

# Assessment and Monitoring of Coagulation in Patients with COVID-19: A Review of Current Literature

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## Abstract

Coagulation abnormalities are common in patients with COVID-19 and associated with high morbidity and mortality. It became a daily challenge to navigate through these abnormal laboratory findings and deliver the best possible treatment to the patients. The unique character of COVID-19-induced coagulopathy necessitates not only a dynamic follow-up of the patients in terms of hemostatic findings but also the introduction of new diagnostic methods to determine the overall function of the coagulation system in real time. After the recognition of the high risk of thromboembolism in COVID-19, several professional societies published their recommendations regarding anticoagulation in patients with COVID-19. This review summarizes common hemostatic findings in COVID-19 patients and presents the societal recommendations regarding the use of coagulation laboratory findings in clinical decision-making. Although several studies have investigated coagulation parameters in patients with COVID-19, the methodological shortcomings of published studies as well as the differences in employed anticoagulation regimens that have changed over time, depending on national and international guidelines, limit the applicability of these findings in other clinical settings. Accordingly, evidence-based recommendations for diagnostics during acute COVID-19 infection are still lacking. Future studies should verify the role of coagulation parameters as well as viscoelastic methods in the management of patients with COVID-19.

## Keywords

- ▶ coagulopathy
- ▶ D-dimer
- ▶ thrombosis
- ▶ fibrinolysis

## Introduction

The COVID-19 pandemic has resulted in considerable morbidity and mortality worldwide in the last 24 months.<sup>1,2</sup> Critically ill patients with COVID-19 can have prominent coagulation abnormalities, including thrombocytopenia and diffuse arterial and venous thrombosis.<sup>3–6</sup> Despite the enormous number of publications on SARS-CoV-2 infection, the mystery of the high incidence of thromboembolic events in critically ill COVID-19 patients remains unsolved. Thromboembolic complications can affect various organs<sup>7,8</sup> and are usually associated with multiorgan failure and high mortality.<sup>9</sup>

In fact, the use of anticoagulation therapy in patients with severe COVID-19 infection has been recommended.<sup>10</sup> Integration of anticoagulation therapy has significantly reduced the COVID-19-related mortality rate.<sup>8</sup> However, despite the common use of anticoagulation and the overall better treatment of COVID-19, patients still have similar rates of thrombotic events in the second wave compared with the first wave.<sup>11</sup> A recent report indicated an adjusted cumulative risk of venous thromboembolism (VTE) and arterial thrombosis of 12 and 1.6% after 10 days, 19 and 2.2% after 20 days, and 23 and 3.1% after 30 days in the ICU, respectively.<sup>11</sup>

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A close follow-up of coagulation parameters is crucial in the treatment of patients with COVID-19. In this article, we summarize common hemostatic findings in COVID-19 patients and present the recommendations of professional societies regarding the use of coagulation laboratory findings in clinical decision-making.

## COVID-19-Associated Coagulopathy

Increasing numbers of studies show that COVID-19 infection induced by SARS-CoV-2 can be associated with a severe clotting disorder.<sup>12</sup>

The pathogenesis of COVID-19-induced coagulopathy has not yet been fully clarified. For the dysregulation of coagulation, the activation of platelets could result from a secondary bacterial infection, excessive production of proinflammatory cytokines, damage-associated molecular patterns, or the stimulation of cell death mechanisms in blood cells and vascular endothelium.<sup>13</sup>

The excessive and uncontrolled release of proinflammatory cytokines is called as cytokine storm.<sup>14</sup> Of particular importance seems to be the involvement of proinflammatory cytokines and chemokines such as the tumor necrosis factor  $\alpha$ , IL-1, and monocyte chemotactic protein 1. An interplay between inflammation and coagulation occurs in the pulmonary vasculature and leads to endotheliopathy and microvascular thrombosis.<sup>15,16</sup> Inflammatory cytokines and chemokines recruit immune cells into the infected tissue and lungs, which, among other things, leads to endothelial activation, inflammatory cell infiltration, and vascular inflammation.<sup>16</sup> Immune activation then stimulates the expression of the tissue factor on the cell surface of the monocytes/macrophages and vascular endothelial cells, which initiates the clotting cascade.<sup>15,17</sup> Coagulopathy, thrombus formation, and microvascular tissue ischemia cause organ dysfunction in patients with severe COVID-19.

