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Cover Page Footnote

I would like to acknowledge Cork University Hospital haematology department for providing me with the opportunity of undertaking this research project.

Haematological Tests: Important Tools for Covid-19 Prognosis?

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ABSTRACT

SARS Co-V2 virus outbreak has resulted in a worldwide pandemic causing the death of approximately 5 million across the globe. The virus particle is transmitted via air droplets or by direct contact with surfaces. Infected individuals may present with moderate flu-like symptoms or may remain asymptomatic. While most cases of SARS Co-V2 resolve, some patients may progress to acute respiratory distress syndrome (ARDS). The onset of ARDS is associated with a broad range of complications leading to increased morbidity and mortality. Sepsis induced coagulopathy is a clinically significant complication associated with the development of ARDS. Approximately 3% of Covid-19 patients will progress to disseminated intravascular coagulopathy, characterised by widespread hypercoagulation. The pathogenesis of coagulopathy is inflammatory mediated and is associated with mass accumulation of cytokines as seen in cytokine storms.

The aim of this literature is to evaluate the prognostic capability of haematological parameters in SARS Co-V2 infection. While there is no definitive haematological pattern, the effect of SARS Co-V2 infection on routine haematological tests is well documented. Approximately 80% of SARS Co-V2 patients present with lymphocytopenia, which may be accompanied by inflammatory related alterations in the cellular population. Covid-19 induced coagulopathy can be monitored using routine coagulation parameters. Poor prognostic outcomes are associated with elevations in prothrombin time, fibrinogen, fibrin degradation products, and D-dimer concentration. The degree of inflammatory mediated dysplasia seen in blood film examination may be used to assess magnitude of immune system dysregulation and severity of respiratory distress. A panhaemocyometric approach examining leukocytes, erythrocytes and thrombocytes is advisable considering SARS Co-V2 infection causes widespread alterations in cellular morphology and number in cell populations.

KEYWORDS: SARS Co-V2 prognosis, complete blood count, advanced haematological tests, coagulation tests, blood film

INTRODUCTION

Coronaviruses (CoVs) are enveloped, positive-sense, single-stranded RNA viruses with characteristic spike glycoproteins that radiate outward when visualized by electron microscopy (Almeida and Tyrrell, 1967). There are four genera of *Coronaviridae*: alpha-, beta-, gamma-, and delta-coronavirus; and in the context of human disease, alpha-coronaviruses and betacoronaviruses can emerge from animal reservoirs as major pathogens (Ye *et al.*, 2020).

To date, there are seven coronaviruses associated with disease in man; four viruses, hCoVHKU1, hCoV-OC43, hCoV-NL63 and hCoV-229E, cause asymptomatic or mild respiratory and gastrointestinal infections, accounting for approximately 5–30% of common colds (Pyrc *et al.*, 2007). The remaining human coronaviruses – SARS-CoV-1, MERS-CoV, and SARS-
CoV-2 – are recognised as highly pathogenic and potentially life-threatening agents (Chen *et al.*, 2020).

SARS-CoV-2, the causative agent of COVID-19, first emerged as an infectious agent of concern in Wuhan, China in December 2019 (Huang *et al.*, 2020). Since then, SARS-CoV-2 has spread rapidly and aggressively and was documented as a public health emergency of international concern and a pandemic on 30th January and 11th March 2020, respectively (World Health Organisation, 2021). As of 1st April 2022, SARS-CoV-2 infection has resulted in over 486 million cases of COVID-19 reported to the World Health Organisation, including over 6 million confirmed deaths (World Health Organisation, 2021).

COVID-19 is associated with a broad range of non-specific symptoms, including headache, sore throat, and fever (Guan *et al.*, 2020). SARS-CoV-2 utilises angiotensin converting enzyme 2 (ACE2) as a cellular entry receptor (Hoffmann *et al.*, 2020), which is commonly found in human epithelial tissue (Wong and Saier, 2021), enabling cellular attachment and cellular infection. As infection progresses, the adaptive immune response is evoked leading to cytokine and antibody response (Aleksova *et al.*, 2021). Although most patients with COVID-19 are either asymptomatic or present with moderate illness, many cases result in severe disease warranting hospitalisation (Li *et al.*, 2021). Patients with severe disease may develop lifethreatening complications associated with the onset of acute respiratory distress syndrome (ARDS) due to cytokine storms (Vinayagam and Sattu, 2020), in addition to acute kidney injury, septic shock and multi-organ dysfunction (Liao *et al.*, 2020).

