Hematological Abnormalities in COVID-19: A Narrative Review

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Abstract. COVID-19 is caused by SARS-CoV-2. Although pulmonary manifestations have been identified as the major symptoms, several hematological abnormalities have also been identified. This review summarizes the reported hematological abnormalities (changes in platelet, white blood cell, and hemoglobin, and coagulation/fibrinolytic alterations), explores their patho-mechanisms, and discusses its management. Common hematological abnormalities in COVID-19 are lymphopenia, thrombocytopenia, and elevated D-dimer levels. These alterations are significantly more common/prominent in patients with severe COVID-19 disease, and thus may serve as a possible biomarker for those needing hospitalization and intensive care unit care. Close attention needs to be paid to coagulation abnormalities, and steps should be taken to prevent these occurring or to mitigate their harmful effects. The effect of COVID-19 in patients with hematological abnormalities and recognized hematological drug toxicities of therapies for COVID-19 are also outlined.

INTRODUCTION

COVID-19 is caused by SARS-CoV-2. It is currently a pandemic, and as of December 2, 2020, there have been more than 64 million cases worldwide and less than 1.5 million deaths.1 Moreover, this has resulted in a significant impact on healthcare systems, socioeconomic aspects, and the livelihoods of many.1–4 Common symptoms of COVID-19 include fever, dry cough, and tiredness.5–6 A subset of patients develops a more severe form of disease, characterized by acute respiratory distress syndrome (ARDS), and hematological, neurological, cardiac, and renal complications.7–9 Many hematological findings have been reported in COVID-19 patients, and this review summarizes the reported hematological abnormalities (changes in platelet, white blood cell, and hemoglobin levels, and coagulation/fibrinolytic alterations), explores their patho-mechanisms, and discusses its management. The effect of COVID-19 in patients with hematological abnormalities and recognized hematological drug toxicities of therapies for COVID-19 are also outlined.

LITERATURE SEARCH

A literature search was performed using the PubMed, Embase, and Google Scholar databases to identify studies on hematological findings of COVID-19 up to November 30, 2020. The keywords used in the search were as follows: SARS-CoV-2, COVID-19, clinical findings, laboratory findings, hematology, and coagulation. The initial selection was based on the article title and abstract, following which the full-text article was read. The reference lists in the full-text articles were scanned to obtain additional references. Articles relevant to the topic were included, after removing duplicates. The findings from primary research articles, case reports, and case series are summarized and discussed.

HEMATOLOGICAL ABNORMALITIES IN OTHER CORONAVIRUSES

Lymphopenia (69.6–100%) and thrombocytopenia (20–55%) have been reported in patients with SARS-CoV-1 infections.10 The corresponding rates in Middle East respiratory syndrome coronavirus (MERS-CoV) infections were as follows: lymphopenia (44–60%) and thrombocytopenia (31–40%).11 Lymphopenia is not a prominent finding in coronavirus OC43 and 229E infections that cause common cold-like symptoms.12 Several studies found coagulation abnormalities (elevated D-dimer level and raised prothrombin time) following SARS-CoV-1 and MERS-CoV infections. For instance, 45% of SARS-CoV-1 patients had elevated D-dimer levels.13 Deep vein and multi-organ (including pulmonary and bronchial) thrombosis have been reported in autopsy studies of SARS-CoV-1 infections.14 Middle East respiratory syndrome–induced disseminated intravascular coagulation (DIC) was observed in fatal cases.15 It is noteworthy that coagulation abnormalities are a feature of the human coronaviruses that cause severe respiratory manifestations and not of all human coronaviruses.

