

# Hematology Laboratory Abnormalities in Patients with Coronavirus Disease 2019 (COVID-19)

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## Abstract

Over the past few months, Coronavirus Disease 2019 (COVID-19) has spread across much of the world leading to a pandemic. Many infected individuals do not experience signs or symptoms, or experience only mild symptoms, whilst a subset experience severe disease, which is often fatal. A number of laboratory tests have been found to be abnormal in hospitalized patients, and some studies suggest some of these tests can predict an unfavorable outcome. These include markers of acute phase reaction (elevated C-reactive protein, erythrocyte sedimentation rate, white blood cell count, fibrinogen, procalcitonin, factor VIII, von Willebrand factor), signs of tissue injury (elevated lactic dehydrogenase, alanine aminotransferase, cardiac troponins), changes in hemostasis and coagulation (elevated D-dimer, prolonged prothrombin time, decreased platelets, decreased antithrombin, elevated factor VIII and von Willebrand factor), and decreased lymphocytes. Additional studies are needed to confirm the most ideal panel of tests, and to confirm the efficiency of laboratory tests to predict clinical outcome, as well as the ideal anticoagulation management.

## Keywords

- ▶ COVID-19
- ▶ coronavirus
- ▶ laboratory abnormalities
- ▶ SARS-CoV-2

In December 2019, the world was introduced to the 2019 novel coronavirus (2019-nCoV), which was later renamed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This virus was established as the cause of coronavirus disease 2019 (COVID-19), a predominantly respiratory illness with potentially life-threatening sequelae.<sup>1</sup> Many infected individuals do not experience signs or symptoms, or only mild symptoms. A subset of patients, however, experience severe illness, which often becomes fatal. In

particular, as highlighted elsewhere in this issue of the journal, severe COVID-19 can be seen as a multiorgan disease, where pathophysiology is driven by derangement of many physiological pathways, including hemostasis and fibrinolysis.<sup>2–6</sup>

Several laboratory tests have been shown to be abnormal in hospitalized patients, and some studies suggest certain laboratory tests can predict a more severe outcome.<sup>7</sup> The aim of this short review is to update readers of this journal in

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**Table 1** Laboratory test abnormalities that are associated with a worse outcome in COVID-19

Markers of tissue injury
<ul style="list-style-type: none"> <li>• Elevated LDH</li> <li>• Elevated ALT</li> <li>• Elevated cardiac troponin</li> <li>• Elevated creatinine</li> </ul>
Markers of acute phase reaction
<ul style="list-style-type: none"> <li>• Elevated CRP</li> <li>• Elevated ESR</li> <li>• Elevated fibrinogen</li> <li>• Elevated procalcitonin</li> <li>• Elevated WBC</li> <li>• Elevated FVIII and VWF</li> </ul>
Coagulation changes suggesting coagulation activation
<ul style="list-style-type: none"> <li>• Elevated D-dimer</li> <li>• Prolonged PT</li> <li>• Shortened (or prolonged) aPTT</li> <li>• Decreased platelets</li> <li>• Decreased antithrombin activity</li> <li>• Decreased antithrombin activity</li> </ul>
Other findings
<ul style="list-style-type: none"> <li>• Decreased lymphocytes</li> </ul>

Abbreviations: ALT, alanine transaminase; aPTT, activated partial thromboplastin time; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; PT, prothrombin time; VWF, von Willebrand factor; WBC, white blood cell.

regard to COVID-19–associated hematology laboratory abnormalities (→ **Table 1**).

