INTRODUCTION

Since the description of the first patients with coronavirus disease 2019 (COVID-19)–associated pneumonia, there is a growing understanding of the derangement of hemostasis in these patients.1-3 Although the clinical course is mostly favorable, patients with coronavirus 2 (SARS-CoV-2) infection may develop severe acute respiratory syndrome requiring admittance in the intensive care unit (ICU).4 Although the infection affects primarily the respiratory system, other organs may be involved. Especially, among the severe ill patients many develop a hypercoagulable state influencing the unfavorable clinical outcome. The high inflammatory burden associated with COVID-19 and inflammation in the vascular system can result in cardiovascular complications with a variety of clinical presentations.5,6 Besides the high prevalence of thrombotic events, critically ill patients with COVID-19 are frequently developing laboratory abnormalities compatible with hypercoagulability.7 It is known that critically ill patients have a high rate, going up to 10%, of venous thromboembolism (VTE). But much higher rates of VTE have been observed in ICU and non–ICU-admitted COVID-19 patients.8,9 There are at least two separate pathologic coagulation processes that are important in developing clinical manifestations in COVID-19. In the microcirculation of the lung, and potentially other organs, local direct vascular and endothelial injury are producing microvascular clots. Due to hypercoagulability, there is also the possibility for large vessel thrombosis in the systemic circulation.7 One of the highest reported incidences of VTE was up to 50% in an ICU patient population of 184 patients.10 A recent systematic review and meta-analysis showed varying incidences of VTE including deep venous thrombosis (DVT) and pulmonary embolism (PE), depending on the studies.9 The overall incidence of VTE was 14.1% with higher prevalence of 22.7% in patients in ICU. The prevalence of PE in non-ICU and ICU patients was 3.5% and 13.7%, respectively.
Interestingly, comorbidities between COVID-19 patients with or without VTE did not differ, either did age. Though, men were 1.5 times more likely to develop VTE.9

Multiple studies, including histopathological reports and clinical studies, have illustrated and convinced us that COVID-19 can be viewed as a prothrombotic disease. While many unanswered questions remain in COVID-related thrombosis, the etiology of COVID-19-associated coagulopathy appears to follow Virchow’s triad.10 Virchow’s triad comprises vascular damage, altered blood flow, and hypercoagulability of blood. Stasis of blood is present in patients immobilized due to their status of illness, turbulent flow in the microcirculation, and hyperviscosity due to high fibrinogen.11,12 The vessel wall is damaged by endotheliitis 7 and intravascular access of devices (central venous catheters, dialysis catheters, extracorporeal membrane oxygenation (ECMO) devices), and several hemostasis laboratory parameters are disturbed pointing to a coagulopathy.1,2,4,6

The pandemic of SARS-CoV-2 virus has hit us hard, all over the world. Starting at the beginning of 2020, the global healthcare system was, and still is, overwhelmed by patients infected with SARS-CoV-2. Correspondingly, the scientific interest was very high. The number of publications since 2020 is huge with over 89 000 articles at the beginning of this year. A more narrow search on COVID and coagulation gives us nearly 2500 hits. Every day, papers focusing on different aspects of COVID-19 are published, and there is still much more to uncover. In this review, I will focus on coagulation laboratory findings related to COVID-19, without claiming to be complete, but with the objective to discuss frequently described deranged coagulation parameters.

2 ROUTINE COAGULATION PARAMETERS

Elevated fibrinogen and D-dimers are frequently observed laboratory abnormalities compatible with hypercoagulability and are regarded as the two most important markers.7,13

As illustrated in the meta-analysis of Nopp et al, patients developing VTE had higher D-dimer levels (weighted mean difference: 3.26 µg/mL (95% CI: 2.76-3.77) than non-VTE patients.9

Several reports described that the increased levels of D-dimers correlate with adverse outcome.2,14,15 Therefore, markedly increased D-dimer levels, arbitrarily set at a three- to fourfold increase, are helpful in triaging and management of patients.16 Patients with such high D-dimer levels should be hospitalized even in the absence of other symptoms, as this indicates an increased thrombin generation with potential thrombotic risk.16,17

Coagulation laboratory tests in COVID-19 patients differ from those find in disseminated intravascular coagulation (DIC). Although increased levels of D-dimers are suggestive for DIC, D-dimer concentrations observed in COVID-19 are much higher than is usually observed in DIC.18,19

Compared with standard DIC findings, which include decreased platelet counts and increased prothrombin times (PT), most standard coagulation tests are usually initially relatively normal in COVID-19 patients, despite hyperfibrinogenemia, a pattern that is different to what is seen in DIC related to sepsis.1,2

To identify deterioration of the coagulation system in ICU-admitted patients, routine hemostatic markers are monitored. Also, in COVID-19 patients it may be useful to include fibrinogen. Fibrinogen is an acute-phase protein, so not unexpectedly, mean fibrinogen concentrations are at the high upper limits of normal or are even strongly increased.12 High fibrinogen levels are associated with thrombosis also independently of the acute phase.20,21 Moreover, high fibrinogen contributes to blood viscosity,22 one of the elements of Virchow’s triad playing a role in the development of thrombosis.