Several laboratory coagulation parameters show abnormalities in COVID-19 patients. However, the observed changes are not typical of a "conventional" disseminated intravascular coagulation (DIC).<sup>18</sup> Levi and Iba suggested that although increased D-dimer, low platelet counts, and (slightly) prolonged coagulation times are observed in COVID-19 coagulopathy similar to DIC, there are significant differences between COVID-19 and DIC/sepsis-induced coagulopathy (SIC).<sup>19</sup> COVID-19 coagulopathy is rather prothrombotic and does not cause hemorrhagic complications. A pooled analysis of recent studies reported a DIC incidence of 3% in COVID-19 patients.<sup>20</sup> In contrast to DIC/SIC, the platelet count is mostly in the normal range in COVID-19 patients.<sup>21</sup> Furthermore, von Willebrand factor (vWF) and factor VIII are markedly high in COVID-19-induced coagulopathy due to endothelial damage.<sup>18,21</sup>

## The Incidence of Thromboembolism in COVID-19 Patients

Several studies have reported a high rate of thromboembolism among COVID-19 patients. In a recent meta-analysis

including 27 studies and 3,342 patients with COVID-19, pooled incidences of 16.5 and 14.8% for pulmonary embolism (PE) and deep venous thrombosis (DVT), respectively, were reported.<sup>22</sup> Importantly, the rate of concurrent DVT was only 42% in patients with PE, suggesting the in situ development of PE. Of note, studies with anticoagulation reported lower incidences of PE than studies with no or unknown anticoagulation.<sup>22</sup>

In a prospective study, Jevnikar et al<sup>23</sup> screened critically ill COVID-19 patients with computed tomography pulmonary angiogram at admission and detected PE in 14.2% (15/106) of patients. Interestingly they did not observe any new PE under anticoagulation during a follow-up of 3 months and suggested that an early screening and prophylactic anticoagulation can prevent new PE.<sup>23</sup> The development of a thrombosis can be accompanied or preceded by significant changes in the laboratory parameters of the coagulation system, including D-dimer, prothrombin time (PT), activated partial thromboplastin time (aPTT), platelet activation markers, and markers of the fibrinolytic system.

## Plasmatic Coagulation Parameters

Prolongation of PT and aPTT has been reported to be common findings in critically ill COVID-19 patients with considerable prognostic value when measured at hospital admission.<sup>24</sup> At a cut-off point of less than 75%, PT activity had a sensitivity of 100% and specificity of 78.08% for predicting mortality.<sup>25</sup> Reyes Gil et al<sup>26</sup> reported that admission PT could significantly differentiate those who were discharged alive and those who died.

Jin et al reported that aPTT was not different between patients with and without thrombosis.<sup>24</sup> However, aPTT was significantly prolonged in critically ill COVID-19 patients compared with those with a mild infection.<sup>24</sup> Furthermore, aPTT was longer in nonsurvivors than in survivors.<sup>24</sup> In a larger cohort, Velasco-Rodríguez did not find a relationship between aPTT and mortality in COVID-19 patients.<sup>27</sup> Additionally, two recent meta-analyses found no significant difference in aPTT between COVID-19 patients with severe and less severe disease<sup>28</sup> and between survivors and nonsurvivors.<sup>29</sup>

Since COVID-19 might also affect the synthesis of coagulation factors in the liver, low levels of vitamin K-dependent factors are not unexpected. Indeed, almost a quarter of hospitalized COVID-19 patients show increased PT/international normalized ratio.<sup>30</sup> Antithrombin levels are significantly lower in ICU COVID-19 patients with VTE compared with those without VTE.<sup>31</sup>

In response to the acute phase during infection, fibrinogen, factor V, factor VIII, and vWF are increased in critically ill COVID-19 patients.<sup>32</sup> Furthermore, increased fibrinogen is associated with intensive care requirement (weighted mean difference [WMD] = 32 mg/dL; 95% confidence interval [CI]: 13–50 mg/dL) and mortality (WMD = 104 mg/dL [95% CI: 66–143 mg/dL]).<sup>33</sup>

Several studies have also investigated novel markers of coagulation activation such as the thrombin–antithrombin

(TAT) complex and prothrombin fragment 1 + 2 (PF1 + 2). TAT is increased in critically ill COVID-19 patients.<sup>34,35</sup> Compared with non-ICU COVID patients, patients in the ICU have higher TAT.<sup>36</sup> Furthermore, TAT correlates with D-dimer in COVID-19 patients.<sup>36</sup> On the other hand, von Meijenfeldt reported that TAT complexes correlate neither with clinical severity nor with mortality but with the intensity of the respiratory support.<sup>37</sup> TAT and PF1 + 2, together with D-dimer, are independent predictors of a VTE within 2 weeks of hospital admission in COVID-19 patients.<sup>38</sup> However, due to different anticoagulation regimens in different countries, these studies are not directly comparable.

