.494 and 2.247 mg/L cutoff, respectively [22, 88]. 2.5 mg/L cutoff had an 80% sensitivity and 51% specificity for PE in a Spanish retrospective study [89]. A complete list of mentioned studies along with a few others is presented in Table 1.

Apart from TE prediction, D-dimer was also shown to be a tool for survival and severity prediction in COVID-19. ICU patients are likely to have higher D-dimer levels than non-critically ill patients (mean plasma levels of 2.4 compared to 0.5 mg/L). D-dimer levels greater than 1 mg/L were observed in 81% of non-survivors, which was found to be 24% in survivors. In another study, it was stated that D-dimer levels greater than 3 mg/L were observed within non-survivor COVID-19 patients [95]. Gudot et al. proposed the use of D-dimer as an ICU referral guide. Their conclusion highlights using a 1 mg/L

Table 1 A summary of the sensitivity, specificity, PPV, NPV, and D-dimer cutoffs considering the CTPA as the standard

Authors	Number of the studied population	Sensitivity	Specificity	Positive predictive value	Negative predictive value	D-dimer cutoff (mg/L)
Cui et al. [80]	81	85%	88.5%	70.8%	94.7%	1.5
Delemo-Rodriguez et al. [79]	156	95.7%	29.3%	19%	97.5%	1.570
Leonard-Lorant et al. [83]	160	100%	67%	N/A	N/A	2.660
Maatman et al. [84]	109	89.7%	59.5%	N/A	N/A	2.600
Ventrua-diaz et al. [76]	242	81%	59%	N/A	N/A	2.903
		90%	51.4%	N/A	N/A	1.733
Tuck et al. [85]	544	81%	71%	N/A	N/A	1.500
		80%	76%	N/A	N/A	2.00
Bledsoe et al. [86]	3583	70.3%	82.4%	N/A	98.5%	2.00
		99.3%	34.3%	N/A	99.9%	0.5
	13,091	70.5%	67.8%	N/A	99.5%	2.00
		92%	17.0%	N/A	99.5%	0.5
Revel et al. [87]	781	98.3%	10.8%	8.4%	98.7%	0.5
		90.0%	41.6%	11.4%	98.0%	1.00
		80%	73.8%	20.3%	97.8%	2.00
		66.7%	83.6%	23.3%	97.1%	3.00
Nadeem et al. [88]	193	100%	90.62%	68.75%	100%	2.494
Ooi et al. [22]	974	72%	74%	N/A	N/A	2.247
Alonso-Fernandez et al. [89]	30	100%	0%	50%	0%	1.00
		93%	13%	52%	67%	1.50
		87%	40%	59%	75%	2.00
		80%	53%	63%	73%	2.50
Vivan et al. [81]	697	98.2%	5.7%	33.3%	87.1%	0.5
Ramadan et al. [72]	139	78%	67%	N/A	N/A	2.00
Planquette et al. [90]	59	100%	9.0%	6.2%	100%	0.5
		76.1%	65.0%	11.6%	97.8%	1.50
		50%	84%	15.9%	96.5%	2.50
		43.5%	90%	20.3%	96.4%	3.50
Loffi et al. [91]	333	70%	62%	N/A	N/A	2.37
Mouhat et al. [92]	349	83.3%	83.8%	72.9%	90.5%	2.590
Taccone et al. [93]	40	75%	92%	N/A	N/A	3.647
Whyte et al. [94]	1477	75%	78%	72.2%	80.9%	4.8

cutoff with sensitivity and specificity of 72.4% and 60.0%, respectively. PPV and NPV were reported to be 58.6% and 74.2%, respectively [96] (Table 1).

Thus, utilizing D-dimer evaluation can help with risk stratification and the earlier start of treatments that may help reduce COVID-19-related morbidity and mortality [75]. However, the D-dimer level (as a static value or as a trend over time), when viewed alone, limits the performance characteristics of COVID-19 as a prognostic test [97].

Conclusions

The COVID-19 pandemic imposed various challenges for treatment and complication controls. Studies revealed a hyper-inflammatory nature of the diseases which can along with other pathophysiological mechanisms such as endothelial dysfunction and hyper-coagulation cause increased risk of TE within patients. D-dimer—a thrombin protein fragment—is a useful test for coagulation and thrombosis screening. Various studies evaluated the use of D-dimer for COVID-19 TE evaluation, especially PE. Even though the results are varied, mostly suggest a significant increase of D-dimer in patients with VTE and adequate sensitivity with controversial specificity. Given the challenges of CTPA such as cost and contrast iatrogenic complications, D-dimer can be easily and frequently used for VTE risk assessment in COVID-19 patients.

Abbreviations

COVID-19	Coronavirus disease 2019
DIC	Disseminated intravascular coagulation
DVT	Deep vein thrombosis
PE	Pulmonary embolism
CTPA	CT pulmonary angiography
SARS-CoV-2	Acute respiratory syndrome coronavirus 2
WHO	World Health Organization
ARDS	Acute respiratory distress syndrome
ICU	Intensive care unit
TE	Thrombotic event
AM	Alveolar macrophages
ACE2	Angiotensin-converting enzyme 2
NK	Natural killer
IL	Interleukin
TNF	Tumor necrosis factor
CRS	Cytokine release syndrome
TGF	Transforming growth factor
NF-κB	Nuclear factor-κB
PRR	Pattern-recognition receptors
VEGF	Vascular endothelial growth factor
MCP-1	Monocyte chemoattractant protein-1
CAC	COVID-19-associated coagulopathy
TFPI	Tissue factor pathway inhibitor
TAFI	Thrombin-activatable fibrinolysis inhibitor
PAI-1	Plasminogen activator inhibitor-1
RT-PCR	Reverse transcription polymerase chain reaction
CT	Computed tomography
CTV	CT venography
MRPA	Magnetic resonance pulmonary angiography
PIOPED	Prospective investigation of pulmonary embolism diagnosis
MDCT	Multi-detector computed tomography
PPV	Positive predictive value
NPV	Negative predictive value

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Authors' contributions

M.P and A.M conducted the main idea of the study and supervision. S.B, F.F, A.S, E.H.N, M.H, F.F, A.S, and A.M drafted the manuscript. All authors reviewed and accepted the manuscript.

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