Overview of the Haematological Effects of COVID-19 Infection

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Abstract

From its early origins, COVID-19 has spread extensively and was declared a global pandemic by the World Health Organization in March of 2020. Although initially thought to be predominantly a respiratory infection, more recent evidence points to a multisystem systemic disease which is associated with numerous haematological and immunological disturbances in addition to its other effects. Here we review the current knowledge on the haematological effects of COVID-19.

Keywords

COVID-19 · SARS-CoV-2 · Pandemic · Haematology · Immunology · Human immunodeficiency virus · Tuberculosis

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14.1 Introduction

The first cases of COVID-19 were diagnosed in China in November to December of 2019, with patients presenting with severe pneumonia and acute respiratory distress syndrome (ARDS) of uncertain origin [1, 2]. Next-generation sequencing and phylogenetic analysis identified the associated pathogen as a novel β-coronavirus strain which has been called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1].

From its early origins, COVID-19 has spread extensively and was declared a global pandemic by the World Health Organization (WHO) on 11th March 2020. As of 15th November 2020, there have been >53,7 million cases reported worldwide and >1,3 million deaths [3]. Although the majority of people infected with COVID-19 are either asymptomatic or mildly symptomatic (>80%), approximately 19% of patients develop severe to critical illness [2] with a variably reported mortality rate of less than 1% to >16% dependent on the country of origin, the testing strategy adopted, and the manner of calculation of the rate [2, 4, 5].

COVID-19 was initially thought to be predominantly a respiratory infection; however, more recent evidence points to a multisystem, systemic disease which is associated with numerous haematological and immunological disturbances [6, 7]. Very little data on COVID-19 have

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been published from South Africa and the African continent as a whole, although South Africa had the fifth highest number of confirmed cases worldwide in July and still has the highest number of cases on the African continent (>751,000 reported cases as of 15th November 2020) [8]. This region is also known to have the highest number of people living with human immunodeficiency virus (PLWHIV) worldwide at 7,7 million, with a high burden of other infectious diseases (including tuberculosis) [9], which may also associate with haematological and immunological complications. The interaction between these epidemics is uncertain [9, 10].

14.2 Full Blood Count (FBC) Changes Associated with COVID-19

14.2.1 Red Cells

Anaemia may be present in COVID-19 but is frequently only mild to moderate in severity [11–14]. The presence of severe anaemia is thought to infer a poorer prognosis [15]. Anaemia may occur as an autoimmune complication of COVID-19 infection, and autoimmune haemolysis has been described in case studies and case series [16, 17].

Severe COVID-19 may be associated with dysregulation of iron metabolism [18, 19]. This is hypothesized to be due to viral mimicry, as a component of the COVID-19 spike glycoprotein cytoplasmic tail displays significant homology with the hepcidin protein [20]. Hepcidin is a major regulator of iron metabolism, and in conjunction with its target receptor ferroportin, it controls iron exit from cells such as macrophages. COVID-19 is thus associated with intracellular iron accumulation (increased ferritin) and with a corresponding decline in serum iron and haemoglobin levels (likely due to restricted iron bioavailability/ reticuloendothelial iron blockade) [19, 20]. Iron accumulation may also drive a pro-inflammatory phenotype within macrophages and exacerbate the cytokine storm typical of severe disease [20, 21], with a negative impact on prognosis.

14.2.2 White Cells

14.2.2.1 Leukocyte Counts

Total leukocyte counts are variable in patients with COVID-19, ranging from decreased to increased in different patient subgroups [11, 12].

14.2.2.2 Lymphopenia

The most significant change associated with COVID-19 is lymphopenia [6, 7, 22, 23]. This is described in the majority of admitted patients (ranging from 30% to more than 80% of patients) [12, 24–28]. The presence and severity of the lymphopenia, in conjunction with its persistence during disease progression, has a negative prognostic implication [12, 22, 25, 29]. It appears to predict patients who develop severe disease with a higher risk of ARDS and who may require intensive care unit (ICU) admission and ventilation, with a potentially fatal outcome [6, 12, 29].

14.2.2.3 Alterations in Lymphocyte Subsets

Abnormalities of lymphocyte subsets and immunological function are described within the setting of lymphopenia. This is typically due to a decrease in both CD4+ and CD8+ T cell subsets, often with decreases in natural killer and B cells [22, 23, 26, 30]. Associated with this immunological disturbance is the activation of the T cells, with CD4 T cells driving a T-helper cell 1 (TH1)-dependent monocyte and macrophage response [31, 32] and increased cytotoxicity within the CD8-positive subset [33, 34]. This may contribute to the presence of a cytokine storm [35], autoimmune complications [36, 37], and immunological lung injury [34]. The normalisation of these counts, with a decrease in naïve and an increase in certain memory and regulatory subsets, is associated with recovery [22, 34].

