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Review Article

Pathology Section

Novel Coronavirus Infection: A Review on Haematological Markers of Disease Severity

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ABSTRACT

The Corornavirus Disease (COVID-19) virus infection has a wide range of presentation- asymptomatic, mild, severe and critical forms that often lead to death from respiratory failure. There is a strong relationship between the severity of COVID-19 infection and some haematological parameters. Patients often present with lymphocytopenia at diagnosis despite having a normal total white cell count. The degree of lymphocytopenia could predict the progression to pneumonia and subsequent need for ventilator support due to respiratory failure. Apart from lymphocytopenia, thrombocytopenia has been linked with increased severity of COVID-19 symptoms. The lymphocyte-platelet ratio has been found to a better marker for disease severity than isolated lymphocytopenia or thrombocytopenia. COVID-19 patients have been found to be at increased risk of Venous Thromboembolism (VTE). There is elevation of D-dimers, abnormalities of the Prothrombin Time (PT) and activated Partial Thromboplastin Time (aPTT) among hospitalised COVID-19 patients. This has necessitated the use of prophylactic anticoagulation even in the early phases of the infection.

Keywords: Anticoagulation, Coagulopathy, Corornavirus disease, Lymphocytopenia, Pneumonia, Thrombocytopenia

INTRODUCTION

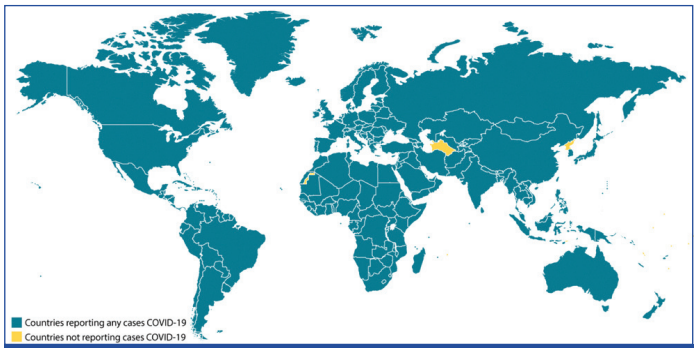
Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) disease also known as COVID-19 was first reported in China in December, 2019 [1]. There were several cases of pneumonia noticed among the residents of Wuhan, China which later on spread to other countries and in March 11 2020, World Health Organisation (WHO) declared this novel coronavirus as a pandemic. COVID-19 has affected millions worldwide and has led to death of thousands. As on 18th July, 2020 about 14, 106, 753 confirmed cases with mortality of 602, 656 globally were recorded [2]. The novel coronavirus is an infectious disease affecting the respiratory system presenting as cough, fever, breathlessness and in severe cases as pneumonia. Other symptoms include anosmia and dysgeusia, headaches, abdominal pain, fatigue, haemoptysis, diarrhoea and chest pain [3,4]. Transmission of this virus is from human to human via droplets from coughing or sneezing.

It is obvious that COVID-19 infection affects other systems outside the respiratory system. The haematological and coagulation systems are commonly affected. The D-dimer level is often elevated and abnormalities of the coagulation system manifesting as Disseminated Intravascular Coagulopathy (DIC) or VTE are often diagnosed. COVID-19 has also been well described as causing a proinflammatory and hypercoagulable state with marked elevations in Lactate Dehydrogenase, Ferritin, C-reactive protein, D-Dimer, and Interleukin levels IL-2R, IL-6, IL-10, and Tumour Necrosis Factor alpha (TNF-α) [5,6]. With this knowledge, one is left to ask how these haematological markers could help clinicians to predict the severity and prognosis of patients who are newly diagnosed with COVID-19. An in-depth review of the haematological markers of COVID-19 severity is presented in this paper.

EPIDEMIOLOGY AND SPREAD

All races are affected. The natural reservoirs of COVID-19 are the bats as seen in other epidemics of coronaviruses- SARS CoV-1 and Middle East Respiratory Syndrome (MERS). The SARS CoV-2 may have undergone mutation in order to infect man. Investigations are currently on-going to find other animal sources of corona virus. The spread of this virus is from human to human and many infected individuals have died from complications of the infection [7-9]. Those patients with severe forms of COVID-19 are known to shed the virus more than the asymptomatic or mild cases [10]. The predominant mode of transmission of the virus is via respiratory droplet, contact with a sufferer or an asymptomatic carrier.

COVID-19 has an incubation period of 1 to 14 days [11]. A mean incubation period of 5.1 days was also reported by Lauer SA et al., and that 97.5% of patients developed symptoms within 11.5 days of acquiring COVID-19 infection [12]. The clinical presentation of this infectious disease has a wide spectrum: asymptomatic, mild, severe (hypoxia, dyspnea, >50% lung involvement) and critical cases (multi-organ failure, shock, respiratory failure) and death from COVID-19 infection [13]. The older populations and individuals with other co-morbidities; cancer, diabetes, asthma and cardiovascular diseases are known to succumb faster to the disease [9,14-17]. The global distribution of COVID-19 is shown in [Table/Fig-1] [18].