Due to the labile natural history of COVID-19, it is critical that SARS-CoV-2 patients are closely monitored, with those presenting with cytokine storm-associated ARDS of greatest concern (Ragab *et al.*, 2020). As such, laboratory testing is critical to diagnose patients with SARS-CoV-2 infection, differentiate mild, moderate, and severe disease, and to evaluate prognosis and recovery. The profound inflammatory response associated with COVID-19 appears to induce an aberrant haematologic and haemostatic system, characterised by abnormal haematological parameters (Rahman *et al.*, 2021). This review aims to examine the effect of SARS-CoV-2 infection on traditional and novel haematological parameters, which could serve as rapid diagnostic and prognostic indicators of SARS-CoV-2 infection, in conjunction with molecular testing.

IMMUNE RESPONSE TO COVID-19 INFECTION

To understand the aberrant haematologic and haemostatic system of COVID-19, it is important to address immune system activation in response to SARS-CoV-2 infection.

Innate immune response

SARS-Co-V 2 infection stimulates both an innate and adaptive immune response (Shi *et al.*, 2020). Pathogen pattern receptors, such as Toll-like receptors, are responsible for the

recognition of the virus particle, which leads to expression of interferons, cytokines, and chemokines (Perico *et al.*, 2021). Activated macrophages are a critical feature of the hyperinflammatory state seen in patients with COVID-19, with evidence to suggest direct viral activation of macrophages in the peripheral circulation (Wang *et al.*, 2020). Analysis of bronchiolar lavage fluid reveals the presence of pro-inflammatory monocytes, infiltrative neutrophils, and monocyte-derived macrophages (Bost *et al.*, 2020; Zhou *et al.*, 2020). Activation of neutrophils, accompanied by the formation of neutrophil extracellular traps (NETs), is associated with a heightened cytokine response, manifesting as a cytokine storm (Barnes *et al.*, 2020). As such, it appears an inappropriately exaggerated innate response contributes the hyperinflammatory state in SARS-CoV-2 patients.

Adaptive immune response

SARS-CoV-2 infection elicits both T-cell- and B-cell-mediated lymphocyte responses (Chen and Wherry, 2020; Röltgen and Boyd, 2021). Lymphopenia, characterised by reduction in the absolute CD4+ and CD8+ lymphocyte count, is a common feature in COVID-19 patients (Perico *et al.*, 2021). T-cells display reactivity towards the spike glycoprotein of the virus particle, suggesting the spike protein is the primary target for adaptive T-cell-mediated response (Taborska *et al.*, 2021). T-cell mediated response is typically rapid with CD4+ and CD8+ cells identified 1 - 4 days post-onset of symptoms (Rydyznski Moderbacher *et al.*, 2020; Schulien *et al.*, 2021). The CD4+ immune response appears to be more prominent than that of the CD8+ in COVID-19 patients (Grifoni *et al.*, 2020). CD4+ cells can differentiate into Th1 cells and T follicular helper cells (Tfh), responsible for production of inflammatory cytokines and aiding the humoral response, respectively (Sette and Crotty, 2021). Rapid CD4+ response is a positive prognostic factor for SARS CoV-2 patients, extended absence of these cells is associated with increased severity and mortality (Braun *et al.*, 2020). Similarly, the presence an adequate CD8+ response is associated with better prognostic outcomes (Sette and Crotty, 2021). CD8+ lymphocytes are responsible for a variety of cytotoxic functions, such as the release of IFN-γ, perforin, and granzyme B (Schulien *et al.*, 2021).

B-lymphocyte immune response produce neutralising antibodies against the COVID-19 antigen (Röltgen and Boyd, 2021). The ACE2 receptor binding domain of the SARS-CoV-2 spike glycoprotein is highly immunogenic and stimulates a potent immune reaction, converting naïve B cells to active antibody secreting B cells (Sette and Crotty, 2021). There is a correlation between viral antigen titre and neutralising antibody titre, like other viruses of the *coronaviridae* family, such as SARS Co-V and MERS (Sariol and Perlman, 2020). Several monoclonal antibodies targeting epitopes seen on SARS Co-V virus particle, demonstrate cross reactivity (Hoffmann *et al.*, 2020). Initial humoral response comprises of IgA and IgM antibodies, while IgG antibodies may be detected in the serum of SARS Co-V patients two weeks following symptom onset (Guo *et al.*, 2020). Rise in antibody titre is associated with presence of plasma cells in the peripheral blood (Arashkia *et al.*, 2021).