PF1 + 2 is another new marker for coagulation activation. It is released during the conversion of prothrombin to thrombin. Among ICU COVID-19 patients, PF1 + 2 levels were similar at admission between survivors and nonsurvivors, but PF1 + 2 levels reduced during follow-up only in survivors, pointing out the importance of the coagulation activation on mortality in COVID-19.<sup>39</sup> Additionally, it is worth noting that patients with COVID-19 have increased thrombin generation despite anticoagulation with low-molecular-weight heparin.<sup>37,40</sup>

## D-Dimer

COVID-19 is associated with several abnormalities in coagulation parameters.<sup>24,25,41,42</sup> The most typical finding in COVID-19 is an increased D-dimer concentration. In fact, D-dimer is one of the five laboratory parameters (C-reactive protein, ferritin, D-dimer, white blood cell count, and IL-6) that were identified by the World Health Organization as the key biochemical parameters for a core COVID-19 outcome set.<sup>43</sup>

Several retrospective clinical studies showed a gradual increase in D-dimer levels from nonsevere, severe, to critically ill COVID-19 patients.<sup>44–46</sup> Moreover, a D-dimer level greater than 1.0 µg/mL was shown to be an independent risk factor for death among hospitalized patients, and increased D-dimer levels (>2.5 µg/mL) predict coagulation-associated complications, critical illness, and death during hospitalization.<sup>46,47</sup> Kiss et al<sup>33</sup> found in a meta-analysis that an increased D-dimer level on admission is a risk factor for mortality (WMD: 1.310 µg/mL [95% CI: 1.050–1.570 µg/mL]) and intensive care requirement (WMD: 0.770 µg/mL [95% CI: 0.500–1.040 µg/mL]).

In addition to its value as a biomarker for thrombosis, dynamic changes in D-dimer levels can be used to predict the development of thromboembolic events. A rapid increase in D-dimer level was shown to be indicative for PE in ICU patients before clinical parameters such as increased alveolar dead space ventilation or reduced PaO<sub>2</sub>/FiO<sub>2</sub> ratio appeared.<sup>48</sup> The positive and negative predictive values for PE at a D-dimer level of 8.460 µg/mL has been determined to be 77 and 86%, respectively.<sup>48</sup>

D-dimer level can predict the presence of PE<sup>23,49–51</sup> and VTE.<sup>32,52</sup> In a recent review of 11 studies,<sup>22</sup> they calculated the sensitivity and specificity for D-dimer to detect PE with cut-off values of 1.0 and 3.0 µg/mL as 91 and 24%, and 72 and

63%, respectively.<sup>22</sup> In addition, a D-dimer cut-off point of 1.570 µg/mL showed positive and negative predictive values for new DVT of 19 and 97.5%, respectively.<sup>52</sup> A higher cut-off (1.730 µg/mL) showed a better performance of D-dimer: 58% (45–70) positive predictive value and 100% (85–100) negative predictive value.<sup>32</sup>

D-dimer can also predict arterial thrombosis. A concentration of D-dimer above 1.250 µg/mL is associated with a 7.6-fold (95% CI: 2.9–20.6) increased risk of arterial thrombosis and has a sensitivity of 76.2% and specificity of 72.7% for arterial thrombosis.<sup>53</sup>

Although several studies have suggested good predictive values, D-dimer elevation is a common finding in up to 60% of COVID-19 patients.<sup>30,54</sup> Even in nonhospitalized COVID-19 patients, abnormal D-dimer levels with a very high standard deviation have been shown (0.757 ± 0.994 µg/mL).<sup>55</sup> In critically ill COVID-19 patients, the mortality was associated with age in multivariate analyses but not with D-dimer.<sup>55</sup> D-dimer was not independently associated with symptomatic VTE<sup>55</sup> or mortality.<sup>56</sup> Therefore, caution should be taken when D-dimer is determined for the diagnosis of thromboembolisms in COVID-19 patients.

## Platelet Count

Increased platelet consumption has been presumed in SARS-CoV-2 infection leading to thrombocytopenia in severe cases of COVID-19. In fact, platelet count is often reduced in hospitalized COVID-19 patients; however, severe thrombocytopenia is rare.<sup>57,58</sup> The mechanism of thrombocytopenia in COVID-19 is not yet fully understood. The proposed mechanisms include clearance of platelets by the immune system and decreased platelet production.<sup>59</sup> Bone marrow aspirates showed impaired megakaryocyte maturation in thrombocytopenic COVID-19 patients.<sup>60</sup>

Several studies have demonstrated a relationship between thrombocytopenia and disease severity as well as mortality. For example, critically ill COVID-19 patients with thrombocytopenia ( $\leq 125 \times 10^9/L$ ) have been shown to have a 2.98-fold (1.48–6.02) increased 28-day mortality risk and 2.45-fold (1.32–4.57) increased 180-day mortality risk compared with those without thrombocytopenia.<sup>61</sup> Admission platelet count was significantly lower in COVID-19 patients who died within 30 days after hospitalization than in survivors.<sup>37</sup>

The dynamic change in platelet count has also been suggested as a predictive marker for disease progression. A decrease in platelet count within 28 days after disease onset is associated with a higher mortality rate.<sup>60</sup> Interestingly, a meta-analysis by Gabbai-Armelin et al<sup>62</sup> failed to find a relationship between thromboembolic events and platelet count. Platelet count should also be considered to guide anticoagulation and assess bleeding risk in COVID-19 patients.