THROMBOCYTOPENIA IN COVID-19

Thrombocytopenia has been reported in 5–21% of COVID-19 patients (Table 1). In a meta-analysis performed early in the pandemic, significant thrombocytopenia was reported in patients with more severe than mild disease.16 Both the meta-analysis and another study (where the median platelet count was 79 × 109/L) found a higher risk of mortality in patients with thrombocytopenia.17 Liu et al.18 studied the dynamic changes in platelet counts among hospitalized patients and suggested that monitoring such counts may have a role in prognosis. A platelet count < 200 × 109/L at admission was associated with three times higher mortality. The degree of thrombocytopenia seen in COVID-19 is generally mild. This contrasts with some other viral diseases such as dengue, where platelet counts may decrease to < 25 × 109/L.19,20 Qu et al.21 and Yang et al.22 found an elevated platelet–lymphocyte ratio (PLR) to be a prognostic marker in...
| First author (country) | Sample size | Findings |
|-----------------------|-------------|----------|
| Chen et al. (China)   | 48          | Platelet 12% | Coagulation parameters Increase in prothrombin time 30% |
|                       |             |           | Increase in D-dimer 36% |
|                       |             |           | Increase in LDH 76% |
|                       |             |           | Increase in CRP 86% |
|                       |             |           | Decrease in Hb-51% |
|                       |             |           | Leucopenia 9% |
|                       |             |           | Neutrophilia 38% |
|                       |             |           | Lymphopenia 35% |
| Fan et al. (Singapore) | 67          | Mild thrombocytopenia 20% | Raised LDH in ICU patients |
|                       |             |           | HB decreased in ICU patients during hospital stay |
|                       | 58 Non-ICU patients 9 ICU patients |           | Lymphopenia 29.2% |
|                       |             |           | Both were more prominent in ICU group |
|                       |             |           | Leucopenia 36.9% |
| Huang et al. (China)  | 41          | NT | Prothrombin time and D-dimer levels are higher in ICU patients |
|                       |             |           | Platelet slightly lower in disease progression |
| Liu et al. (China)    | 78          | NT | CRP significantly elevated in disease progression; albumin significantly decreased in disease progression group; D-dimer slightly higher in disease progression |
|                       |             |           | No significant difference in WBC in disease progression and stabilization groups. Lymphocytes are slightly lower in disease progression group |
|                       |             |           | Leucopenia 25% |
|                       |             |           | Lymphopenia 63% |
| Qian et al. (China)   | 91          | Thrombocytopenia 10.9% | Elevated D-dimer 24.2% |
|                       | 82 Non-severe |           | High CRP 53.8% |
|                       |             |           | Hb decreased- 36.3% |
|                       |             |           | Lower Red blood cell- 11% |
| Qin et al. (China)    | 452         | NT | Higher procalcitonin, CRP, and serum ferritin in severe patients than in non-severe patients |
|                       |             |           | NT |
|                       |             |           | Severe patients had a significantly higher leukocyte, higher neutrophil, higher neutrophil to lymphocyte ratio, lower monocyte, lower eosinophil than non-severe patients |
| Ruan et al. (China)   | 150         | Platelet count significantly lower in non-survivors than in survivors | Albumin, serum ferritin, and CRP higher in non-survivors than in survivors |
|                       | 68 Non-Survivors 82 Survivors |           | NT |
|                       |             |           | WBC count higher in non-survivors than in survivors |
|                       |             |           | Lymphocyte count significantly lower in non-survivors than in survivors |
| Wan et al. (China)    | 135         | Thrombocytopenia 17% | D-dimer 0.4 (0.2-0.6)* Prothrombin time 10.9 (10.5-11.4)* |
|                       | Mild 95     |           | D-dimer and LDH were higher in severe patient than in mild patients |
|                       | Severe 40   |           | 133.00 (122.00-141.00)* |
| Wang et al. (China)   | 69          | 171.00 (142.00-211.00)* | Elevated lactate dehydrogenase 41% |
|                       | 36 in ICU   |           | Increased CRP 67% |
|                       | 102 Non-ICU 201 |           | More prominent in SpO2 <90% group |
|                       |             |           | Lymphocytopenia 42% |
| Wang et al. (China)   | 138         | Median platelet count was slightly lower in ICU patients than in non-ICU patients | Elevated D-dimer, creatine kinase, and lactate dehydrogenase significantly in ICU patients compared with non-ICU patients |
|                       | 36 in ICU   |           | NT |
|                       |             |           | Higher WBC, higher neutrophil count in ICU patients than in non-ICU patients |
|                       |             |           | Median lymphocyte count was below the normal level |
|                       |             |           | Lymphocytopenia 64% |

(continued)
COVID-19. The specificity and sensitivity were 0.44 and 0.77, respectively, with a cutoff value of 180. There were some limitations in these studies, as the PLR was not measured at a specified time point in the disease course, and other comorbidities may also affect the PLR. Chan et al. did a meta-analysis of five studies and found the PLR to be elevated in severe compared with non-severe COVID-19 patients. However, high heterogeneity was seen in the observed PLR values.

Case studies of patients developing idiopathic thrombocytopenia purpur (ITP) and thrombotic thrombocytopenic purpura (TTP) following SARS-CoV-2 infection have been published. Platelet counts were found to decrease from around day 4 of symptoms. In a systematic review of the COVID-19–associated ITP cases, 71% were older than 50 years and had moderate to severe disease. Intravenous immunoglobulin and dexamethasone were found to be effective treatment options. The mechanisms of disease association between COVID-19 and ITP/TTP needs to be further studied.

Ethylenediaminetetraacetic acid (EDTA)-dependent pseudothrombocytopenia is characterized by a spurious decrease of platelets in vitro due to the aggregation of platelets in EDTA anticoagulant blood samples. Some cases of COVID-19–related pseudothrombocytopenia have been reported. In one case, the platelet count was normal at admission, but then decreased progressively with no signs of bleeding. As the peripheral blood smear showed platelet aggregation, the platelet count was measured in a blood sample anticoagulated with citrate and was found to be normal. The phenomenon disappeared 17 days later. In a further case, Kuhlman et al. describe a patient with pan-pseudothrombocytopenia associated with an arterial occlusive event leading to death.

**COAGULATION ABNORMALITIES IN COVID-19**

A number of studies have reported coagulopathy in patients with COVID-19. This was distinct from other coagulopathies such as DIC. Elevated D-dimer levels (> 1,000 ng/mL) and increased prothrombin times were seen in COVID-19 patients compared with controls (Table 1). Patients with severe disease had higher levels than those with non-severe disease, and thus may serve as a good prognostic marker for identifying
patients for early therapeutic intervention.\textsuperscript{28} An admission D-dimer level > 2.0 μg/mL was able to predict in-hospital mortality in COVID-19 patients.\textsuperscript{29} Three to six times higher rates of thrombosis are noted in COVID-19.\textsuperscript{28}