Along with increased D-dimers, a decrease in fibrinogen was observed in nonsurvivors at day 10 and day 14.2 A sudden decrease in fibrinogen to less than 1 g/L was observed shortly before death in a number of patients.2 This indicates that monitoring fibrinogen can be helpful as prognostic marker in hospitalized COVID-19 patients.16 The increased fibrinogen is correlated with interleukin-6, a biomarker of inflammation as well, and associated with lung injury due to the inflammatory, reactive, and viral effects on pulmonary tissue.13,24

Although changes in fibrinogen and D-dimers are more prominent, prolonged prothrombin times (PT) were found in COVID-19 patients compared with healthy controls.1 Very modest prolonged PT (expressed in seconds) were observed in nonsurvivors and in critically care COVID-19 patients.2,14 Mildly prolonged activated partial thromboplastin time (aPTT) has been reported too. Prolonged aPTT is difficult to interpret in COVID-19 patients, as many causes of prolonged aPTT can be identified, such as presence of heparin, lupus anticoagulant, and elevated C-reactive protein (CRP), which are all underlying conditions often present in these patients.25-27 The aPTT is also reported as shortened, potentially due to elevated factor (F) VIII and fibrinogen in acute-phase situation.28

Platelet count is a test frequently performed in ill patients. Thrombocytopenia is a sensitive marker for sepsis-induced coagulopathy and DIC.29 However, the incidence of thrombocytopenia is relatively low in COVID-19 patients. An overview of studies focusing on platelet count illustrates that a minority of patients presents with a platelet count lower than 100 × 10⁹/L. Milder thrombocytopenia (platelet count below 150 × 10⁹/L) has been found in the majority of severe ill COVID-19 patients.30 A meta-analysis showed that low platelet count (weighted mean difference: −31 × 10⁹/L) was related to increased disease severity and mortality in COVID-19 patients.31 However, there are plenty of studies published on the topic, with conflicting evidence whether thrombocytopenia can be used as a prognostic biomarker or not.30 Also, thrombocytosis has been described in patients with a longer hospital stay.30,32 Probably, the occurrence of thrombocytopenia versus thrombocytosis may depend on the stage of the illness, resulting from consumption coagulopathy.
on the one hand, and cytokine storm induced stimulation of the megakaryocytes on the other hand.\textsuperscript{17,30} Many mechanisms can be responsible for thrombocytopenia and thrombosis, which need further research.\textsuperscript{30}

Therefore, at this moment platelet count is regarded less important compared with D-dimer and PT analysis for stratification of patients for hospital admission or close monitoring.\textsuperscript{16}

Coagulopathy in patients with COVID-19 is related to high risk of VTE\textsuperscript{5} and is associated with an increased risk of death.\textsuperscript{2} An algorithm based on laboratory tests available in all laboratories may help the management of coagulopathy in COVID-19 and has been proposed by the International Society on Thrombosis and Hemostasis, starting with D-dimers, PT, platelet count, and fibrinogen, in decreasing order of importance.\textsuperscript{16}

3 | CHANGES IN FIBRINOLYSIS

High levels of D-dimers, prolongation of PT, and thrombocytopenia suggest secondary fibrinolysis following the coagulation activation in COVID-19 infection. Animal models point toward an urokinase-driven pathway in SARS-CoV-1 infection–stimulated fibrinolysis.\textsuperscript{33} Little information evaluating fibrinolysis in COVID-19 patients is available. Inflammation-induced endothelial cell damage could result in massive release of plasminogen activators.\textsuperscript{17} On the other hand, one of the major factors accelerating thrombus formation in COVID-19 is the suppression of the fibrinolytic system by decreased activity of urokinase-type plasminogen activator and increased release of plasminogen activator inhibitor-1 (PAI-1).\textsuperscript{7} Attenuated fibrinolysis has been described in COVID-19 patients in ICU with a strong correlation with thrombotic events.\textsuperscript{34} However, the presence of elevated D-dimers in COVID-19 patients contradicts the role of PAI-1 that is expected to induce hypofibrinolysis with low levels of D-dimers. The question of whether fibrinolysis is activated or suppressed remains to be answered.\textsuperscript{17}