However, it is important to note that not all studies demonstrated a relationship between thrombocytopenia and mortality. A recent meta-analysis of 93 studies reported inconsistent results regarding the admission platelet count

as a prognostic factor.<sup>33</sup> While a platelet count  $<125 \times 10^9/L$  was associated with a significantly higher risk for mortality among all COVID-19 patients, a platelet count  $<100 \times 10^9/L$  or  $<150 \times 10^9/L$  was not significant. Furthermore, no threshold could be identified to predict the risk for intensive care requirement.<sup>33</sup>

## von Willebrand Factor

vWF, which is produced exclusively by endothelial cells and megakaryocytes, is stored as ultra-large multimers in Weibel-Palade bodies of endothelial cells and  $\alpha$ -granules of platelets.<sup>63</sup> vWF is released upon stimulation or endothelial damage. SARS-CoV-2 directly damages endothelial cells, causing increased release of vWF.<sup>64,65</sup>

In fact, vWF antigen levels are higher in critically ill COVID-19 patients (median: 507%, interquartile range: 428–596) than in noncritical COVID-19 patients (288%, 230–350,  $p < 0.0001$ ) or COVID-19 outpatients (144%, 133–198,  $p = 0.007$ ).<sup>66</sup> After adjusting for age, body mass index, C-reactive protein, and D-dimer, vWF:Ag ( $>423\%$ ) remained the best predictor of in-hospital mortality with a hazard ratio of 9.46 in Cox proportional hazard analysis.<sup>66</sup> Several studies showed higher levels of vWF antigen and activity in hospitalized COVID-19 patients.<sup>67</sup> vWF antigen and activity levels were significantly higher in patients who died than in survivors.<sup>36,68</sup> One of the possible explanations for these observations, alongside the excessive release from the inflamed endothelial cells, is the reduced activity of the cleaving protease ADAMTS13. Increased vWF antigen is associated with decreased ADAMTS13 levels in COVID-19 patients.<sup>69</sup>

Interestingly, a correlation between vWF, ADAMTS13, and survival was shown in COVID-19 patients, suggesting that ADAMTS13 could be a potential therapeutic target to mitigate coagulopathy in COVID-19 patients.<sup>67</sup> Recombinant ADAMTS13 can reduce vWF multimer size and high vWF activity in plasma samples from critically ill COVID-19 patients.<sup>70</sup> The imbalance between ADAMTS13 and vWF antigen levels may indicate an increased risk for microthrombosis. Recently, a unit increase in ADAMTS13/vWF antigen ratio was shown to be associated with a 20% decreased odds of severe acute kidney injury in COVID-19 patients.<sup>69</sup> They suggested that a low ADAMTS13/vWF antigen is associated with the progression of severe COVID-19 and acute kidney injury with a pattern suggestive of microangiopathy.

## Platelet Activation Markers

SARS-CoV-2 infection has been described to be associated with platelet hyperreactivity, which may contribute to COVID-19 thromboembolic pathophysiology.

Platelet morphology and platelet functions are altered in patients with COVID-19. Besides low platelet count in critically ill patients with COVID-19, several platelet parameter abnormalities were observed. Patients with SARS-CoV-2 infection have increased mean platelet volume (MPV),<sup>71</sup>

MPV is even higher in COVID-19 patients who have acute kidney injury<sup>71</sup> or who require eventually intensive care.<sup>72</sup> Immature platelet fraction (IPF) is also related to platelet size and can be measured automatically by some automated hematological analyzers.<sup>73</sup> In a study by Cohen et al,<sup>74</sup> 47 COVID-19 patients were compared with 100 patients with acute myocardial infarction. IPF was increased in both groups and the authors postulated that patients have an increased IPF as a sign of increased platelet turnover and reactivity.

Some studies have shown that platelets from COVID-19 patients are hyperreactive.<sup>72,75</sup> COVID-19 patients presented a significantly higher P-selectin (CD62P) expression after stimulation with ADP and TRAP-6 compared with healthy controls by flow cytometry.<sup>76</sup> On the other hand, platelet activation with TRAP-6 resulted in decreased PAC-1 binding in COVID-19 patients.<sup>76</sup>

Zaid et al investigated platelet functions as well as the production and secretion of cytokines by platelets in COVID-19 patients.<sup>75</sup> They found that platelets from COVID-19 patients adhere more efficiently than healthy platelets on collagen under flow conditions and aggregate even at sub-optimal thrombin concentrations, suggesting that platelets in COVID-19 patients have a lower threshold for stimulation.<sup>75</sup> The levels of inflammatory cytokines such as IL-1 $\beta$ , IL-18, sCD40L, and TxB<sub>2</sub> were increased in blood and in platelets upon stimulation with thrombin.<sup>75</sup> Although platelet factor 4 and serotonin levels increased in plasma, their levels in platelets were reduced, suggesting increased platelet degranulation during SARS-CoV-2 infection. Together, these data suggest that platelets contribute not only to the hypercoagulable state in COVID-19 patients but also to the systemic inflammatory response (cytokine storm) by releasing inflammatory mediators.<sup>75</sup>