Thrombotic complications are seen in approximately 25–31% of intensive care unit (ICU)-admitted COVID-19 patients.\textsuperscript{30,31} This includes pulmonary embolism, venous thromboembolic events such as proximal deep vein and upper extremity thrombosis, and arterial thromboembolic events such as ischemic strokes. Lodigiani et al.\textsuperscript{32} analyzed the timing of the arterial and venous thromboembolism (VTE) and found 50% to be detected within 24 hours of hospital admission. Middeldorp et al.\textsuperscript{33} detected VTE in 20% of ICU versus 3.3% of non-ICU COVID-19 patients. The corresponding rates were 50% versus 18% in another study.\textsuperscript{34} In a prospective cohort study, Helms et al.\textsuperscript{35} reported a range of thrombotic complications in 42.7% of COVID-19 patients. Even with the use of anticoagulation, patients with ARDS developed life-threatening thrombotic complications, suggesting the need for further refinements of the anticoagulation regimes. COVID-19 patients admitted to the ICU may have other risk factors (such as old age, obesity, and smoking) that may exacerbate coagulopathy. Clinicians should be aware of coagulopathy-related complications in COVID patients undergoing emergency interventions or surgery.\textsuperscript{36} Understanding coagulation alterations related to COVID-19 is a vital area of further research.

RED CELL AND HEMOGLOBIN ABNORMALITIES IN COVID-19

Reduced hemoglobin levels have been noted in some severe COVID-19 patients (Table 1) A meta-analysis of four studies found hemoglobin concentrations to be lower in severe disease than in mild infections.\textsuperscript{37} A few studies found no significant changes in hemoglobin levels in COVID-19 patients.\textsuperscript{38,39} Although Lippi et al.\textsuperscript{37} suggested monitoring hemoglobin levels to detect poor prognosis, more exploratory studies are needed on this aspect. No significant effects on red blood cell (RBC) counts have been found, but structural changes have been noted.\textsuperscript{40} Red blood cells of COVID-19 patients had increased oxidation of structural proteins and altered lipid metabolism.

WHITE BLOOD CELL ABNORMALITIES IN COVID-19

Twenty to 40% of COVID-19 patients have leucopenia, and 3–24% have leukocytosis (Table 1). Lymphopenia (lymphocyte count ≤1,100 cells/μL) was seen in 30–75% of COVID-19 patients (Table 1). A meta-analysis performed by Huan and Pranata found a strong association between lymphopenia and severe COVID-19.\textsuperscript{41} CD4\textsuperscript{+} and CD8\textsuperscript{+} T lymphocytes are predominantly reduced in the COVID-19 patients requiring ICU care. There was increased expression of PD-1 and Tim-3 in surviving T cells, suggesting functional exhaustion.\textsuperscript{42} Neutrophilia has been reported in severe COVID-19 patients (Table 1). An elevated neutrophil to lymphocyte ratio was identified as a marker for in-hospital mortality and severe COVID-19 disease.\textsuperscript{43} Reactive lymphocytes have been described in many viral infections including COVID-19.\textsuperscript{44} Reactive lymphocyte and antibody secreting lymphocytes identified based on automated hematology analyzer scattergrams were shown to rise toward the second week of infection.\textsuperscript{45} Although not many studies have commented on changes in eosinophil counts in COVID-19, Zhang et al.\textsuperscript{46} found 52.9% COVID-19 patients to have reduced eosinophils count.

Zini et al.\textsuperscript{47} found morphological changes in neutrophils (such as abnormal shape of the nucleus and cytoplasmic granulation) and platelets (hyperchromatic forms). Apoptotic and immature granulocytes were observed in the peripheral blood smear and may be due to the perturbation of normal granulopoiesis. The cytokine storm and hyperinflammation were proposed as possible causal factors for these changes. Immature granulocytes (small myelocytes and metamyelocytes) were also observed. Following antiviral treatment, the neutrophil morphology reverted to normal, and lymphocytes showed morphological heterogeneity suggesting activation. Further studies would clarify the clinical relevance of the observed changes.

EFFECTS ON THE BONE MARROW IN COVID-19

Hemophagocytosis has been noted in the bone marrow aspirates of three severe COVID-19 patients.\textsuperscript{62} There was an increase in pleomorphic megakaryocytes, plasma cells, macrophages, and hemophagocytosis. Rapkiewicz et al.\textsuperscript{63} found increased numbers of megakaryocytes in the bone marrow, with morphology pointing to active platelet production. Rare virions were also identified in bone marrow megakaryocytes using electron microscopy.

EFFECTS ON THE SPLEEN IN COVID-19

The angiotensin-converting enzyme-2 (ACE-2) receptor is expressed in the spleen, at lower concentrations than in the lung, heart, and intestines.\textsuperscript{64} On postmortem examination of six COVID-19 patients, ACE-2 was found to be expressed in the splenic red pulp and medulla of lymph nodes.\textsuperscript{65} Angiotensin-converting enzyme-2 receptors were also expressed on CD68 and CD169 macrophages in the spleen and lymph nodes. Viral nucleocapsid antigens were predominantly noted in the splenic red pulp and occasionally the white pulp. Virus-infected macrophages may cause lymphocyte apoptosis via production of IL-6.\textsuperscript{65} Xu et al.\textsuperscript{66} studied the pathological changes in the spleen of 10 COVID-19 patients, and found a decrease in T and B lymphocytes, a reduction and atrophy of lymphoid follicles, atrophy of the white pulp, and neutrophil/plasma cell infiltration. Yao et al.\textsuperscript{67} found a reduced number of lymphocytes and cell degeneration/necrosis in the spleen. These may have an impact on immune cells, particularly a decrease in lymphocytes. Studies on COVID-19 on the bone marrow and spleen are summarized in Table 2.