4 | OTHER COAGULATION FACTORS

High FVIII and Von Willebrand factor (VWF) are other characteristic features of COVID-19 coagulopathy.\textsuperscript{28,35-37} Depending on the study, high FVIII levels parallel disease severity or not.\textsuperscript{35,36} Both FVIII and VWF are acute-phase reactants and expected to be elevated in patients with inflammatory processes. However, in one study, VWF antigen (VWFag) was even higher than FVIII, reducing the FVIII/VWFag ratio proportionally to the degree of disease severity and thus suggesting that endothelial cell perturbation corresponds with hypercoagulability.\textsuperscript{35}

One study described decreased activity levels of ADAMTS13, with disturbed values similar to those observed in patients with thrombotic thrombocytopenic purpura, indicating a consumption coagulopathy.\textsuperscript{37} Markedly elevated FV has been described as a feature of severe COVID-19 and was associated with an increased risk of venous thrombosis.\textsuperscript{38}

5 | THROMBOPHILIA MARKERS

Normal coagulation is counteracted by natural occurring anticoagulant proteins. Outside COVID-19 context, in thrombophilia screening, we investigate for inherited protein C (PC), protein S (PS), and antithrombin (AT) deficiencies.\textsuperscript{37} These deficiencies can also be acquired. Viral infections can trigger acquired thrombophilia, which can then lead to thrombotic complications.\textsuperscript{40} The very strong thrombotic tendency in patients hospitalized for COVID-19 infection is rather unusual for viral infections and seems specific to COVID-19 infections, especially in their severe form. The exact role of underlying inherited thrombophilia is unclear. Whether anticoagulant proteins are disturbed and to what extend acquired changes contribute to the hypercoagulable state are not established yet. Some studies investigated the levels of PC, PS, and AT. One study found a strong prevalence of acquired thrombophilia in patients hospitalized for COVID-19, especially for PS with 20% of the patients showing deficiency. This was not more frequent in patients with severe versus nonsevere COVID-19 illness and did not correlate with other biological parameters or with clinical events.\textsuperscript{45} Borderline low levels of AT, PC, or PS have been shown in other studies.\textsuperscript{36,42} Studies could not identify a correlation between the prevalence of acquired thrombophilia and the severity of illness or thrombosis in patients hospitalized with COVID-19 infection.\textsuperscript{36,42} Tang et al observed a decrease in AT levels in the nonsurvivors, but levels are rarely below 80%.\textsuperscript{5} One study reported an increased PC, with higher PC levels in patients at low-intensity intensive care (ie, 120 U/dL) and even more so in those at intermediate (ie, 126 U/dL) or high-intensity of care (ie, 143 U/dL).\textsuperscript{35}

Despite it is clear that the balance of coagulation in COVID-19 tips toward hypercoagulability with an increased risk of thrombosis, the role of natural anticoagulants remains unclear.