Role of traditional and advanced haematological parameters

Beckmann Coulter haematology analysers allow for advanced haematological testing based on VCS technology, cells are characterised based on their volume, conductivity, and scatter (Vasse *et al.*, 2021). In addition to volume and conductivity there are several measures of scatter employed by these analysers including median angle light scatter (MALS), lower median angle

light scatter (LMALS), low angle light scatter (LALS) and upper median light scatter (UMALS) (Jean *et al.*, 2011). SYSMEX haematology analysers can be used to provide necessary morphology details on leukocytes, enabling identification of altering leukocyte morphology. These analysers discriminate cellular populations based on internal cellular complexity, nucleic acid content and cell size (Urrechaga *et al.*, 2021). Given that SARS-CoV2 infection stimulates an extensive immune response, and the magnitude of immune system activation shows correlation with severity of respiratory distress, these advanced haematological parameters could prove to be important prognostic tools for ARDS associated with SARS-CoV-2 infection.

Effect on routine coagulation tests

Routine coagulation tests may be used as early indicators of coagulation defects associated with SARS-CoV-2 infection (see Figure 1.1). Sepsis-induced coagulopathy is a serious complication seen in patients with severe COVID-19 (Hosseini *et al.*, 2021).

Parameters	SARS-CoV-2 patients (n=94)	Controls (n=40)
APTT, s	29.01±2.93	28.65±3.03
AT, %	85.46±14.43	98.82±12.91
D-dimer, mg/L	10.36±25.31	0.26±0.18
FDP, mg/L	33.83±82.28	1.55±1.09
FIB, g/L	5.02±1.53	2.90±0.53
PT, s	12.43±1.00	12.08±5.28
PT-INR	1.07±0.09	1.05±0.49

Figure 1.1 Comparison of the coagulation parameters of SARS Co-V2 patients and healthy individuals (Han et al., 2020)

Prothrombin Time and Activated Partial Thromboplastin Time

Many studies report a prolongation of the PT in SARS-CoV-2 patients correlating with more severe illness (Han *et al.*, 2020; Huang *et al.*, 2020; Wan *et al.*, 2020), although other studies report no significant difference between critical and non-critical cases (Gao *et al.*, 2020; Wang *et al.*, 2020; Wu *et al.*, 2020). Despite these findings, elevated PT is associated with increased ICU admissions (Luo *et al.*, 2020). Prolonged activated partial thromboplastin time (APTT) may be indicative of increased risk for these patients (Wan *et al.*, 2020; Wu *et al.*, 2020), although other studies report no significant increase or even a decrease in APTT in critical COVID-19 cases (Tang *et al.*, 2020; Wu *et al.*, 2020). Thus, the association between APTT and COVID-19 severity is complex and may rely on other factors. Many COVID-19 patients admitted to hospital, present with PT and APTT values within the reference range of healthy individuals, therefore baseline PT and APTT values have limited use as early prognostic markers for coagulopathy in SARS-CoV-2 patients (Luo *et al.*, 2020).

Fibrinogen

There is conflicting evidence regarding fibrinogen as a prognostic marker for SARS-CoV-2 patients, although it is suggested that increased fibrinogen may be indicative of severe cases, the significance of fibrinogen as an isolated prognostic marker of COVID-19 induced coagulopathy is questionable (Han *et al.*, 2020; Luo *et al.*, 2020).

Fibrin degradation products

The concentration of fibrin degradation products is higher in COVID-19 patients than in healthy individuals, with critical COVID-19 cases exhibiting the most elevated FDP concentrations (Han *et al.*, 2020). Thus, FDP may be used to monitor gradual progression of coagulopathy in COVID-19. Although there is a positive correlation between increased FDP and the D-dimer concentration, the D-dimer is a more specific marker of COVID-19-induced coagulopathy (Asakura, 2014).