14.2.2.4 Neutrophils and Monocytes

Neutrophilia is common in severe COVID-19 disease [22, 23, 29] and reflects the immunological dysregulation. It may also indicate secondary bacterial infection. In contrast, peripheral blood monocyte numbers were reported to be decreased in one study among patients with COVID-19 [38], which is hypothesized to be due to mono-

cyte trafficking into the lungs. Circulating monocytes also display severity-specific immunophenotypic changes, including downregulation of surface HLA-DR expression [39] and an enrichment of a pro-inflammatory CD14+CD16+ monocyte subset [32, 38, 40]. The latter produce interleukin-6 (IL-6) and are likely to be important contributors to the cytokine storm seen in severe COVID-19 infection. The neutrophil–lymphocyte ratio (NLR) [12, 23] and the monocyte–lymphocyte ratio (MLR) may both be increased, which are also thought to be predictive of poorer outcome [41].

14.2.2.5 Changes in Eosinophil and Basophil Counts

Eosinophils and basophils play a role in COVID-19 in driving the immune pulmonary hyper-reactivity which is a feature of more severe disease [42]. Decreased peripheral blood eosinophils and basophils are potential predictors of more severe disease [22, 23], with a normalisation of these counts documented in recovery from COVID-19 [42].

14.2.3 Platelets

Thrombocytopenia may be present, although the prognostic significance differs between studies with some showing no association with severe disease [6, 25, 29] and others suggesting that thrombocytopenia predicts a poorer outcome [12, 14, 24, 43, 44]. Immune thrombocytopenic purpura (ITP) and thrombotic thrombocytopenic purpura (TTP) have been associated as autoimmune complications of COVID-19 leading to decreased platelet counts [45–49]. Disseminated intravascular coagulopathy (DIC) may also contribute to thrombocytopenia [7, 50].

14.3 Peripheral Blood Smear Morphological Findings

Multi-lineage atypical peripheral smear morphological features have been described in COVID-19 patients [51, 52]. Dysplasia is noted within the granulocyte lineage in a large proportion of patients with severe disease, including acquired Pelger-Huët and monolobate neutrophils with left-shift and apoptotic cells [51–53]. Dysplastic platelet morphology has also been reported with large hyperchromatic platelets and pseudopodia formation [52].

Circulating large plasmacytoid lymphocytes [54], plasma cells [27, 53–58], and plasmablasts [27, 51, 57] have been documented morphologically and on printouts from haematology analysers, which is suggestive of COVID-19 infection [55, 56, 58]. However, these cells are not specific for COVID-19 as they have been described in other viral infections, such as HIV [59] and viral haemorrhagic fevers particularly dengue fever [54, 60]. These cells differ from the atypical lymphocytes which more typically associate with other viral infections (such as Epstein-Barr virus and cytomegalovirus) although these later atypical cells may also be seen with COVID-19 infection [27, 54, 56, 57]. Other reactive changes may also be seen, including the presence of atypically large and vacuolated monocytes [40].

14.4 Coagulation Abnormalities

A comprehensive overview of COVID-19-associated abnormalities of coagulation is beyond the scope of this review. In brief, coagulopathy has been described in severe COVID-19 infection, with increased D-dimers [7, 12, 25, 29, 61] and prolongation of the prothrombin time (PT)/international normalized ratio (INR) [29] suggesting a poorer outcome, with possible development of DIC [7, 50]. Arterial and venous thrombosis has been associated with COVID-19 and may contribute to multiorgan failure [62, 63].

14.5 Autoimmune Haematological Complications

The significantly deranged immunological function in patients, particularly those who develop severe disease [35], may manifest in autoimmune

complications including haematological and non-haematological disorders. This is hypothesized to occur through viral molecular mimicry [36, 37, 64]. Viral proteins (such as the viral spike and nucleoproteins) can cross-react with human antigens and may lead to the production of autoantibodies by the host [37, 65]. There have been case reports and case series of autoimmune haematological complications, including autoimmune haemolytic anaemia (AIHA) [16, 17], cold agglutinin disease [16], ITP [45, 46, 48], TTP [47, 49, 66], antiphospholipid antibodies [67, 68], lupus anticoagulant [69], and development of antibodies directed against the endothelium. Formation of antibodies against the endothelium may occur particularly in situations when the vascular endothelium is already activated and under stress due to comorbidities such as diabetes, hypertension, and cardiovascular disease. These may contribute to the development of severe disease, including ARDS, multiorgan failure, arterial and venous thrombosis, and DIC [64].