Patients with severe COVID-19-associated acute respiratory distress syndrome (ARDS) may need extracorporeal circulation. Platelets from patients with COVID-19 showed elevated CD62P expression on their surface and the expression of CD62P above the control group median was associated with in-hospital mortality.<sup>17</sup> Interestingly, they also showed that platelets are not activated in patients with a mild or asymptomatic COVID-19 infection. Patients in the ICU have more platelet-monocyte aggregates compared with controls and to patients with mild/asymptomatic infection.<sup>17</sup> Platelet-monocyte interactions lead to tissue factor expression on monocytes, which might contribute to hypercoagulability in critically ill COVID-19 patients.<sup>17</sup> Higher tissue factor expression on platelet/monocyte aggregates also correlated with 28-day survival.<sup>17</sup> They also found that surface expression of CD62P and CD63 is correlated with D-dimer levels in severe COVID-19 patients, suggesting an association between platelet and/or endothelial activation and COVID-19-associated coagulopathy.<sup>17</sup> Similarly, Comer et al demonstrated that platelets from COVID-19 patients are prone to delta granule release after low-dose agonist stimulation, suggesting that platelets are sensitized in COVID-19.<sup>72</sup> Soluble P-selectin was higher in critically ill COVID-19 patients compared with non-severe COVID-19 patients. Goshua et al measured soluble P-selectin as a



marker of platelet activation, which was significantly higher in critically ill COVID-19 patients than in controls and non-ICU COVID-19 patients.<sup>36</sup>

Several studies have shown that sera from COVID-19 infection induce platelet activation in an Fc-gamma-RIIA receptor (FcγRIIA)-dependent manner.<sup>77–80</sup> In our laboratory, we have shown that immunoglobulin G fractions from severe COVID-19 patients induce a procoagulant phenotype in platelets from healthy donors.<sup>78</sup> The increased thrombus formation in severe COVID-19 patients is FcγRIIA dependent, and cyclic-adenosine monophosphate elevation prevents antibody-induced procoagulant platelet generation and clot formation.<sup>79</sup>

## Fibrinolysis System

The balance between coagulation and fibrinolysis systems is crucial for hemostasis. In COVID-19, dysfunction of the latter was proposed as another potential mechanism for the increased risk of thromboembolisms. A main fibrinolytic inhibitor in plasma is plasminogen activator inhibitor (PAI)-1, which is known to be elevated in severe ARDS<sup>81</sup> and is also increased in our cohort of COVID-19 patients. In fact, a recent study investigated longitudinal samples from COVID-19 patients and showed an elevated PAI-1 activity in COVID-19 patients.<sup>82</sup> Additionally, an increased level of PAI-2, but not of tissue plasminogen activator (tPA), followed by an inhibition of fibrinolysis in patients who did not survive COVID-19 infection have been described.<sup>39</sup> tPA and PAI-1 levels are associated with worse respiratory status and poor clinical outcomes; in particular, high levels of tPA were strongly associated with death.<sup>83</sup> There is a balance between PAI-1 and tPA; however, a marked increase in PAI-1 in proportion to tPA can shift the balance to a prothrombotic state. PAI-1 can be released from different cells including platelets and endothelial cells. Zuo et al demonstrated a correlation between PAI-1 and platelet count suggesting platelets as the source of the increased PAI-1.<sup>83</sup> In fact, data from our group showed that platelets from critically ill COVID-19 patients are activated and present a procoagulant phenotype.<sup>78</sup>

In addition, recent studies have shown that fibrinolytic therapy can improve survival in ARDS<sup>84</sup> and might be beneficial for COVID-19 patients.<sup>85</sup> Since higher PAI-1 and tPA levels are associated with a worse outcome in COVID-19 patients, determination of PAI-1 and tPA levels is important.<sup>35,83</sup>

Several studies have demonstrated impaired function of the fibrinolysis system in severe COVID-19.<sup>86–88</sup> The function of the fibrinolysis system and the interplay between its different components can be assessed using whole blood viscoelastic assays, which can analyze dynamic changes in whole blood samples and provide information related to the cumulative effects of plasma clotting factors, platelets, leukocytes, and erythrocytes during all stages of the coagulation and fibrinolytic processes. Thrombelastography (TEG) shows a hypercoagulable state in COVID-19 patients.<sup>89,90</sup> Most importantly, fibrinolysis shutdown has been described in

more than 50% of critically ill COVID-19 patients.<sup>86,88,91</sup> A recent method (TPA test) was introduced to assess resistance to tissue plasminogen during all stages of the coagulation and fibrinolytic processes.<sup>92,93</sup> Significantly increased lysis resistance and a significantly longer time of lysis were observed in blood samples from 20 ICU COVID-19 patients compared with healthy controls.<sup>92</sup> The lysis time was positively correlated with PAI-1 activity.<sup>92–94</sup> These data support the use of viscoelastic assays to evaluate the fibrinolysis system and potentially identify patient subsets who might benefit from the administration of fibrinolytic drugs.