D-dimer concentration

D-dimer is a haematological parameter used to monitor the coagulation system, elevation in this degradation product is indicative of activation of the coagulation system (Sathe and Patwa, 2014). Morbidities caused by SARS-CoV-2 infection have a greater likelihood of an increased D-dimer concentration (Li *et al.*, 2020). The D-Dimer concentration has been reported to increase by as much as five-fold the upper limit of normal in those with severe respiratory disease and is significantly greater than those with moderate respiratory illness (Huang *et al.*, 2020). SARS-CoV-2-induced activation of the coagulation system is associated with pulmonary embolism (Vinayagam and Sattu, 2020). However, thrombosis is not limited to the lungs; blood clots in the large arteria of the brain may lead to ischemic stroke (Qureshi *et al.*, 2021).

Disseminated intravascular coagulopathy (DIC) is characterised by widespread deposition of fibrin in the coagulation system and has been highlighted as a potential complication associated with SARS-CoV-2 infection (Asakura, 2014). Meta-analysis reveals approximately 3% of COVID-19 patients develop DIC (Zhou *et al.*, 2021). Although DIC is regarded as a systemic coagulation disorder, it is possible that coagulopathy begins in the lungs in SARS-CoV-2 patients and spreads systemically to other organs (Magro, 2020). A significant elevation in Ddimer concentration is observed in critically ill patients (Luo *et al.*, 2020). Important markers for coagulopathy are fibrin degradation products (FDP) and D-dimer (Hong *et al.*, 2021). COVID-19 patients suffering from coagulopathy may exhibit increased FDP and D-dimer concentrations accompanied by prolonged prothrombin time (PT) and prolonged activated partial thromboplastin time (APTT) (Han *et al.*, 2020).

Patients with severe illness and markedly elevated D-dimer concentration may benefit from treatment with low molecular weight heparin (LMWH) (Tang *et al.*, 2020). Treatment with heparin inhibits platelet aggregation and blood coagulation, thereby stalling the pathogenesis of SARS-CoV-2-induced coagulopathy (Zhou *et al.*, 2021). This therapy should however be limited to patients meeting the criteria for coagulopathy and elevated D-dimer concentrations. By monitoring the D-dimer concentration, it may be possible to assess the risk of a thrombotic

event for patients with COVID-19 and to determine the possible eligibility of said patients for anticoagulant therapy.

POTENTIAL AETIOLOGY OF COVID-19-INDUCED COAGULOPATHY

Cytokines have been identified as important mediators of the coagulation cascade (Levi *et al.*, 2003). In a cytokine storm, there is release of a broad range of cytokine such as IL-A, IL-B, IL-6, IL-7, IL-8 and TNF-α (She *et al.*, 2020). There is a correlation between increased IL-6 levels and serious complications associated with SARS-CoV-2 infection, this is as expected as increased levels of IL-6 and IL-8 correlate with increased risk of coagulation events such as venous thromboembolisms (VTEs) (van Aken *et al.*, 2002). IL-6 induces the expression of tissue factor, increases the expression of fibrinogen, factor VIII, von Willebrand's factor (vWf) and has been reported to reduce the expression of haemostasis inhibitors such as anti-thrombin and protein S (Kerr *et al.*, 2001). IL-6 STAT signalling has been identified as a potential cause of acute respiratory syndrome through activation of cytokine storms (Zhou *et al.*, 2020). IL-6 acts as an amplifier for inflammation causing increased levels of serum angiotensin II (Ang II), and reduced expression of ACE2 due to interaction between the virus spike protein and ACE2 receptors (Hojyo *et al.*, 2020). Ang II is a pro-inflammatory cytokine; Ang II increments are associated with lung injury (Kuba *et al.*, 2006). Therefore, it is plausible that Ang II could be used as a predictive marker for SARS-CoV-2 severity (Hojyo *et al.*, 2020). However, it is IL8 which displays the most prominent procoagulant activity activating thrombin, fibrin and promoting platelet activation (Magro, 2020). Based on this evidence, it is possible to suggest cytokine storms releasing inflammatory interleukins such as IL-6 and IL-8 may be responsible for hypercoagulation events seen in COVID-19 patients.