14.6 Hemophagocytic Lymphohistiocytosis (HLH)

Hemophagocytic lymphohistiocytosis (HLH) is a severe life-threatening disease which may occur as an inherited disorder or as a secondary phenomenon in other conditions, including infections [70]. It is associated with fever, organomegaly, severe cytopenias, increased serum ferritin and triglyceride levels, and multiorgan failure. HLH and macrophage activation syndrome (MAS) have been described in COVID-19 and may reflect the severe hyperinflammatory state [39, 70, 71]. This may contribute to a poor outcome.

14.7 High-Risk Patients with Haematological Disorders

Recent evidence suggests that patients with certain haematological disorders should be considered as being at high risk, in particular, patients with haemoglobinopathies such as sickle cell disease (SSD) and red cell enzymopathies such as glucose-6-phosphate dehydrogenase (G6PD) deficiency [72–74].

COVID-19 infection may interact with SSD in a number of ways. COVID-19 is associated with the development of pneumonia and, in particular, may cause severe hypoxia. Hypoxia increases red cell sickling and haemolysis in patients with SSD, potentiating COVID-19 vascular disturbances and thrombosis, which may contribute to the onset of painful vaso-occlusive crises and acute chest syndrome [74, 75]. Many patients with SSD have chronic lung damage from recurrent acute chest syndrome which may predispose to COVID-19 pneumonia. SSD is associated with auto-splenectomy and immunosuppression which predisposes to severe infections, including bacterial infections which may present with COVID-like symptoms or complicate COVID-19 infection [72, 74]. It has been suggested that haemoglobinopathies, including SSD, should be considered a comorbidity which predisposes to severe COVID-19 disease [76].

G6PD deficiency is the most common enzyme deficiency worldwide and may lead to haemolysis due to infections, including COVID-19 infection [73, 77]. These patients may also be susceptible to haemolysis precipitated by potential drugs researched in the treatment of COVID-19 such as hydroxychloroquine [78].

There is a theoretically increased risk of severe COVID-19 infection in patients with haematological malignancies. However, the presence of immune suppression has been hypothesized to be protective against severe COVID-19 disease. This remains controversial with some studies showing no increased risk of COVID-19 in patients with haematological malignancy [79] and others showing a higher risk of more severe disease [79–81]. Some of the autoimmune haematological complications have been precipitated by COVID-19 in patients with underlying haematological malignancies including lymphoproliferative disorders (such as chronic lymphocytic leukaemia) and multiple myeloma [16].

14.8 COVID-19 and HIV

As COVID-19 is associated with lymphopenia and immunological dysfunction, concern is raised for its interaction with other infections which impair immunological function such as HIV and/or tuberculosis, especially in the setting of comorbid diabetes mellitus. This remains a poorly quantified risk [10, 82, 83], although case studies and small case series, predominantly in higher income countries, suggest that PLWHIV may not be at higher risk of developing COVID-19 or a more severe disease [84–87].

Of particular interest is the similarity noted between the haematological complications of HIV and SARS-CoV-2. Although HIV has a tendency to a more chronic disease course, it associates with many similar features, including lymphopenia, immunological disturbance, molecular mimicry, autoimmune complications (AIHA, ITP, TTP, anti-phospholipid syndrome), morphological dysplasia, coagulopathy, thrombosis, and endothelial activation [88–90]. This suggests that the potential interaction between the viruses may lead to more severe disease or a greater frequency of the above complications.

Data from areas where the majority of PLWHIV reside, such as South Africa, are limited. This is further impacted by socioeconomic issues and healthcare accessibility [10, 82]. Within these regions, not all patients are on effective antiretroviral therapy [9], and patients may not be virologically suppressed or show immunological recovery [82]. This may increase the risk and severity of lymphopenia in COVID-19 infection in PLWHIV with low CD4 T-cell counts. Preliminary data on a small group of PLWHIV in Johannesburg, South Africa, supported findings in other centres of a lack of increased risk in HIV-positive patients [13]. Despite this, early data originating from Cape Town, South Africa, suggests that HIV-positive patients and patients with current or previous tuberculosis are at approximately twofold higher risk of COVID-19-related mortality, particularly if not virologically suppressed and in the presence of lymphopenia with low CD4 T-cell counts [82].

14.9 Haematological Markers of COVID-19 Severity

Although many of the haematological indices may be significantly different when COVID-19 patients are compared to normal controls, the results may still be within the normal reference ranges and may thus not be useful in distinguishing patients with and without COVID-19 [11, 12]. In addition, the differences in counts between COVID-19 patients and patients with other viral causes of respiratory disease (such as influenza) may not be significantly different or useful in distinguishing causes of pneumonia [11].