POSTULATED MECHANISMS OF HEMATOLOGICAL ABNORMALITIES IN COVID-19

Platelets. The potential reasons for thrombocytopenia include direct effect of SARS-CoV-2 on platelet production, autoimmune destruction of platelets, or increased platelet consumption. Secondary hemophagocytic lymphohistiocytosis causes excessive proliferation and activation of macrophages, and in turn produces a surge in inflammatory cytokines. It has been postulated this cytokine storm...
Coagulation and fibrinolytic system. Several mechanisms have been postulated for altered coagulation in COVID-19. The antiviral inflammatory response may shift the balance in the anticoagulant and procoagulant pathways, leading to altered coagulation.\(^{15}\) von Willebrand Factor (VWF) is a procoagulant that is released in the presence of endothelial cell damage and has been found to be elevated in COVID-19.\(^{80}\) He et al.\(^{81}\) described the COVID-19-pericyte hypothesis, where ACE-2 receptors are present on specific pericytes rather than endothelial cells. Pericytes are located in the basement membranes of capillaries where it is wrapped around endothelial cells. Invasion of pericytes by the SARS-CoV-2 virus may lead to an inflammatory and pro-thrombotic response.\(^{81}\) Further experiments are needed to assess the degree of invasion of pericytes by SARS-CoV-2.

Injury due to neutrophil extracellular traps (NETs) may be a factor for thrombosis. Excess neutrophil infiltration to the alveolar space (associated with acute capillaritis) was observed in three autopsy cases of COVID-19.\(^{82}\) Targeting NETs may be a potential therapeutic option for preventing and controlling the thrombotic tendency, and further research in the area should be undertaken. There is evidence that activation of different complement pathways may lead to activation of the coagulation system.\(^{83}\) This may be due to an increase of platelet activity/aggregation, increase of prothrombinase and tissue factor activity, and the stimulation of endothelial cells to release VWF. Studies have described the over-activation of the complement system in COVID-19, and this in-turn may account for the observed hypercoagulable state.

Red blood cells and hemoglobin. Using a bioinformatics approach, Liu and Li\(^{84}\) proposed certain SARS-CoV-2 proteins may attack the beta chain of hemoglobin, thus reducing its level. A reduction in hemoglobin (and thus oxygen content) may explain some of the symptoms of respiratory distress. Experimental confirmation of these bioinformatics findings would be needed.

White blood cells. The presently favored explanation for lymphopenia is invasion of lymphocytes by the virus, as ACE2 receptors are found on lymphocytes.\(^{85}\) The virus may directly attack lymphocytes causing apoptosis, invade bone marrow cells, or cause destruction of the spleen or lymph nodes. Raised lactic acid levels in COVID-19 may lead to reduced lymphocyte proliferation.\(^{86}\) The cytokine storm may adversely impact T-cell numbers and function.\(^{42}\) Neutrophilia may be due to viral-induced inflammation or due to secondary bacterial infections (seen in approximately 10% of COVID-19 patients).\(^{50}\)

Bone marrow. The ACE2 receptor has been found to be expressed in the bone marrow,\(^{70}\) including hematopoietic stem cells.\(^{87,88}\) Direct viral effects on the hematopoietic stem cells may affect hematopoiesis. Similar effects are observed in HIV, as receptors of HIV are expressed in hematopoietic stem cells (HSCs).\(^{89}\) Abnormalities in platelet and lymphocyte counts and function may at least in part be due to this mechanism. Ratajczak and Kucia\(^{72}\) have postulated a role for the nucleotide-binding domain (NOD)-like receptor protein 3 (Nlrp3) inflammasome expressed in hematopoietic stem cells for the abnormalities of hematopoiesis. Activation of the Nlrp3 inflammasome may exacerbate the observed cytokine storm.

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| Study | Description |
|-------|-------------|
| Santos Leite Pessoa et al.\(^{68}\) | Three cases of splenic infarction as a thrombotic complication in COVID-19 |
| Chen et al.\(^{79}\) | Showed that ACE2 receptor expressed on tissue-resident CD169 + macrophages in the spleens |
| Li et al.\(^{70}\) | SARS-CoV-2 infection induces severe tissue damage such as splenic nodule atrophy |
| Xu et al.\(^{71}\) | Studied the ACE2 expression in a wide variety of human tissue. ACE2 expression was seen in the spleen, however, in a low amount |
| Bone marrow | Pathological changes of the spleen in 10 patients. T and B lymphocytes of the spleen are reduced to varying degrees; the spleen nodules are atrophied, reduced, or absent |
| Li et al.\(^{70}\) | Studied the ACE2 expression in a wide variety of human tissue. Angiotensin-converting enzyme-2 expression was seen in the bone marrow, however, in a low amount |
| Ratajczak and Kucia\(^{72}\) | Angiotensin-converting enzyme-2 and the entry-facilitating transmembrane protease TMPRSS2 are expressed on very small CD133 + CD34 + Lin−CD45− cells in human umbilical cord blood (UCB), which can be specified into functional hematopoietic stem cells and endothelial progenitor cells |
| Joshi et al.\(^{73}\) | In human, very small embryonic-like stem cells (VSELs) and HSCs, the interaction of the ACE2 receptor with the SARS-CoV-2 spike protein activates the Nlrp3 inflammasome, which may lead to cell death |

\(^{ACE2} = \text{angiotensin-converting enzyme-2}; \ HSCs = \text{hematopoietic stem cells.} \)