## Background

It is well established at this time that this virus uses the same receptor angiotensin-converting enzyme 2 (ACE2) present on alveolar epithelium and other cells as does the original SARS virus (now renamed SARS-CoV-1) for cell entry. Reportedly introduced into the human population initially through exposure to infected animals, probably bats, COVID-19 has quickly transformed into a global pandemic through symptomatic and asymptomatic person-to-person transmission mainly through respiratory droplets.<sup>1</sup>

The clinical features of COVID-19 are well documented, and most commonly include fever, dyspnea, anosmia, and taste alteration, along with myalgia, fatigue, and nonproductive cough.<sup>8–11</sup> Additional signs/symptoms, such as anorexia, pedal acro-ischemia (“COVID-toes”), diarrhea, and sore throat, have also been reported. Current epidemiologic evidence shows that up to 80% of patients infected by SARS-CoV-2 may be asymptomatic or only mildly symptomatic (i.e., exhibiting only mild respiratory symptoms, as in other typical coronavirus infections), while 15 and 5% of patients are at risk of developing a severe or even critical form of disease, respectively, evolving toward acute respiratory distress syndrome (ARDS), systemic inflammation, and widespread thrombosis, especially in the lung.<sup>12</sup>

Early identification and timely treatment of COVID-19 patients at enhanced risk of developing critical disease are hence pivotal to prevent unfavorable clinical outcome and unsustainable burden on the health care system due to subintensive or intensive care of thousands of affected patients. The pivotal role of abnormal laboratory values in patients with COVID-19 has recently emerged, and it has become clear that particular laboratory parameters may aid in earlier risk stratification and prognostication of these patients, ultimately leading to earlier interventions and ideally more favorable outcomes.<sup>7,9,11,13–17</sup>

## Laboratory Abnormalities

The most common laboratory abnormalities identified in patients with COVID-19 include decreased albumin and lymphocyte count and elevated C-reactive protein (CRP), lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), aspartate transaminase (AST), alanine transaminase (ALT), and D-dimer.<sup>7,9,14,15</sup> Comparably, data from the SARS epidemic of 2002–2003 show similar laboratory abnormalities (decreased lymphocytes, decreased platelets, and elevated LDH, ALT, AST, and sometimes also creatine kinase), thus suggesting that these two infectious diseases not only are caused by a rather similar microorganism (i.e., two  $\beta$ -coronaviruses, sharing over 85% genetic identity), but they also generate a similar clinical picture.<sup>9</sup>

There are multiple reports of elevated D-dimer associated with COVID-19. For example, Han et al reported elevated D-dimer and fibrinogen levels among patients with COVID-19 compared with healthy controls (D-dimer: 10,400 vs. 260 ng/mL; fibrinogen: 500 vs. 290 mg/dL) and decreased antithrombin activity levels (85% among COVID-19 patients vs. 99% among healthy controls).<sup>15</sup> In another study, 10 of 11 patients with COVID-19 had antithrombin levels below the reference range, while protein C was not decreased in any of the 11 patients.<sup>18</sup>

In hospitalized patients, the elevations in D-dimer and fibrinogen are frequently striking, often higher than commonly seen with other conditions.<sup>4,19,20</sup> In contrast, prothrombin time (PT) and activated partial thromboplastin time (aPTT) are commonly normal or mildly<sup>15,17,18</sup> or less often moderately (Van Cott E, April 2020, unpublished observations) prolonged. aPTT prolongations that are more marked are sometimes found to be due to heparin, which could be either heparin that was administered or heparin contamination from collecting the specimen through a heparinized line or port (Van Cott E, April 2020, unpublished observations). Infections are known to be associated with the transient appearance of lupus anticoagulants, which appear to be a common cause of a prolonged aPTT in COVID-19 patients.<sup>21</sup> The aPTT is also often reported as shortened, potentially due to acute phase elevations in fibrinogen and factor VIII, while PT may be prolonged in patients with critical disease, due to onset of multiple organ failure (MOF), including liver injury.<sup>22</sup>

Many of the laboratory abnormalities observed thus represent a balance between an acute phase reaction to

the infection, including high CRP, high fibrinogen, high factor VIII, and high von Willebrand factor (VWF),<sup>19</sup> and “consumption” events due to systemic or localized thrombosis that ultimately lead to reduction in some coagulation factors and increase in D-dimer and fibrin/fibrinogen degradation products (FDPs).

aPTT waveform analysis has been reported in three patients with COVID-19.<sup>23</sup> A biphasic waveform (which is a marker for disseminated intravascular coagulation [DIC]) was not present in any of the patients, and all three survived. Other waveform parameters worsened during their hospital stay. The traditional tests for DIC (platelet count, D-dimer, fibrinogen, and PT) are also used to monitor for DIC in patients with COVID-19.