The most useful parameters in suggesting the presence of COVID-19 and predicting its severity include the presence and severity of lymphopenia and neutrophilia, the NLR, coagulation disturbances, and increase in D-dimers [7, 11, 12, 22, 41, 50, 61].

Table 14.1 summarises the haematological parameters associated with a higher risk of severe COVID-19 infection, which may predict the development of ARDS and increase the risk of ICU admission and mechanical ventilation and potentially a fatal outcome.

14.10 Conclusions

Patients with COVID-19 may have changes in all haemopoietic cell lineages and show atypical peripheral smear morphological findings. Coagulation disturbances are marked, and autoimmune haematological complications are increasingly described. Haematological changes may be suggestive of COVID-19 disease, although they may not be conclusive in confirming the diagnosis. Haematological parameters may also be useful in predicting patients who have more severe disease and may require ICU admission and mechanical ventilation.

Table 14.1 Peripheral blood haematological results in admitted patients with severe COVID-19 disease which may predict ARDS and ICU-admission

Parameter	Comments/Prognostic implications	References
Lymphopenia	Severe lymphopenia, failure of lymphocyte recovery, and/or persistent decline in lymphocyte counts associated with progressive disease and demise	[7, 11, 12, 22, 23, 25, 28, 29, 42]
Lymphocyte subsets	Lower T-cell counts (CD4- and CD8-positive T cells), failure of T-cell subsets, and T-cell activation to normalise and disturbance of memory and regulatory subsets predicts poorer outcome	[22, 26, 30, 34, 42]
Neutrophils and monocytes	Neutrophilia associates with poorer outcome. Increased monocytes with an activated immunophenotype and decreased expression of molecules associated with antigen presentation (HLA-DR) are suggestive of progressive disease and macrophage activation syndrome	[12, 22, 23, 25, 29, 32, 38–40]
Increased NLR and MLR	Suggests more aggressive disease	[7, 11, 23, 41]
Eosinophils and basophils	Decreased circulating eosinophils and basophils have negative prognostic implications. These cells increase with recovery	[22, 23, 42]
Multi-lineage haemopoietic dysplasia, large activated monocytes, and circulating plasmacytoid lymphocytes and plasmablasts	Improvement in dysplasia associates with recovery	[31, 40, 52]
Anaemia and thrombocytopenia	Predictive value is contradictory in different studies. Some studies suggest this is more common in patients requiring ICU admission, although may only be mildly to moderately reduced. More severe anaemia and thrombocytopenia is associated with poorer outcome in some studies	[12, 14, 15, 24, 43, 44]
Iron metabolism	Disturbances in iron metabolism described in COVID-19. Low serum iron associates with a poorer outcome	[18, 19]
Coagulopathy	Raised D-Dimers and prolonged INR associates with poorer prognosis	[7, 12, 24, 25, 29, 50, 61]

ARDS Acute respiratory distress syndrome, *ICU* intensive care unit, *INR* international normalized ratio, *NLR* neutrophil:lymphocyte ratio, *MLR* monocyte: lymphocyte ratio

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15 The Novel Coronavirus and Haemostatic Abnormalities: Pathophysiology, Clinical Manifestations, and Treatment Recommendations

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Abstract

The COVID-19 pandemic, caused by the SARS-C0V-2 virus, was initially considered and managed in a similar manner to the previous SARS epidemic as they are both caused by coronaviruses. What has now become apparent is that a major cause of morbidity and mortality in COVID-19 is abnormal thrombosis. This thrombosis occurs on a macro- and microvascular level and is unique to this disease. The virus has been demonstrated in the endothelium of the pulmonary alveoli and as such is thought to contribute to the devastating respiratory complications encountered. D-dimer concentrations are frequently raised in COVID to levels not frequently seen previously. The optimal anticoagulation treatment in COVID remains to be determined, and the myriad of pathophysiologic effects caused by this virus in the human host have also yet to be fully elucidated.

Keywords

COVID-19 · SARS-CoV-2 · Coagulopathy · Thrombosis · Biomarkers · Treatment

15.1 Background

In December 2019, a disease (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus (SARS-C0V-2), was documented in the city of Wuhan in the Hubei province in China, which rapidly spread to the rest of the world. To date, according to the World Health Organisation (WHO), there have been more than 17 million COVID-19 infections and 677 thousand deaths in 216 countries, with an estimated mortality rate of approximately 3.9% (as of July 31, 2020). As the world struggles with the health, social, and economic impact of this pandemic, the medical fraternity is assessing various aspects of this viral disease with scientific publications

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