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|-------|-------------|
| Chaudhry et al.\(^{69}\) | Showed that ACE2 receptor expressed on tissue-resident CD169 + macrophages in the spleens |
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COVID-19 INFECTIONS IN PATIENTS WITH HEMATOLOGICAL DISORDERS

**Red blood cell disorders.** In general, patients with sickle cell disease (SCD) and thalassemia have a higher risk for developing infections (especially respiratory tract infections). Hydroxycarbamide, a commonly used medication in SCD, has immunosuppressive actions, and needs extra care when used.\(^9\) A small study on 11 thalassemia patients did not find an increased severity of COVID-19.\(^9\) Using multiple regression analysis, it has been hypothesized that patients with heterozygous beta-thalassemia may be protected against...
COVID-19. However, this analysis relied solely on statistical methods and used a simulated COVID-19 tracker. Patients with red blood cell disorders are advised to strictly follow practices for avoiding SARS-CoV-2 infections.

**Bleeding and coagulation disorders.** At present, large cohort studies are lacking on patients with bleeding and coagulation disorders getting COVID-19. In a hemophilia patient, the COVID-19 clinical manifestations were similar to other patients, and there were no bleeding events. It is not certain if patients with idiopathic ITP or TTP are at increased risk of COVID-19 or if they would get more severe disease. If the patient is receiving immunosuppressive drugs, extra care may be advisable.

**Hematological cancers.** As hematologic malignancies directly affect the immune system, these patients are at significantly higher risk of a variety of severe infections including COVID-19. Patients with hematologic malignancies often receive myelosuppressive chemotherapy which further increases their risk of infections.

**Impact of COVID-19 on clinical outcomes in patients with hematologic malignancies.** Several factors may influence outcomes in patients with hematologic malignancies. Direct immunosuppressive effects and therapeutic side effects such as myelosuppression and lymphodepletion may make such patients more prone to infections. An Italian study found high mortality in hematologic malignancy patients with COVID-19 infection when compared with those with a hematologic malignancy alone. A study conducted at two centers in Wuhan, China, among hematologic malignancy patients found no differences in baseline characteristics between subjects who did or did not develop COVID-19. However, the hematologic malignancy patients with COVID-19 had higher mortality than those without COVID-19.

A multicenter study found patients with hematologic, lung, or metastatic (stage IV) cancer had more severe disease than those without malignancy. Jose Luis and team concluded that in patients with hematologic malignancies and COVID-19, mortality was directly associated with older age, disease status, performance status, immune parameters, and levels of inflammation, and the use of azithromycin and low dose corticosteroids may be beneficial. In addition, Julio Garcia and others concluded that in patients with hematologic malignancies and COVID-19, death was associated with higher age, comorbidities, type of hematologic malignancy, and class of antineoplastic therapy. Lattenist and others found patients with hematologic malignancies to be vulnerable to SARS-CoV-2, with age and low hemoglobin levels to be risk factors for poor outcome. In one study, elderly patients (age > 65 years) with hematologic cancers did not have an increased risk of death following COVID-19.

**Impact of COVID-19 on hematologic malignancy clinical services.** Prevention of infections is a crucial part of the management of hematologic cancer patients. During the pandemic, clinicians have had to rethink and remodel the provision of curative care for such patients. Schrag and others suggested that although appropriate therapy is continuing, physicians should take steps to reduce the risk from COVID-19, such as the selection of oral over intravenous treatment regimens wherever there is equipoise, the more judicious use of growth factor support, and reducing surveillance laboratory and radiologic evaluations when possible. Shirke et al. suggested the use of tele-oncology services to reduce the risk of cancer patients being exposed to the SARS-CoV-2 virus. Humaid and team suggested the need for clear communication and education about hand hygiene, infection control measures, high-risk exposure, and awareness on signs and symptoms of SARS-CoV-2. They also suggested the need to individually evaluate the necessity of active intervention, postponing elective surgery or adjuvant chemotherapy for patients with low risk of progression, and minimizing outpatient visits for mitigating exposure and transmission.

Optimal protection of healthcare staff is important during the pandemic. Rapid response by institutions, adjustments to organizational structure, strategic planning, developing and implementing effective guidelines, and providing effective and alternative ways to protect and support clinical staff and employees and patients are key to achieve good care during the pandemic. Many hematologic malignancy patients rely on clinical trials to receive their care, but during the pandemic, the conduct of several clinical trials has been affected. The risk of adverse events from cancer therapies is unlikely to be increased. Hematological malignancy units should be SARS-CoV-2-free zones, dedicated solely to hematologic treatment. Patients should strictly comply with social distancing, and hospital outpatient visits should be reduced.

Lee et al. studied mortality patterns from COVID-19 in cancer patients (8% and 14% had lymphomas and hematological malignancies, respectively) and found no increased risk of death. On the other hand, He et al. studied 13 patients with hematological cancers (acute myeloid leukemia, acute lymphoblastic leukemia, plasma cell myeloma, and myelodysplastic syndromes) who developed COVID-19, and found more severe disease and a higher case fatality rate than other hospitalized patients. The higher case fatality rates may be attributed to the therapy they were receiving or due to other comorbid conditions such as diabetes, which is common in this group of patients. There was no association between the type of cancer and risk of developing COVID-19. In another study on cancer patients (8.6% had hematological cancers—leukemia, myeloma, and lymphoma) with SARS-CoV-2 infections, those with hematological cancers had the highest severity and death rate (33%). This may be because patients with hematological cancers receive more immunosuppression than those with solid tumors.