### Severity of Illness and Intensive Care Unit Admission

Other studies have investigated the differences in laboratory values based on illness severity or intensive care unit (ICU) admission. Although few studies published the exact laboratory values for each group, it appeared that CRP, ESR, LDH, D-dimer, creatinine, cardiac troponin I, ALT, AST, leukocytes, neutrophils, and PT were more elevated in COVID-19 patients requiring ICU admission or with severe disease, usually defined as dyspnea, tachypnea, hypoxia, ARDS, shock, or multiorgan dysfunction.<sup>13–17,24,25</sup> For example, patients with COVID-19 requiring ICU admission were found to have an elevated D-dimer 2.5 times more often with a median value 4.8 times higher than patients with COVID-19 not requiring ICU admission.<sup>16</sup>

### Mortality and Laboratory Tests

In addition to analyzing the association between disease severity and laboratory abnormalities, some studies have explored the relationship between mortality and laboratory abnormalities. These studies described elevated values of CRP, ESR, LDH, D-dimer, creatinine, cardiac troponins, leukocytes, ALT, PT, and procalcitonin and decreased values of lymphocytes, platelets, and antithrombin in nonsurvivors compared with survivors.<sup>9,11,13,14,16,17,25,26</sup> One study, for example, described a median D-dimer value of 5.2 µg/mL among nonsurvivors, compared with 0.8 µg/mL among survivors.<sup>11</sup> Tang et al found that the admission PT, fibrinogen, D-dimer, and FDPs were higher in nonsurvivors than in survivors, suggesting significant coagulation derangement in patients with poor outcomes. This same study revealed that 71.4% of nonsurvivors met the ISTH criteria for DIC, compared with only 0.6% of survivors.<sup>17</sup> In more recent studies, DIC was not common.<sup>4</sup> Antithrombin did not become significantly lower in nonsurvivors than in survivors until hospital day 7, albeit the median for both groups remained within the reference range.<sup>17</sup> The aPTT tended to be slightly prolonged on admission in some patients in both groups, slightly more so for nonsurvivors, but the difference between survivors and nonsurvivors was not significant.<sup>17</sup> Although the aPTT may not offer prognostic value, obtaining

a baseline aPTT is of value, both for potential monitoring and in case heparin therapy is subsequently required. During hospitalization, fibrinogen remained high in both groups, likely due to an acute phase reaction, but starting on day 10, fibrinogen decreased to ~100 mg/dL or less in nonsurvivors.<sup>17</sup> One meta-analysis reported a 5.1 times higher odds of severe disease and mortality in patients with thrombocytopenia, defined as a platelet count less than  $150 \times 10^9/L$  in some studies or  $100 \times 10^9/L$  in others.<sup>13</sup> Zhou et al reported median platelet counts of  $220 \times 10^9/L$  in survivors and  $166 \times 10^9/L$  in nonsurvivors.<sup>11</sup>

### Pathogenesis

Although further research is needed, understanding the laboratory abnormalities seen in COVID-19 can add to the growing list of parameters used for risk stratification of patients with COVID-19, which may offer guidance in determining which patients require admission, and of those, which patients require the additional services provided by an ICU care team.<sup>9,11,14–16</sup> The earlier identification of patients most at risk for poorer outcomes may also potentially support more aggressive initial therapy in an effort to prevent the negative complications seen in severe COVID-19 infections, such as ARDS, extensive pulmonary thrombosis, acute cardiac injury, acute kidney injury, shock, MOF, DIC, and death.