As mentioned previously, COVID-19 infection elicits a hyperinflammatory state characterised by cytokine storm-mediated organ damage. Despite this potent inflammatory response, lymphocytopenia is a common feature amongst COVID-19 patients, contributing to increased risk of mortality and morbidity (Vardhana and Wolchok, 2020). While cytokine stormmediated coagulopathy is still believed to be the primary cause of SARS-CoV-2-induced ARDS, depletion of lymphocytes leading to host cell immunity may also prove significant (Laterre *et al.*, 2020). COVID-19 patients with dramatically reduced lymphocyte counts demonstrate impaired immune competence and are at greater risk of acquiring secondary infections (Ripa *et al.*, 2021). The importance of host immunity as a prognostic factor in SARSCoV-2 patients is highlighted by IL-7 therapy, interleukin-7 (IL-7) contributes to increased lymphocyte survival and expansion (Mackall *et al.*, 2011). IL-7 therapy has demonstrated its importance in increasing CD4+ CD8+ lymphocytes by 3-4-fold, contributing to restoration of the adaptive immune response (Francois *et al.*, 2018). Critical COVID-19 patients treated with IL-7 therapy demonstrate a restored lymphocyte count without IL-7 contributing to increased hyperinflammation and lung damage (Laterre *et al.*, 2020). Thus, IL-7 therapy appears to be a promising treatment option for SARS-CoV-2 patients exhibiting lymphocytopenia.

EFFECT OF ON LEUKOCYTE PARAMETERS

Granulocytes

Patients with COVID-19 typically present with neutrophilia and an increased neutrophillymphocyte ratio (NLR) (Cavalcante-Silva *et al.*, 2021). Cell population data

parameters are emerging as novel indices of immune cell activation (Hoffmann, 2014; Harte and Mykytiv, 2021). Sysmex XN-series analysers provide morphological and functional data relating to the internal cellular complexity (SSC), nucleic acid content (FSL), and cellular size (FSC) (Urrechaga *et al.*, 2021). Neutrophil cell population data parameters, including NE-SSC, NEFSC, and NE-FSL, are significantly different in between COVID-19 patients and non-COVID19 patients (Harte and Mykytiv, 2021; Pozdnyakova *et al.*, 2021). However, these results should be interpreted in the context of the peripheral blood film. The neutrophils exhibit evidence of a reactive blood picture, containing cytoplasmic vacuoles, toxic granulation, and heavily clumped chromatin (Singh *et al.*, 2020). Cells indicative of a left shift in the myeloid line, such as myelocytes and promyelocytes, may appear in a blood film (Vadillo *et al.*, 2021). The presence of immature erythroid and immature myeloid cells suggests a leucoerythroblastic blood picture may be associated with SARS-CoV-2 infection (Mitra *et al.*, 2020). Immature granulocytes (IG), such as metamyelocytes, myelocytes and promyelocytes, can be used to monitor the pathogenesis of sepsis; IG% of greater than 3% is linked with increased risk of sepsis (Ayres *et al.*, 2019). Thus, monitoring abundance of immature granulocytes in SARSCoV-2 patients can monitor progression of sepsis and enable intervention (Jeon *et al.*, 2021). This is particularly relevant to critical COVID-19 cases which may progress to sepsis and septic shock (Olwal *et al.*, 2021). Reduced basophil count may be a poor prognostic feature for SARS-CoV-2 patients due to their role in innate immune response; similarly, eosinopenia may be associated with poorer patient outcomes (Sun *et al.*, 2021; Xie *et al.*, 2021).

Lymphocytes

Approximately 80% of SARS-CoV-2 patients display lymphocytopenia which may cause leukocytopenia (Lee *et al.*, 2021). Lymphocyte counts of less than 1 x 10^9 /L are associated with SARS-CoV-2 patients suffering from severe respiratory disease (Singhal, 2020). Thus, there is greater incidence of lymphocytopenia seen in COVID-19 patients admitted to ICU (Ziadi *et al.*, 2021). The reactive lymphocyte subset is largely comprised of antibodysynthesizing lymphocytes, suggesting that the immune response to SARS-CoV-2 infection may be predominantly B-cell-mediated rather than T-cell (Linssen *et al.*, 2020). Increased activation of lymphocytes has been well documented in COVID-19 infection (Fan *et al.*, 2020). Sysmex XN-series analysers differentiate leukocytes according to fluorescent properties, generating a leukocytic differential scattergram (Kawauchi *et al.*, 2014). In COVID-19, the lymphocyte clusters in the differential scattergram resemble an atypical ‘’sandglass’’, this finding is suggestive of the presence of plasmacytoidal lymphocytes in the peripheral blood (Osman *et al.*, 2020).

