Introduction
Since the initial reports of a human-to-human transmissible “pneumonia” in Wuhan, China in December 2019 and the assignment of the name COVID-19 to this disease, the SARS-CoV-2 virus has spread to all continents across the Globe. The number of confirmed cases, recoveries and deaths, continues to rise. At the time of writing, 10 185 633 confirmed cases and 503 862 deaths had been reported globally. In South Africa, 151 209 cases and 2 657 deaths had been reported. COVID-19 continues to cause associated spectacular socio-economic disruption globally.

South Africa’s diversity in terms of the ethnicity and socio-economic status of its inhabitants poses a particular challenge in terms of predicting the epidemiological and clinicopathological direction which COVID-19 will follow. Furthermore, the burden of human immunodeficiency virus (HIV) and tuberculosis (TB) infections, compounded by the high prevalence of non-communicable diseases, increase the difficulty in extrapolating data from other COVID-19 ravaged countries, to the South African situation. COVID-19-related haematological abnormalities are likely to be modified by the aforementioned South African health challenges, and thus it is important to understand their underlying pathophysiological mechanisms. The body of knowledge is expanding rapidly, as is the frenetic profusion of information based on dubious scientific evidence. It is therefore important to separate conjecture and assumption from the evidence-based knowledge regarding the pathophysiology of haematological abnormalities in COVID-19. In this regard, accurate knowledge will help in developing the correct diagnostic, prognostic and therapeutic approaches. The appropriate basic and clinical research questions can then be framed to expand the requisite knowledge.

Haematopoiesis and peripheral blood cell counts
The most common abnormalities of peripheral blood cell counts in COVID-19 infection include lymphopenia, neutrophilia, monocytosis, eosinopenia, mild thrombocytopenia and less frequently, thrombocytosis. A leucoerythroblastic reaction has been reported on the peripheral blood films of COVID-19 patients. One inference which can be drawn is that bone marrow failure purely as a result of COVID-19 is extremely rare.
Platelet changes

In the initial stages of COVID-19, the platelet count may be raised, possibly due to increased levels of thrombopoietin of liver origin as found in past studies on the SARS Coronavirus.15,16 It then gradually declines but the nadir is usually above 50x10^9/L.6,10,11 Several mechanisms may cause the thrombocytopenia, individually or in combination. These mechanisms include direct infection of bone marrow progenitors, stromal cells and megakaryocytes, increased destruction of platelets due to autoantibodies and increased platelet consumption due to lung injury and damaged endothelium.17 There is widespread use of low molecular weight heparin in different settings among critically ill and ICU patients.18 The role of heparin as a contributor to the thrombocytopenia among these patients needs to be elucidated.

Infection of bone marrow stromal cells required for the survival of megakaryocyte progenitors has been reported.19 The inhibitory and apoptotic cytokines produced by these perturbed cells were proposed as a potential mechanism of thrombocytopenia in a SARS Coronavirus study.19 Confirmatory evidence for this mechanism in SARS-CoV-2 infection still needs to be established.

The angiotensin converting enzyme 2 (ACE2) receptor which is found in large numbers on alveolar epithelial cell surfaces and the endothelium of the vascular beds, is the main point of entry for SARS-CoV-2.20,21 An intense inflammatory process, massive cell injury and the secretion of large amounts of various cytokines and other markers of inflammation follows. Coagulation is triggered, with the formation of thrombi in a bid to repair the endotheliopathy.22-24 This process leads to local consumption of platelets with resultant thrombocytopenia. The localised platelet consumption may be associated with release of activated platelets into the circulation, which are destined for destruction and or sequestration.22,25

Leucocyte changes

Lymphopenia

Lymphopenia, the most consistently reported cytopenia in COVID-19, is of multifactorial aetiology including direct infection of lymphocytes,19,26 the effect of abnormal cytokine production,27 migration of lymphocytes to the injured lung tissue,22 and the use of glucocorticoids in the management of COVID-19.1,28 In an elegant study, Chan and Chen showed that the infection of monocytes, macrophages and dendritic cells by the SARS Coronavirus in the absence of any other infection, resulted in lymphocyte death through apoptosis or necrosis.29 The monocytes, macrophages and dendritic cells also produced significant amounts of chemokines and cytokines. This study failed to demonstrate the direct infection of lymphocytes reported by other groups.19,26 Nevertheless, it demonstrated a causal link between the SARS Coronavirus and lymphopenia albeit via other mediators.27

A postmortem study of COVID-19 patients revealed the consistent localisation of lymphocytes in the lungs compared to the control lung tissue from matched patients dying from influenza A (H1N1) and normal organ-donor lungs. The lymphocytes lined the precapillary and postcapillary vasculature which suggests that the COVID-19-infamed lung is a possible site of lymphocyte loss.22 Other studies suggest that exudation of circulating lymphocytes into inflamed lung tissues may further contribute to the loss of lymphocytes.22,24

Glucocorticoids have been used under various settings since the start of this pandemic.5,28 Recently, randomised trials have confirmed the efficacy of glucocorticoids for select patients.29 In these cases, the lymphopenia is therefore, at least in part, due to the use of glucocorticoids.30,31