Furthermore, this understanding may clarify the pathogenesis of the virus. SARS-CoV-2 binds to its natural receptor ACE2 on alveolar epithelium, causing the respiratory symptoms commonly seen in COVID-19.<sup>10,15,27</sup> The virus, however, also binds to endothelial cells, presumably causing the endothelial damage necessary to initiate platelet aggregation and activate coagulation, leading to thrombosis and ischemia.<sup>13,27</sup> Another very plausible theory is that the virus sets off a so-called “cytokine storm,” which may mediate vessel injury through local inflammation and recruitment of leukocytes and cells of the macrophage/monocyte lineage, which can then worsen local inflammation and cell injury, thus aggravating the endothelial damage as described earlier.<sup>9,11,13,25</sup> Notably, neutrophils are the main source of chemokines and cytokines and neutrophil extracellular traps (NETs), and are seen at elevated levels in more severe disease.<sup>25</sup> This may explain the leukocytosis and neutrophilia associated with more severe disease. Lymphopenia, on the other hand, may be explained by virus binding to lymphocytes, causing the depletion of CD4- and CD8-positive T-cells in an effort to evade the host immune system.<sup>9,25</sup>

Regardless of how SARS-CoV-2 leads to activation of coagulation, the subsequent thrombosis eventually leads to consumption of coagulation factors and accelerated fibrinolysis,<sup>6</sup> thus providing a possible explanation for the pathogenesis of pulmonary thrombosis and subsequent DIC, which are commonplace in patients with severe COVID-19.<sup>2,4,15,17,26,27</sup> Perhaps COVID-19-related thrombosis in small vessels explains the cardiac injury and multiorgan damage (especially kidney, liver, and pancreas) seen in critically ill COVID-19 patients.<sup>27</sup>

## Opinions on Anticoagulation

Although D-dimer values appear in a majority of articles discussing parameters associated with COVID-19 infection, disease severity, or mortality, the study of other coagulation parameters, such as the PT or antithrombin, might also help clinicians determine whether anticoagulant therapy would benefit their patients. Prophylactic anticoagulation with low-molecular-weight heparin (LMWH) has been suggested in various guidance documents,<sup>12,14,28–30</sup> based on studies demonstrating decreased mortality among patients with severe COVID-19 or patients with D-dimer values greater than sixfold the upper limit of normal who received LMWH.<sup>26</sup> Thachil et al proposed an algorithm for managing COVID-19 coagulopathy through risk stratification at presentation, based on D-dimer, PT, platelet count, and fibrinogen. The authors recommended all patients admitted with elevated D-dimer, regardless of PT, platelet count, or fibrinogen levels, should receive prophylactic doses of LMWH unless they clinically worsen or are at significant risk of bleeding.<sup>14</sup> Others have reported various differing opinions regarding anticoagulation.<sup>12,19,30</sup> For instance, administering higher-than-usual prophylactic dosage of LMWH has been suggested, especially for patients at risk of developing extensive pulmonary thrombosis or other forms of severe intravascular coagulopathy.<sup>12</sup> In these subsets of patients, even 2× or 3× the LMWH prophylactic regimen may be considered. Unfractionated heparin may also be an option.<sup>12</sup> The authors also suggest that extended (45 days) postdischarge prophylaxis be considered for patients with D-dimer greater than twofold over the upper limit of normal, if they have a high risk for thrombosis and a low risk for bleeding.<sup>12</sup>

Some experts advise caution against “serial panic ordering” of many laboratory tests such as the ones described in this short review, since repeat testing puts a strain on finite phlebotomy and laboratory resources, and may even cause iatrogenic anemia from repeated phlebotomy.<sup>30</sup> Nevertheless, a baseline set of tests is useful, and then additional test ordering should follow local guidelines and the clinical status of the patient. Some regular monitoring to identify early signs of organ damage may also be beneficial.<sup>7</sup>

## Conclusion

The growing knowledge surrounding the effect of SARS-CoV-2 on human hematologic and coagulation systems continues to add to the clinician's toolkit, refining our ability to diagnose and manage patients with COVID-19. Additional studies would be needed to confirm the most ideal panel of tests and confirm the ability of laboratory tests to predict clinical outcome.

### Conflict of Interest

None declared.

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