The plasmin–antiplasmin (PAP) complex is a new marker to evaluate the magnitude of fibrinolysis. In a small cohort, Ranucci et al demonstrated that although PAP and PAI-2 were similar at admission to the ICU between survivors and nonsurvivors, the PAI-2/PAP ratio at baseline was significantly higher in survivors of COVID-19, showing the importance of fibrinolysis in mortality.<sup>39</sup> The net effect on fibrinolysis is important in COVID-19 patients. Furthermore, PAP complex levels correlate with SOFA scores in COVID-19 patients but not in those with other sepsis.<sup>95</sup> In a small study from Spain, increased PAP complex levels were shown in COVID-19 patients. However, there was no difference between ICU and non-ICU COVID-19 patients in this study.<sup>40</sup> Similarly, von Meijenfeldt found that PAP levels were not different between survivors and nonsurvivors.<sup>37</sup>

## Risk Stratification Based on Laboratory Coagulation Parameters

Thachil et al<sup>96</sup> suggested a staging system for hospitalized COVID-19 patients using D-dimer, PT, and aPTT in addition to the clinical severity of the infection. In stage 1, patients present with pulmonary symptoms and D-dimer is two to three times greater than the upper limit of normal (ULN). In this stage, PT and aPTT are normal but platelet count and fibrinogen are increased. These patients could be either hospitalized or treated in an outpatient setting. In stage 2, patients present with more severe symptoms requiring critical care, and D-dimer is three to six times higher than ULN. Additionally, patients in this stage might have a decreased platelet count and minor prolongation of the PT. In stage 3, patients have worsening clinical symptoms requiring high-level critical care such as extracorporeal membrane oxygenation (ECMO) support. Patients in this stage have a very high D-dimer level, reduced platelet count and fibrinogen level, and marked prolongation of PT and aPTT.

The IMPROVE (International Medical Prevention Registry on Venous Thromboembolism) Risk score is designed to assess the VTE risk in hospitalized patients. The IMPROVEDD score incorporates D-dimer (higher than two times of ULN) as an additional risk factor.<sup>97</sup> Greco et al investigated the association between the IMPROVE score and the IMPROVEDD score and the need for intensive care and in-hospital mortality in 51 COVID-19 patients.<sup>98</sup> The IMPROVEDD score but not D-dimer was associated with intensification of therapy in hospitalized COVID-19 patients.<sup>98</sup>

**Table 1** Recommendations of societal guidelines/opinions on the use of laboratory parameters for risk stratification for anticoagulation prophylaxis and patient triage

Recommendation	Date of publication or last update	D-dimer	PT	PTT	Platelet count	AT	Fibrinogen	Remarks
ISTH Interim Guidance <sup>100</sup>	March 25, 2020	+	–	+	+	–	+	Recommend intensive monitoring of patients with D-dimer > 3 to 4 times of upper limit of normal, prothrombin time prolonged, platelet count < 100 × 10 <sup>9</sup> , fibrinogen < 2.0 g/L
American Society of Hematology <sup>101</sup>	January 29, 2021	+	+	+	+	–	+	Recommend monitoring platelet count, PT and/or aPTT, D-dimer, and fibrinogen
Global COVID-19 Thrombosis Collaborative Group <sup>10</sup>	April 17, 2020	+	+	–	–	–	+	Recommend PT, D-dimer, fibrinogen monitoring to diagnose the worsening of coagulopathy
Anticoagulation Forum <sup>105</sup>	May 21, 2020	+	–	–	–	–	–	Recommend the use of anti-Xa assay rather than aPTT to monitor unfractionated heparin dosing
American College of Chest Physicians <sup>106</sup>	June 2, 2020	–	–	–	–	–	–	Not mentioned
Scientific and Standardization Committee of ISTH <sup>84</sup>	May 27, 2020	+	–	–	–	–	–	D-dimer > 6 times of upper limit of normal predicts thrombotic events and poor prognosis
NIH Expert Opinion <sup>104</sup>	February 11, 2021	–	–	–	–	–	–	Not sufficient data
GTH <sup>103</sup>	June 04, 2020	+	+	–	+	+	+	Recommend D-dimers, PT/international normalized ratio, platelet count, fibrinogen, and antithrombin

Abbreviations: (–), not recommended; (+), recommended; AT, Antithrombin; GTH, the German Society for Thrombosis and Hemostasis Research; ISTH, International Society of Thrombosis and Hemostasis; NIH, National Institute of Health; PT, prothrombin time; PTT, partial thromboplastin time.