Lymphocyte subsets

Studies in SARS patients and early studies in COVID-19 showed reduced numbers of T cells (both CD4 and CD8-positive), B cells and natural killer (NK) cells.32,33 In COVID-19, clinical improvement of the patient’s condition has been associated with increased total lymphocyte counts and an increase in the number of B cells and CD8-positive T cells. Poor treatment outcomes have been correlated with reduced B cells, reduced CD8-positive T cells and an increased CD4/CD8 ratio during the course of the illness.33

Granulocyte changes

Several early studies reported neutrophilia and eosinopenia in COVID-19 patients.5,6,9,12,28 Due to the wide variation in the patient populations in the various studies, it is difficult to establish the cause of these granulocyte changes and several mechanisms are likely to be involved. The immune dysregulation with resultant elevated levels of cytokines and chemokines including granulocyte colony-stimulating factor (G-CSF) is at least partially involved in COVID-19-associated neutrophilia. G-CSF stimulates neutrophil progenitor cell proliferation, differentiation and mobilisation. The role of the cytokine storm of COVID-19 in the observed granulocyte morphological changes needs to be elucidated.

Morphological changes in the granulocytic lineage include toxic granulation, left shift, dysplastic features and increased apoptotic leucocytes, which are non-specific features seen in infective/inflammatory states.34,15 These changes do not offer any additional information on the pathophysiology of the neutrophilia and eosinopenia in COVID-19

Erythrocyte changes

Studies reporting on full blood count (FBC) parameters in COVID-19 patients reported at least a percentage of patients with low haemoglobin levels either at admission or during hospital stay.5,7,12 Some studies showed a decrease in patient’s haemoglobin from baseline after ICU admission.5,6 Anaemia in ICU patients is of multifactorial aetiology, with inflammation and occult gastrointestinal blood loss contributing.36 This is aggravated by repeated blood sampling to perform frequent blood gas analysis and other laboratory tests.37,38 An interesting study postulated that iron metabolism dysregulation due to the hepcidin-like effect of SARS-CoV-2 viral spike protein could play a role in COVID-19-associated anaemia. This postulation was
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Thrombosis and thromboembolism

The main reported haemostatic abnormality of COVID-19 is thrombosis with widespread severe endothelial injury and arterial thrombosis occurring in infected and inflamed lung tissue.62-66 Ischaemic cerebrovascular accidents, ischaemic heart disease, mesenteric ischaemia and lower limb ischaemia have also been reported.32,33 In advanced COVID-19 and in the context of the recently hypothesised “viral sepsis”, systemic deposition of thrombi occurs in various other organs.52 This is confirmed by the limited number of post-mortem reports which show widespread vascular thrombosis with microangiopathy and occlusion of alveolar capillaries.22,23,49 Furthermore, post-mortem and other evidence suggests that venous thromboembolism may be a significant contributor to mortality.22,23

Endothelial cell injury and subsequent tissue injury due to circulatory abnormalities cause multi-organ failure.22 The thrombotic tendency in COVID-19 is characterised by the suppression of fibrinolysis due to endothelial dysfunction and increased release of plasminogen activator inhibitor-1 (PAI-1).53 Other reasons for the increased thrombotic risk in COVID-19 include markedly increased Factor VIII and von Willebrand factor levels due to the severe inflammatory response, the reduction of natural anticoagulants due to endothelial cell injury and activation of the complement pathway.46,54-56 Activation of the complement pathway results in platelet activation and increased activity of TF on endothelial cells.54-56 The exact role of platelets in the pathogenesis of thrombosis in COVID-19 is still incompletely understood. However, one study has shown platelet hyperactivation with increased platelet-leucocytes aggregates and increased responses to low doses of agonists.57

SARS Coronavirus directly activates the C3 component of complement which induces an inflammatory response with immune cell recruitment and cytokine release, leading to alveolar and endothelial cell damage.43,58-60 This results in the formation of microvascular thrombi and reduced oxygen exchange.35 In addition to its role in innate immunity, it is well established that complement “cross talks” with the coagulation cascade.

FXa, FVIIa and plasmin may cleave both C5 and C3 and robustly generate C5a and C3a. C5a and C3a are anaphylatoxins that work as chemotaxins and recruit further immune cells.56

The thrombotic risk in these patients is thus multifactorial with a direct endothelial effect of SARS-CoV2, in combination with other risk factors for VTE such as prolonged hospitalisation, hypoxia, mechanical ventilation and superinfection.51,62