6 | ANTIPHOSPHOLIPID ANTIBODIES

The prevalence of arterial thrombosis in COVID-19 is high, and the involvement of antiphospholipid antibodies (aPL) has been suggested.\textsuperscript{7} Indeed, antiphospholipid syndrome (APS), an autoimmune disease associated with the presence of aPL, one of the major clinical symptoms is thrombosis either venous, arterial, or small vessel thrombosis.\textsuperscript{44} Very soon in the outbreak of COVID-19, reports have been published on aPL in SARS-CoV-2 patients,\textsuperscript{5,45-48} and many others followed. Investigators started to measure aPL in these patients because of the hypercoagulable state. In some of the published reports on aPL and COVID-19, there is concern on the methodology.\textsuperscript{27} It is important that aPL testing should be done according to the guidelines.\textsuperscript{49-51} In the first published reports, only one point of measurement was obtained without confirmation after at least three months, as defined in the laboratory criteria of APS.\textsuperscript{52} Lupus anticoagulant testing (LAC) has many pitfalls, and one of the major drawbacks in LAC testing, performed with phospholipid-dependent coagulation tests, is the interference of CRP and anticoagulant
therapy, both present in COVID-19 patients.\textsuperscript{50} Especially, interference with CRP is a concern, as most of these critically ill patients have raised levels of CRP. In some publications, we can rule out false positivity,\textsuperscript{5,46} but in others we cannot. Interference of heparins is probably not a real issue, as reagents dedicated for LAC testing contain heparin neutralizers, and LAC analysis is reliable if anti-Xa levels of heparins are within the therapeutic range.\textsuperscript{53} We compared the published studies with our own data.\textsuperscript{27} Although we also tested during the acute phase, in our study we are confident not having false-positive LAC as we checked for CRP and anti-Xa levels. Nevertheless, we observed 52% of single LAC-positive patients. In published studies, not all criteria aPL were tested (LAC, anticardiolipin antibodies (aCL), and anti-β2glycoprotein I antibodies (ap2GPI) IgG/IgM\textsuperscript{52}) and no antibody profiles could be made. In our cohort, the majority of patients showed a low-risk profile for thrombosis. In the published studies so far, no triple-positive patients were reported.\textsuperscript{5,45-48} In our patient cohort, only two patients were triple-positive of whom none showed thrombotic complications. In previous studies,\textsuperscript{5,45-47} the association between aPL and thrombosis is strongly highlighted; however, in our cohort we observed no strong association between aPL and thrombotic complications.\textsuperscript{27} Noncriteria aPL (aCL and ap2GPI IgA and antiphosphatidylserine/prothrombin antibodies\textsuperscript{51}) had no added value, as all patients positive for noncriteria aPL were also LAC-positive. Repeat testing of the patients at a second time point showed that the majority of patients retested became negative and thus indicated the transient character of the antibodies.\textsuperscript{27} Transient antibodies have been described in infectious diseases or drugs and are thought not being of clinical significance.\textsuperscript{54,55} The hypercoagulability observed in COVID-19 patients is certainly multifactorial, but the role of aPL is unclear. More well-designed prospective studies are required before clear conclusions can be made on routine testing of aPL in COVID-19 patients.\textsuperscript{27}

7 | GLOBAL COAGULATION ASSAYS

Thromboelastometry performed on whole blood includes the contribution of blood cells, platelets, and plasma and can indicate hyper- and hypercoagulable states.\textsuperscript{56} This might give the possibility to measure the multifactorial-induced hypercoagulability in COVID-19 patients. A role to fibrinolysis shutdown has been contributed to the pathophysiology of thrombosis in COVID-19 patients.\textsuperscript{17} A study in critically ill COVID-19 patients illustrated that clot lysis at 30 minutes measured by thromboelastography (TEG) predicts thromboembolic events and need for hemodialysis.\textsuperscript{34} A complete lack of lysis of clot at 30 minutes was seen in 57% of patients (n = 44) and predicted venous thromboembolic events with high probability.\textsuperscript{34} Viscoelastic measurements showed an elevated maximum amplitude and low lysis of clot at 30 minutes.\textsuperscript{34,57} Equally, rotational thromboelastometry (ROTEM) showed an acceleration of the propagation phase in clot formation illustrated by shorter clot formation times (CFT) and higher clot strength (MCF).\textsuperscript{57,58} No indication of secondary hyperfibrinolysis at ROTEM analysis was observed.\textsuperscript{58} Although thromboelastometry parameters denote hypercoagulability in severe ill COVID-19 patients, their value as prognostic markers should be investigated in further studies.

Another global coagulation assay, the thrombin generation assay measured by calibrated automated thrombography performed on plasma, could not demonstrate an increased thrombin generation in critical and noncritical COVID-19 patients.\textsuperscript{43}

8 | HEPARIN MONITORING IN COVID-19 PATIENTS

It is clear that alterations in the hemostatic balance in COVID-19 patients are strongly disturbed and contribute to a high prothrombotic status, justifying the use of anticoagulant therapy. A prophylactic dose of low molecular heparin (LMWH) should be considered in all patients with COVID-19–related critical or acute illness.\textsuperscript{59} If LMWH is contra-indicated (for instance, renal failure or ECMO), unfractionated heparin can be administered.\textsuperscript{60,61} Anticoagulation clinical trials are ongoing to identify optimal prophylactic and treatment options.\textsuperscript{62}

Monitoring heparin therapy, especially UFH, in the setting of an inflammatory status as in COVID-19 patients, is a challenge for the hemostasis laboratory. In the setting of profound coagulopathy, the use of aPTT for monitoring treating with UFH may be hampered by the inability to use the aPTT in acute-phase conditions. As previously discussed, underlying conditions in COVID-19 patients can prolong aPTT (presence of lupus anticoagulant, elevated CRP) or shorten aPTT (high FVIII and high fibrinogen). This may lead to over- or underestimation of the anticoagulant effect of UFH.