These findings are consistent with evidence gathered from blood film examination. SARSCoV-2 patients may exhibit atypical reactive lymphocytes or plasmacytoidal lymphocytes, characterised by an eccentric nucleus and basophilic cytoplasm (Foldes *et al.*, 2020). Large granular lymphocytes may be present containing nuclei with condensed chromatin and azurophilic cytoplasmic granules (Singh *et al.*, 2020).

Monocytes

Initially these patients may present with monocytopenia followed by a subsequent monocytosis (Singh *et al.*, 2020). Patients with critical respiratory symptoms display monocytosis, with a marked elevation in reactive monocytes seen (Linssen *et al.*, 2020). Advanced haematology

parameters reveal increased fluorescent intensity monocytes (MO-FSL) in COVID-19 patients in comparison to non-COVID-19 patients, indicating these monocytes may be more transcriptionally active (Pozdnyakova *et al.*, 2021). In addition, patients with COVID-19 have monocytes of increased intracellular complexity, as measured by an elevated MO-SSC score on the Sysmex XN-series analysers (Harte and Mykytiv, 2021). Changes in this advanced haematological parameter are present in 86% of COVID-19 patients (Harte *et al.*, 2021 [unpublished]), and is the haematological parameter of greatest diagnostic utility at admission (Harte and Mykytiv, 2021). Moreover, Beckmann Coulter haematology analysers allow for advanced haematological testing based on VCS technology, whereby cells are characterised based on volume, conductivity, and light scatter (Vasse *et al.*, 2021). Changes in monocyte cell population data on the Beckman Coulter series analysers, particularly the monocyte distribution, has been shown to predict COVID-19 severity (Ognibene *et al.*, 2020; Vasse *et al.*, 2021).

Large atypical, activated monocytes have also been reported in the peripheral blood of COVID19 patients, these cells are CD90+ CD206+, indicating they are inflammatory monocytes (Zhang *et al.*, 2021). The peripheral blood of SARS-CoV-2 shows significant expansion of CD14+CD16+ monocytes which as responsible for producing IL-6 (Y. Zhou *et al.*, 2020). The monocytic nuclei are large with condensed chromatin, monocytes may display granulation and prominent cytoplasmic vacuolisation (Singh *et al.*, 2020). Large, atypical monocytes are indicative of monocyte activation and accumulation of inflammatory cells as seen in a cytokine storm (Vanderbeke *et al.*, 2021)**.** Blue-green cytoplasmic inclusions within monocytes and/or neutrophils have been reported in Covid-19 patients (Cantu *et al.*, 2020). Such neutrophilic inclusions were previously associated with acute hepatic failure and multiorgan failure, contributing to significant morbidity and mortality (Soos *et al.*, 2019). Although the pathogenesis of blue-green inclusions within neutrophils and monocytes is not fully understood, presence of such inclusions is indicative of poor prognostic outcome in Covid-19 patients (Cantu *et al.*, 2020)**.**

Analysis of bronchoalveolar fluid highlights an increased proportion of mononuclear phagocytes, cells which are associated with SARS-CoV-2 inflammation (Kvedaraite *et al.*, 2021). This is accompanied by a reduced count of tissue resident macrophages and presence of inflammatory macrophages derived from monocytes (Merad and Martin, 2020). Accumulation of neutrophils and myeloid cells in the lung may be indicative of local inflammation associated with acute lung injury (Rodriguez *et al.*, 2020).

EFFECT ON ERYTHROCYTE PARAMETERS

Hospitalized SARS-CoV-2 patients exhibit a reduction in haemoglobin concentration, typically critical cases and non-critical cases can be differentiated by a marked reduction in haemoglobin concentration in critical cases after day 5 of hospitalisation (Linssen *et al.*, 2020). Critical SARS-CoV-2 patients exhibit an increased reticulocyte response after day 7 of hospitalisation in comparison with non-critical SARS-CoV-2 patients, a sharp increase in NRBC is seen in critical cases during this period (Linssen *et al.*, 2020). Increased NRBC in the peripheral blood of SARS-CoV-2 patients is indicative of bone marrow stress (Purtle *et al.*, 2017)**.** The prevalence of nucleated red cells in the peripheral blood may be used as prognostic tool to access risk of mortality associated with ARDS (Menk *et al.*, 2018)**.** Although the underlying