Endotheliopathy/Endothelialopathy

SARS-CoV-2 gains entry into vascular endothelial cells via ACE2 receptors.20,21,23 Viral replication in endothelial cells causes an inflammatory cell infiltrate, endothelial cell apoptosis, and microvascular thrombosis.22 This leads to disruption of the endothelial barrier which further increases the risk of thrombosis.64 The inflammatory effects of cytokines result in activated vascular endothelial cells and endothelial cell injury with resultant prothrombotic properties.46,53
Postmortem studies have demonstrated the presence of viral inclusions within endothelial cells, and endothelial cell apoptosis with cellular infiltrates of sequestered mononuclear and polymorphonuclear cells.\(^{22,23,49}\) The endothelial cells showed disruption of intercellular junctions, cell swelling and loss of contact with the basement membrane. This endothelial cell damage is due to the direct effect of the virus as well as perivascular inflammation. One of the main vascular features of COVID-19 patient autopsies as reported by Ackerman et al. was the significant new vessel formation by intussusceptive angiogenesis. Intussusceptive angiogenesis, unlike the usual sprouting angiogenesis, is nonsprouting and is characterised by the presence of a pillar or post spanning the lumen of the blood vessel.\(^{23}\)

**Immune phenomena and their potential influence on haematological findings**

The novel nature of SARS-CoV-2 means that there is a lack of immunity in those it infects for the first time. Toll-like receptors on the surface of macrophages recognise single stranded RNA (ssRNA) from viruses such as SARS-CoV-2. This results in downstream signalling with activation of nuclear factor-kB (NF-kB) that triggers the production of multiple inflammatory cytokines and chemokines.\(^{64,65}\) Patients with severe COVID-19 have elevated blood levels of multiple inflammatory cytokines and chemokines such as interleukin-1β (IL-1β), IL-6, IL-7, IL-8, IL-9, IL-10, G-CSF, granulocyte macrophage colony-stimulating factor, interferon-γ, monocyte chemoattractant protein-1 and macrophage inflammatory protein-1α.\(^{66}\) This virus-induced hyperinflammatory response or cytokine storm shares biological characteristics with the macrophage activation syndrome. The immune dysregulation seen in SARS-CoV-2 infection has been hypothesised to be a major pathogenic mechanism of ARDS in these patients through modulation of pulmonary macrophages, dendritic cells, and/or neutrophils.\(^{67}\) This immune dysregulation in patients with COVID-19 is speculated to be responsible for COVID-19-associated autoimmune disorders including autoimmune haemolytic anaemia (AIHA), immune thrombocytopenia (ITP), antiphospholipid syndrome (APS), Guillain-Barré syndrome and a Kawasaki-like syndrome in children.\(^{68-72}\)

**Autoimmune haemolytic anaemia**

An association between AIHA and Coronavirus infection has been found with both warm and cold antibodies reported.\(^{69,73}\) Various pathophysiological mechanisms, similar to those established in other forms of virus-associated AIHA, have been postulated although no specific SARS-CoV-2 link has been established.

**Immune thrombocytopenia**

There are reports of ITP in patients with COVID-19,\(^{72}\) however, the causal link between SARS-CoV-2 and ITP is yet to be established. The same pathophysiological mechanisms as in virus-associated ITP, have been proposed and require further investigation.\(^{75}\)

**Antiphospholipid antibody syndrome**

Reports have shown that COVID-19 patients may develop anticardiolipin antibodies as well as anti-β₂ glycoprotein I, IgA and IgG antibodies.\(^{78}\) In one study, 20% of COVID-19 patients had a prolonged aPTT, and the majority of the patients were found to have lupus anticoagulants.\(^{74}\) However, these antibodies commonly arise transiently in patients with critical illness and various infections.\(^{75}\) If persistent, these antibodies may be associated with the thrombotic tendency of antiphospholipid syndrome. However, it is difficult to differentiate the role of these antibodies from other causes of thrombosis in critically ill patients with or without SARS-CoV-2 infection.\(^{70}\)

**Guillain–Barré syndrome**

Guillain-Barré syndrome (GBS) is an acute severe paralytic neuropathy in which the immune system attacks the peripheral nerves due to molecular mimicry. GBS is typically a post-infectious disorder with possible genetic susceptibility.\(^{76}\) An association between GBS and Coronavirus infections has been reported.\(^{71}\)

**Kawasaki-like disease**

Kawasaki disease (KD) is an acute vasculitis of medium-sized blood vessels most common in children.\(^{77}\) The aetiology of KD is not clearly understood, however, data suggests an underlying genetic susceptibility with an additional superimposed infectious trigger.

Verdini et al. reported on 10 cases of a Kawasaki-like syndrome during the SARS-CoV-2 pandemic in Bergamo province, Italy.\(^{68}\) They demonstrated a 30-times greater incidence of KD compared to the age-matched population. SARS-CoV-2 is thus regarded as a trigger of KD. The exact pathophysiology of the leucopenia, severe lymphopenia and thrombocytopenia, which have all been described in KD, is not yet clear in the context of COVID-19.\(^{68}\) Many features of the Kawasaki-like syndrome are similar to the cytokine storm of COVID-19.

**Conclusion**

Substantial valuable information regarding the widespread effects of SARS-CoV-2 on human haematology has been published. A key objective of this review is to provide an inclusive current summary of the areas of established, hypothetical and unknown pathophysiological processes involved in the haematological changes seen in COVID-19 patients. The development of appropriate diagnostic, prognostic and therapeutic interventions in COVID-19, depends on a clear understanding of the pathophysiology of the disease.

**Conflict of interest**

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