It has been described that treatment in patients with COVID-19 was complicated by the need of very high UFH doses to achieve adequate anticoagulation based on the aPTT ratio, a phenomenon described as heparin resistance (defined as the need for greater than 35 000 units of heparin in 24 hours to reach therapeutic aPTT levels).\textsuperscript{63} The phenomenon can be explained by high FVIII levels.\textsuperscript{64} True heparin resistance, where the aPTT and anti-Xa activity levels are concordantly lower than expected, is commonly associated with decreased AT. Measurement of AT in patients with COVID-19 might be helpful in this context to detect acquired AT deficiency.\textsuperscript{1}

Previous studies have shown the anti-Xa level as a more suitable parameter for monitoring the antithrombotic activity than the aPTT,\textsuperscript{65} although the debate continues. Also in COVID-19 patients, the anti-Xa assay seems more reliable to monitor UFH therapy.\textsuperscript{61} However, despite the advantage of the lower sensitivity to biological variables, anti-Xa measurement’s main disadvantages are the variability of composition of reagents between assays, the expense, and the lower availability in the laboratories.\textsuperscript{66,67}

Exposed to heparin in prophylaxis and treatment of COVID-19 thrombosis, HIT (heparin-induced thrombocytopenia) is a potential complication of COVID-19. Reports have been published of HIT occurrence in COVID-19 patients.\textsuperscript{68} Platelet count monitoring in COVID-19 patients helps detecting the development of
thrombocytopenia or the rapid decrease that is suggestive for HIT. Along with the estimation of the clinical probability by the 4T score, a diagnosis of HIT can be made. However, in the complex situation of COVID-19, the 4T score has its limitations (other reasons for thrombocytopenia, presence of thrombosis due to disturbed coagulation balance in COVID-19, thrombosis at the absence of thrombocytopenia). In case of thrombocytopenia with suspicion of HIT, one group of experts recommended to use nonheparin anticoagulants, such as danaparoid, argatroban, or bivalirudin, over fondaparinux. Giving the importance of HIT diagnosis, positive immunoassays detecting platelet factor 4–dependent antibodies should be confirmed by a functional assay to avoid overdiagnosis as enzyme immune assays may give false-positive results. Not only the clinical diagnosis of HIT is a challenge but also the real-time laboratory confirmation of a HIT diagnosis is difficult.

9 | CONCLUSION

To conclude, it is clear that alterations in the hemostatic balance in COVID-19 patients are strongly disturbed and contribute to a high prothrombotic status, justifying the use of anticoagulant therapy. High rates of VTE have been observed in COVID-19 patients, going together with hemostatic changes. Hemostasis testing (summarized in Table 1) has an important role in diagnosed COVID-19 patients. Elevated D-dimer levels were found to be a crucial laboratory marker in the risk assessment of thrombosis in COVID-19 patients. The diagnostic approach also includes PT and platelet count. Fibrinogen might give an indication for worsening coagulopathy. In therapeutic patient management, monitoring the heparin anticoagulant therapy by anti-Xa activity plays an important role in optimizing anticoagulant therapy. Other markers have been described as being deranged and may help understanding the pathophysiology of thrombosis in COVID-19 patients but have currently no place in diagnosis or management in COVID-19 patients.

CONFLICTS OF INTEREST

The author has no conflicts of interest.

TABLE 1 Hemostasis laboratory markers in patients with COVID-19

| Management of coagulopathy | Therapeutic management | Observed derangements |
|-----------------------------|------------------------|-----------------------|
| Decreased                  | Increased              | Increased | Equivocal |
| D-dimers                   | Anti-Xa                | FVIII      | aPTT      |
| PT (sec)                   | VWF                    | AT         |
| Platelet count             | Clot formation         | PC         |
| Fibrinogen                 | PS                     |
| Fibrinolysis parameters    | aPL                    |

Abbreviations: aPL, antiphospholipid antibodies; aPTT, activated partial thromboplastin time; AT, antithrombin; FVIII, factor VIII; PC, protein C; PS, protein S; PT, prothrombin time; TEG, thromboelastography; VWF, von Willebrand factor.

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How to cite this article: Devreese KMJ. COVID-19–related laboratory coagulation findings. *Int J Lab Hematol*. 2021;43(Suppl 1):36-42. https://doi.org/10.1111/ijlh.13547