## Laboratory-Guided Management of COVID-19 Patients

Despite the common use of anticoagulation, an increased rate of thromboembolic events is still being reported in COVID-19 patients. Recently, it was shown that patients treated with 5,700 IU nadroparin twice daily still demonstrate increased clot strength in viscoelastic tests, although anti-Xa activity was within the antithrombotic prophylactic range recommended by the International Society of Thrombosis and Hemostasis (ISTH).<sup>99</sup> These data indicate that antithrombotic treatments should be monitored and guided by laboratory investigations. Several biomarkers have been suggested to be useful in the management of the anticoagulation in COVID-19 including D-dimer, platelet count, fibrinogen, PT, aPTT, and antithrombin.<sup>100–103</sup> **Table 1** summarizes the recommendations of different bodies<sup>10,84,100–106</sup> regarding the use of laboratory parameters for risk stratification for anticoagulation prophylaxis and patient triage.

Due to the strong correlation between D-dimer and the development of thrombotic events, D-dimer-based anticoagulation strategies were proposed. Horiuchi et al<sup>107</sup> surveyed 399 hospitals in Japan and found that the most frequent indications of starting anticoagulation were elevated D-dimer and worsening of the clinical condition.<sup>107</sup> In a retrospective case-control study ( $n=240$ ), Tassiopoulos et al used an anticoagulation protocol based on D-dimer level and reported improved organ function and overall survival (27 vs. 59%,  $p < 0.001$ ) in intubated COVID-19 ICU patients.<sup>108</sup> In a prospective noncontrolled study, COVID-19 patients with a D-dimer  $< 5 \mu\text{g/mL}$  received regular prophylactic dose anticoagulation, and those with a D-dimer  $\geq 5 \mu\text{g/mL}$  received intermediate-dose anticoagulation for VTE prophylaxis.<sup>109</sup> None of the patients treated with this strategy developed DVT during hospitalization.

The ISTH recommends the monitoring of D-dimer, aPTT, and platelet count in all patients at admission to decide on hospitalization and intensive monitoring.<sup>100</sup> Patients with increased D-dimer ( $> 3$  to  $4$  times of ULN), prolonged PT, reduced platelet count ( $< 100 \times 10^9$ ), and reduced fibrinogen

( $< 200 \text{ mg/dL}$ ) require hospitalization and intensive monitoring.<sup>100</sup> A similar recommendation has also been made by the American Society of Hematology.<sup>101,102</sup> On the contrary, the American College of Chest Physicians recommends against the use of D-dimer to guide the intensity of anticoagulation.<sup>106</sup> Notably, these recommendations are based mainly on expert opinions and are not tested in prospective studies. Although they might be helpful in clinical decision-making, further prospective studies are urgently needed.

An optimal cut-off for D-dimer in the prediction of thrombosis or prognosis has yet to be determined. The Scientific and Standardization Committee of ISTH indicated that a D-dimer greater than six times of ULN might predict thrombotic events and poor prognosis in COVID-19 patients.<sup>84</sup> Studies have estimated the sensitivity and specificity of D-dimer at different cut-offs (**Table 2**). When equal weight is given to sensitivity and specificity, D-dimer has a mediocre power for the prediction of thrombotic events.

In general, aPTT is used to estimate the effectiveness of unfractionated heparin (UFH) therapy. However, for several reasons, aPTT should not be used in COVID-19 patients to monitor heparin dosing. First, decreased levels of factor XII can lead to longer aPTT values and overestimation of heparin effectiveness. On the other hand, increased factor VIII and fibrinogen levels can shorten aPTT and lead to the underestimation of the heparin effect. A dose increase can cause major bleeding events. Another cause of heparin resistance could be that the SPIKE protein of the SARS-CoV-2 virus can bind to heparin and heparin sulfate with a high affinity.<sup>86</sup> Therefore, aPTT is not the appropriate test to guide or monitor heparin treatment. A better option is to determine heparin activity with the anti-Xa activity.<sup>110</sup> In critically ill COVID-19 patients under therapeutic anticoagulation with UFH, 42% of determinations of anti-Xa activity are out of the target range.<sup>111</sup> Accordingly, the Anticoagulation Forum recommends the use of an anti-Xa assay rather than aPTT to monitor UFH dosing.<sup>10</sup> Although the German Society of Thrombosis and Hemostasis Research (GTH) suggests the monitoring of aPTT (target: 1.5- to 1.8-fold prolongation of the baseline aPTT) in ECMO-treated patients receiving UFH, they also recommended additional monitoring of anti-Xa