**ABO BLOOD GROUPS AND COVID-19**

A number of studies have suggested an association between ABO blood groups and SARS-CoV-2 infection risk, with group O individuals having a lower risk. Multiple single nucleotide polymorphisms were examined in a genome-wide association study on severe COVID-19 patients. Significant associations were found with single nucleotide polymorphism on chromosome 3p21.31 and 9q34.2. Interestingly, the chromosome nine association was linked to the ABO locus.

**TRANSFUSION AND COVID-19**

The requirement of transfusions is low in patients with COVID-19 including severe cases. In a retrospective study by Barriteau et al., 13.4% hospitalized COVID-19 patients received transfusions, of which 11% received RBCs and less than 2% received each of the other components such as...
platelets or plasma. This study showed that hospitalized COVID-19 patients had a lower requirement for transfusions than other hospitalized patients. The pandemic has impacted blood donations due to lockdowns in certain areas and safety concerns. Corman et al.114 assessed the risk of transfusion-related transmission by testing for SARS-CoV-2 virus in the blood of 18 symptomatic and asymptomatic patients. RNA was not detected; however, the study should be conducted in larger numbers of patients to explore this further.

MANAGEMENT OF HEMATOLOGICAL ABNORMALITIES IN COVID-19

Platelets. As severe thrombocytopenia is not common in COVID-19 patients, treatment of this aspect is usually not needed. There are some case reports of patients with COVID-19, who developed ITP or TTP, and all of them had favorable outcomes.24,115,116

Coagulation and fibrinolytic system. The routine use of antithrombotic prophylaxis with low-molecular-weight heparin is recommended for inpatients by the International Society on Thrombosis and Hemostasis.111 Moreover, the role of heparin as an anti-inflammatory agent is of additional benefit in patients with COVID-19.118 However, severe COVID-19 infections may be complicated by liver dysfunction which may worsen the coagulopathy and increase the risk of bleeding. Therefore, the dose and the type of anticoagulants should be adjusted based on the clinical severity of the disease and associated organ impairment.117 Higher doses in obese patients were shown to be necessary. In a study by Wang et al.,119 in those with higher body mass index (>40 kg m⁻²), a higher antithrombotic prophylaxis dose decreased the odds of symptomatic venous thrombosis by 50%.

There is increasing debate over antithrombotic prophylaxis post-discharge. During the 6-week post-discharge period, 4.8/1,000 discharges were associated with VTE. However, the odds were not significantly higher than hospitalization for other acute medical illnesses. Therefore, the role of routine post-discharge thromboprophylaxis remains uncertain.120

The treatment with a full dose of anticoagulation may be beneficial for patients with sepsis-induced coagulopathy (SIC).121 In a retrospective study by Tang et al.,122 the use of heparin was shown to reduce mortality in patients who met the SIC criteria or had a markedly increased D-dimer levels. In patients with a thromboembolic event or an increased suspicion for thromboembolic disease, therapeutic anticoagulation is recommended.123 Furthermore, therapeutic anticoagulation should be considered in patients on continuous renal replacement therapy, extracorporeal membrane oxygenation, or diagnosed thrombosis of extracorporeal filters or catheters.120 Heparin resistance has been reported among critically ill COVID patients. In such patients, anti-factor Xa levels may be of use to guide therapy.124

Importantly, greater than 50% of VTE were diagnosed on the first day of admission, emphasizing the need for early detection and management.32 However, routine screening is not practical in the context of a pandemic and, therefore, not recommended.125 The need for imaging is assessed based on clinical grounds.121 As an alternative to sophisticated imaging modalities, bedside ultrasound has been used with acceptable sensitivity (100%) and specificity (95.8%) in the diagnosis of VTE.126 Bedside cardiac ultrasonography may suggest a diagnosis of pulmonary embolism based on the analysis of right ventricular function in clinically suspicious patients.121

Patients on warfarin should be converted to other anticoagulants such as heparin, as close monitoring of international normalized ratio would be difficult during isolation for COVID-19.121 Low molecular weight heparin (LMWH) would be preferred over unfractionated heparin, as the need for regular monitoring is lower. The patients may be transitioned to direct oral anticoagulants if they are able to tolerate oral intake. However, clinicians should be aware of possible drug interactions with antivirals such as ritonavir, lopinavir, or darunavir, and anti–IL-6 such as tocilizumab which may be used for treatment of COVID-19 infections. Moreover, in the context of critical infection with associated renal impairment, decreased excretion of direct oral anticoagulants may increase the risk of bleeding.125 Therefore, direct oral anticoagulants are best avoided in the critically ill.

Several clinical trials are underway on the use of anticoagulants in patients with COVID-19. Anticoagulants should be given carefully in patients with some hematological disorders such as hemophilia and von Willebrand disorder. D-dimer has no utility in the diagnosis of VTE; it has a poor positive predictive value but a high negative predictive value so may be used to exclude pulmonary embolism (PE) in patients with a low clinical suspicion. Thachil et al.126 have suggested thromboprophylaxis for patients requiring hospital admission with a view to reducing poor outcomes. Further well-designed clinical trials on thromboprophylaxis would be helpful. Table 3 summarizes the studies using anticoagulation.