cause of NRBC release into the peripheral blood of ARDS patients is not fully understood, it is believed systemic inflammation and arterial hypoxemia are triggering factors (Danise *et al.*, 2011). Mushroom shaped erythrocytes known as Pincer cells have been reported in the peripheral blood of COVID-19 patients (Gérard *et al.*, 2021). These cells are indicative of oxidate stress and are also seen in cases of Protein Band 3 deficiency as seen in hereditary spherocytosis (Gérard *et al.*, 2021). The pathophysiology of SARS-CoV-2 infection involves oxidative stress induced cytokine storm, which may cause damage to the erythrocytes, altering their morphology see figure 1.2 (Dienstmann *et al.*, 2021).

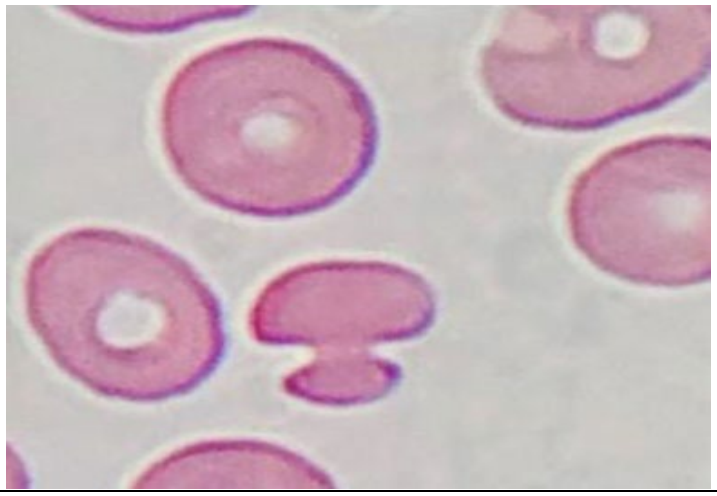

Figure 1.2 *Pincer erythrocyte in the peripheral blood of a SARS CO-V2 patient (taken from Deinstmann et al 2021).*

Effect on platelet parameters

The correlation between disease severity and platelet count is not clear, with reports presenting conflicting evidence regarding its use as a prognostic marker (Luo *et al.*, 2020; Wan *et al.*, 2020). Initially, COVID-19 patients may present with platelet counts within the reference range of a healthy individual (Harte and Mykytiv, 2021). Many ARDS patients suffer from thrombocytopenia characterised by a platelet count <140 x 10^9/L, this may be followed by reactive thrombocytosis where there is further elevation in the platelet count (Wong *et al.*, 2003). This may help to explain the fluctuation in platelet count associated with ARDS, and the inconsistent reports on the utility of platelets as prognostic markers. Based on this evidence, using platelet counts alone may not be appropriate for monitoring coagulopathy associated with COVID-19-induced ARDS. SARS-CoV-2 patients display thrombosis, with hospitalisation cases demonstrating an elevated platelet-lymphocyte ratio (PLR) outside the typical range (Linssen *et al.*, 2020).

CONCLUSION

Deviations in the cellular population are evident across all cell lines, thus it is advisable to adopt a panhemocytometric approach when considering prognosis SARS Co-V2 patients. Although haematological tests may serve as prognostic tools for SARS Co-V2 patients, prognosis may vary based on a wide range of parameters such as demographic factors relating to patient age, gender, smoking and patient history factors referring to patient's underlying conditions

(Patanavanich and Glantz, 2021; Zandkarimi *et al.*, 2022). Thus, these factors should be considered when accessing prognostic outcome. Increased or prolonged coagulation tests may be utilised to monitor pathogenesis of COVID-19 induced coagulopathy. Monitoring such patients enables earlier intervention and enhanced prognostic outcomes. The aetiology of SARS Co-V2 induced coagulopathy is mediated by atypical cytokine storms. Advanced haematological parameters enable characterisation of activated and reactive cells, thus accessing the magnitude of immune dysregulation, which offers prognostic utility. These parameters may be interpreted in conjunction with cellular morphology seen in blood film examination. Alterations in cell number, typically characterised by lymphocytopenia and increased neutrophil:lymphocyte ratio offer prognostic value for SARS Co-V2 patients.

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