**Table 2** Proposed cut-off levels for D-dimer in the diagnosis of arterial or venous thrombosis

Study	Condition	Patient group	Cut-off	Sensitivity	Specificity	PPV	NPV
Fournier et al <sup>53</sup>	AT	ICU/Ward	1.267 $\mu\text{g/mL}$	76.2	72.7	n.d.	n.d.
Suh et al <sup>22</sup>	PE	ICU	1.0 $\mu\text{g/mL}$	91	24	28	89
Suh et al <sup>22</sup>	PE	ICU	3.0 $\mu\text{g/mL}$	72	63	39	87
Tuck et al <sup>49</sup>	PE	ICU/Ward	1.5 $\mu\text{g/mL}$	81	70	n.d.	n.d.
Mouhat et al <sup>51</sup>	PE	Severe COVID-19	2.590 $\mu\text{g/mL}$	83	83	73	91
van den Berg et al <sup>48</sup>	PE	ICU	8.460 $\mu\text{g/mL}$	74	88	77	86
Demelo-Rodríguez et al <sup>52</sup>	VTE	Ward	1.570 $\mu\text{g/mL}$	95.7	29.3	19	97.5
Voicu et al <sup>32</sup>	VTE	ICU	1.730 $\mu\text{g/mL}$	100	45	58	100
Reyes Gil et al <sup>26</sup>	Mortality	Ward + ICU	2.100 $\mu\text{g/mL}$	61	73	n.d.	n.d.

Abbreviations: AT, arterial thrombosis; ICU, intensive care unit; n.d., not determined; NPV, negative predictive value; PE, pulmonary embolism; PPV, positive predictive value; VTE, venous thromboembolism.

activity levels (target range: 0.3–0.7 IU/mL) in cases of severe inflammation with heparin resistance.<sup>103</sup>

## Conclusions

To date, evidence-based recommendations for diagnostics during acute COVID-19 infection are still lacking. However, D-dimer levels and low platelet count seem to be good prognostic markers and, in addition to the global coagulation parameters, the determination of fibrinogen should be considered to exclude a DIC and to monitor antithrombotic treatments in critically ill COVID-19 patients. From our point of view, TEG seems to be a useful tool to recognize the need to intensify anticoagulation. Since COVID-19 patients rarely experience bleeding tendencies, a special diagnosis of the bleeding tendency is not necessary. Future studies should verify the role of increased platelet activation in thrombotic and cardiac events.

We think that serial assessment of coagulation parameters could represent the clinical progress of the patients more accurately than a single measurement due to the dynamic nature of the hemostatic changes in critically ill COVID-19 patients. This may also partially explain the contradictory findings of different studies that were reported in this review. Second, the use of non-disease-specific changes such as acute phase reactants as prognostic markers is questionable, since the specificity of the parameters will be very low to predict thromboembolic events or mortality.

A large number of studies have investigated coagulation parameters in patients with COVID-19. However, the methodological shortcomings of published studies such as low patient number, retrospective design, and lack of systematic screening for thromboembolic complications limit the applicability of these findings in other clinical settings. Furthermore, since the anticoagulation regimens differed between centers depending on local and international recommendations, direct comparison of these studies is not always possible.

While most available data are currently reporting on clinical experience with COVID-19 in 2020, the impact of recent virus variants should be addressed in future studies. Furthermore, there are only a few data on the impact of breakthrough COVID-19 infection on the coagulation system in vaccinated people, although most likely clinically irrelevant.<sup>112</sup>

We need well-designed prospective studies to better understand changes in the coagulation system in patients with COVID-19. Future studies should report clinical data in sufficient detail to facilitate a better understanding of the relationship between laboratory findings and clinical presentation. Furthermore, to better interpret the findings and increase the applicability of the results, laboratory methods (producer of the test, kit, measurement time, sampling time) should also be reported in sufficient detail.

## Authors' Contributions

G.U., K.A., S.H., and T.B. searched the literature, reviewed the available articles, and wrote the manuscript. All authors read and approved the final manuscript.

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## Conflicts of Interest

T.B. has received research funding from CoaChrom Diagnostica GmbH, DFG, Robert Bosch GmbH, Stiftung Transfusionsmedizin und Immunhämatologie e.V., Ergomed, Surrey, DRK Blutspendedienst, Deutsche Herzstiftung, and Ministerium für Wissenschaft, Forschung und Kunst Baden-Württemberg. T.B. has also received lecture honoraria from Aspen Germany GmbH, Bayer Vital GmbH, Bristol-Myers Squibb GmbH & Co., Doctrina Med AG, Meet The Experts Academy UG, Schoechl Medical Education GmbH, Mattsee, Stago GmbH, Mitsubishi Tanabe Pharma GmbH, Novo Nordisk Pharma GmbH. T.B. has provided consulting services to Terumo. T.B. has provided expert witness testimony relating to heparin-induced thrombocytopenia (HIT) as well as to other thrombocytopenic and coagulation disorders. All of these are outside the current work.

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