Red blood cells. Although anemia has been reported in some patients, no studies have shown transfusion support for this indication alone, to improve outcomes. Patients with hemoglobinopathies and COVID-19 should continue to receive transfusions and chelation therapy as needed.90

White blood cells. The use of corticosteroids for reducing COVID-19–related inflammation has been studied. The RECOVERY trial gained much attention when it found an 8–26% lower mortality among patients who received 6 mg/day of dexamethasone for up to 10 days.134 Several clinical trials on the use of mesenchymal stem cells (MSCs) as therapy for COVID-19 are underway. Leng et al.135 treated seven patients with MSCs and observed an increase in the lymphocyte count and a decrease in C-reactive protein (CRP) and cytokine secreting T and natural killer cells within 3–6 days. However, the cost of such procedures and the prolonged time period needed for gaining treatment approval are factors that need to be considered.

CONVALESCENT BLOOD PRODUCT THERAPY IN COVID-19

Convalescent blood product (CBP) therapy is a promising treatment option. In the systematic review of five studies (and 27 patients), Rajendran et al.136 found a positive outcome for CBP therapy. A reduced viral load and an increase in neutralizing antibody titers were noted. An increased transfusion-transmitted infections and other blood product–related adverse reactions are possibilities, but CBP therapy was otherwise well tolerated.

A study by Salazar et al.137 including 25 severe or life-threatening SARS-CoV-2 patients who were administered CBPs documented uneventful recovery. The average length of
### Table 3
Anticoagulation and thrombotic events in COVID-19

| Author (year) | Setting | Study type | Methodology | N | Details of anticoagulation | Thrombotic events and associated factors |
|---------------|---------|------------|-------------|---|----------------------------|----------------------------------------|
| Artifoni et al.127 | Ward | Single center retrospective analysis | Hospitalized confirmed COVID patients | 71 | Daily administration of weight-appropriate enoxaparin following institutional recommendations (40 mg/day for BMI < 30 kg/m², 60 mg/day for BMI 30–40 kg/m², and 40 mg twice daily for BMI > 40 kg/m²) and covering the whole hospital stay | 16 developed VTE (22.5%) and seven PE (10%) despite adequate thromboprophylaxis. D-dimers at baseline were significantly higher in patients with DVT (P < 0.001) |
| Demelo-Rodríguez et al.128 | Ward | Single center retrospective analysis | Hospitalized COVID patients with D-dimer > 1,000 ng/mL | 156 | All but three patients received standard doses of thromboprophylaxis: enoxaparin 40 mg/day or bemiparin 3,500 UI/day | DVT in 23 patients (14.7%), of whom only one was proximal DVT. D-dimer levels > 1,570 ng/mL were associated with asymptomatic DVT (OR 9.1; CI 95% 1.1–70.1). D-dimer showed an acceptable discriminative capacity |
| Helms et al.35 | ICU | Prospective multicenter cohort study | COVID-19 patients with acute respiratory distress syndrome admitted to the ICU | 150 | Around 70% received prophylactic dosing (4,000 UI/day for LMWH or if contraindicated, UFH at 5–8 U/kg/h), and 30% received therapeutic dosing | 64/150 had thrombotic events (pulmonary embolisms: 16.7%). No patient developed disseminated intravascular coagulation. vWF activity, vWF antigen, and FVIII were increased. 50/57 tested patients (87.7%) had positive lupus anticoagulant |
| Kok et al.30 | ICU | Retrospective analysis | COVID-19 patients admitted to the ICU were studied | 184 | All patients received at least standard doses thromboprophylaxis (nadroparin 2,850–5,700 IU once daily to twice daily), with 9.2% receiving therapeutic anticoagulation at admission | The majority of thrombotic events were PE (65/75; 87%). Chronic anticoagulation therapy at admission was associated with a lower risk |
| Leonard-Lorant et al.129 | Ward and ICU | Retrospective analysis | Pulmonary CT angiograms performed for COVID-19 patients were reviewed with clinical details | 106 | Subgroup of patients received anticoagulation. Agent not specified | D-dimer cutoff of 2,660 μg/L had 100% sensitivity for PE. In PE-positive group, 25/32 (78%) were on prophylactic doses and 2/32 (6%) were on therapeutic doses |
| Llitjos et al.130 | ICU | Retrospective analysis | Critically ill COVID patients admitted to the ICU | 26 | All patients were anticoagulated from admission: 31% (n = 8) with prophylactic anticoagulation and 69% (n = 18) with therapeutic anticoagulation | The overall rate of VTE in patients was 69%. The proportion of VTE was significantly higher in patients treated with prophylactic rather than therapeutic anticoagulation (100% vs. 56%, P = 0.03). |
| Lodigiani et al.32 | Ward and ICU | Single center retrospective analysis | Symptomatic COVID patients | 388 | ICU cohort (n = 61): LMWH: The dosage was weight-adjusted in 17 patients and therapeutic in two patients on ambulatory treatment hospital. General ward cohort (n = 327): 75% received initial in-hospital thromboprophylaxis. A | Thromboembolic events occurred in 28 patients, corresponding to a cumulative rate of 21% (27.6% ICU, 6.6% general ward). Half of the thromboembolic events were diagnosed within 24 hours of hospital admission. A total of eight (2.1%) patients met the laboratory (continued) |
| Author (year) | Setting | Study type | Methodology | N | Details of anticoagulation | Thrombotic events and associated factors |
|--------------|---------|------------|-------------|---|---------------------------|----------------------------------------|
| Maatman et al.\textsuperscript{131} | ICU     | Multicentre observational study | Confirmed COVID patients requiring intensive care | 109 | prophylactic dosage was used in 41% of patients, 21% were treated with inter-mediate-dosage thromboprophylaxis, and 23% received therapeutic-dose anticoagulation | criteria for overt disseminated intravascular coagulation |
| Middeldorp et al.\textsuperscript{33} | Ward and ICU | Retrospective study | Hospitalized confirmed COVID patients | 198 | Ward patients received prophylaxis with nadroparin 2,850 IU once daily or 5,700 IU for patients with a body weight of \( \geq 100 \) kg. Patients in ICU received a double dose of nadroparin, which was nadroparin 2,850 IU twice daily (bid) for patients with a body weight < 100 kg and 5,700 IU bid for those \( \geq 100 \) kg | VTE was diagnosed in 31 patients (28%). Elevated admission d-dimer and peak d-dimer were associated with VTE \( P < 0.05 \). D-dimer greater than 2,600 ng/mL predicted VTE |
| Poissy et al.\textsuperscript{132} | ICU     | Single-center retrospective analysis | COVID patients with ICU admission for pneumonia | 107 | All patients received thromboprophylaxis (UFH or LMWH). | The cumulative incidences of VTE at 7, 14, and 21 days were 16%, 33%, and 42%. The cumulative incidence of VTE was higher in the ICU |
| Roberts et al.\textsuperscript{120} | Post-discharge | Single-center retrospective analysis | Discharged patients following hospitalized treatment for COVID-19 | 1877 | Anticoagulation not given | At the time of PE diagnosis, 20/22 patients were receiving prophylactic antithrombotic therapy. Hospital-acquired VTE rate was 4.8 per 1,000, with an odds ratio of 1.6 compared with medical admissions (95% CI, 0.77–3.1) |
| Tang et al.\textsuperscript{124} | Ward | Single-center retrospective analysis | Hospitalized patients with severe COVID-19 | 449 | Heparins \( n = 99; 94 \) received 40-60 mg enoxaparin/d and five received UFH 10,000–15,000 U/d vs. control \( n = 350 \) | No difference in overall 28-day mortality was found between heparin users and nonusers. However, the 28-day mortality of heparin users was lower than that of nonusers in patients with sepsis-induced coagulopathy score \( \geq 4 \) (40.0% vs. 64.2%, \( P = 0.029 \)), or D-dimer > 6-fold of upper limit of normal (32.8% vs. 52.4%, \( P = 0.017 \)) |
| Zhang et al.\textsuperscript{133} | Ward | Single-center retrospective analysis | Hospitalized critically ill patients with COVID-19 | 143 | 53 (37.1%) patients were given DVT prophylaxis with LMWH vs. cont. | 66/142 patients developed lower extremity DVT. DVT was present in 18 (34.0%) of the subgroup receiving VTE prophylaxis vs. 35 (63.3%) in the non-prophylaxis group \( P = 0.010 \) |

\( \text{DVT} = \text{deep vein thrombosis} \); \( \text{ICU} = \text{intensive care unit} \); \( \text{LMWH} = \text{low-molecular-weight heparin} \); \( \text{UFH} = \text{unfractionated heparin} \); \( \text{PE} = \text{pulmonary embolism} \); \( \text{VTE} = \text{venous thromboembolism} \).
hospital stay and posttransfusion length of stay were 14.3 days and 11 days, respectively, and there were no significant adverse events. However, patients were concomitantly receiving other treatment such as antivirals, steroids, and immunomodulators. Therefore, the study did not provide satisfactory data because of other confounding factors.

A multicenter open-label randomized control study using a stratified sampling technique based on disease severity showed no improvement in the group that received convalescent products compared with the control group. However, it was shown to be safe with minimal adverse effects. Although CBPs may be useful as a monotherapy or combination with other drugs, there is a lack of robust evidence showing convincing results. Furthermore, data regarding the optimal time of administration, the dosage, and the optimal antibody titer are not available. Therefore, future prospective studies are needed. Furthermore, monoclonal antibody therapy has been used as prophylaxis for COVID-19, and studies are ongoing for identifying and purifying therapeutic neutralizing antibodies.

POSSIBLE HEMATOLOGICAL EFFECTS OF THERAPIES USED FOR COVID-19

The positive and negative hematological effects of medications used to treat COVID-19 are under review. The role of favipiravir and remdesivir in COVID-19 has been studied. Clinicians need to be mindful of potential drug interactions that may exacerbate coagulopathy. An increase in prothrombin time was observed in < 5% of patients receiving remdesivir.

HEMATOLOGICAL ABNORMALITIES AND SEVERITY OF COVID-19

Lymphocytopenia is significantly more common in patients with severe COVID-19. Non-survivors had a lower lymphocyte count and higher prothrombin time than survivors. Antibody synthesizing lymphocytes as a percentage of total lymphocytes were also shown to be predictive of severe disease. D-dimer level is the most useful and consistent marker for identifying COVID-19 disease severity. Yao et al. found a D-dimer level of > 2.14 mg/L to predict hospital mortality, with a sensitivity of 88.2% and specificity of 71.3%.

CONCLUSION

Common hematological abnormalities in COVID-19 are lymphopenia, thrombocytopenia, and elevated D-dimer and CRP levels. These alterations are significantly more common/prominent in patients with severe COVID-19 disease, and thus may serve as a possible biomarker for those needing hospitalization and ICU care. As performing complex tests for identification of coagulation abnormalities is not practical in a pandemic setting, the use of serial D-dimer levels may be considered in view of practical clinical decisions. Close attention needs to be paid to coagulation abnormalities and steps taken to prevent these occurring or to mitigate their harmful effects.

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