[Table/Fig-1]: Global distribution of COVID 19 cases as of 10:30 am ET 28th May, 2020 [18].
International locations with confirmed COVID. Center for disease control. Available at https://www.cdc.gov/coronavirus/2019-ncov/global-covid-19/world-map.html. Accessed on 28th May, 2020

COMPLETE BLOOD COUNT AND ITS RELEVANCE

As part of the initial investigations that will help in case management, COVID-19 patients are requested to do Full Blood Count (FBC). The components of FBC include: haemoglobin level, total white cell count and differentials (neutrophil, lymphocyte, basophil, eosinophil) and platelet count. On admission most patients were found to have normal haemoglobin level, white cell count and platelet count.

These findings were commonly seen in early clinical stage or mild cases of the infection [19]. In another study by Huang C et al., it was noted that 25% of patients on admission had leukopenia with a total white cell count of less than 4×10^9/L while 63% had lymphocytopenia (<1.0X 10^9/L) [20]. The disparity seen on the FBC depends on the clinical stage of the patient at the time of admission. The haematological parameters often become deranged with progressive disease. Marked cytopenias are more commonly seen in severe forms than in milder forms of the infection [21,22]. Therefore, FBC plays a key role as an independent predictor of severity of the COVID-19 symptoms.

White Cell Count

A reduced lymphocyte count has been noted by several scholars [23,24]. Early in the disease, the FBC is usually normal but a peripheral blood film shows a reduced lymphocyte count which progressively decreases as the severity of the COVID-19 infection worsens [19,25]. Data from several studies across different geographical regions from China to Singapore to Washington DC were reviewed and showed that lymphocytopenia is a marker of severity for COVID-19 infection [19,26-28]. The proposed reason for the lymphocytopenia has been attributed to factors such as: 1) increased IL production (IL-6, IL-2, TNF alpha) which promotes apoptosis of the lymphocytes; 2) direct infection and destruction of the lymphocyte by the virus through the Angiotensin Converting Enzyme (ACE) receptors; and 3) atrophy of the spleen and other lymphoid organs which occur with the cytokine storm leading to reduced lymphocyte mobilisation [29-33]. It was found that COVID-19 survivors had their lowest lymphocyte count on the 7th day of the illness, and that lymphocyte count improves as patient recovers from the infection [30].

Platelet Count

Platelets are blood cells that are involved in coagulation, haemostasis, maintenance of the integrity of the blood vessels, and in inflammatory responses. Yang M et al., in 2005 noted a consistent feature of thrombocytopenia in critically ill patients with severe acute respiratory syndrome [34]. Patients with COVID-19 infection are known to have a low platelet count which worsens as the disease progresses. Thus, lower the platelet count, the worse the severity or the prognosis of the infection. Yang X et al., in 2020, found that 20.7% of patients had thrombocytopenia [35,36]. The underlying mechanism of thrombocytopenia as proposed by Xu P et al., included inhibition of platelet synthesis by direct infection of the progenitor cell by the virus and increased platelet consumption from the cytokine storm [37]. Qu R et al., however, demonstrated that a better marker for prognosis would be a Platelet Lymphocyte Ratio (PLR). The reason is that since both parameters are involved in immunity, a more sensitive measure would be the use of PLR which depicts the extent of systemic inflammation. He also noted that a high PLR was seen among COVID-19 patients who stayed sick for a longer period of time. The platelet peak occurs as a result of platelet activation by the cytokine storm [38]. FBC could therefore help to quickly determine the clinical severity of COVID-19 infection. This will aid in prompt intervention and may save many lives.

Coagulation and Thrombosis

Critically ill patients admitted into critical care wards are known to develop coagulation disorders including Pulmonary Embolism (PE) and Deep Vein Thrombosis (DVT). PE and DVT make up VTE. Several factors such as hypertention, obesity, inherited thrombophilias (Factor V Leiden), immobilisation, critical illness, surgery and malignancies are all predisposing factors to VTE [39]. Patients with COVID-19 who are critically ill also have these risk factors and have been found to have abnormal coagulation results. According to Klok FA et al., COVID-19 patients especially those admitted into the Intensive Care Unit (ICU) are predisposed to arterial (myocardial infarction, ischemic stroke) and venous thrombosis. The reasons stem from hypoxia, chronic inflammation and immobility of these patients [40]. Furthermore, the organ dysfunction observed in several COVID-19 patients such as liver dysfunction and renal dysfunctions are common factors which can increase their bleeding risk or thrombotic risk [41].

It has been demonstrated by several studies that critically ill COVID-19 patients especially those with Acute Respiratory Distress Syndrome (ARDS) have abnormal coagulation parameters. Those who died from COVID-19 complications were found to have had DIC with prolongation of the PT/International Normalized Ratio (INR) and APTT. This could be explained by the fact that infections and inflammatory processes are notable mechanisms that could activate and accelerate the coagulation system. Excessive consumption of coagulation factors during sepsis leads to DIC in COVID-19 patients with severe clinical illness. Therefore, it is necessary to carry out routine screening for any derangements in coagulation functions in all newly diagnosed COVID-19 patients [42]. The D-dimer test is a negative predictor of thrombosis and when the levels are markedly elevated, thrombosis should be suspected and treatment commenced. There has been an increased D-dimer level above the upper limit of normal which is also seen in non-COVID-19 patients who are critically ill [43]. It has also been used as a way to assess the severity of the disease and its mortality too [44]. PE has been reported as the most frequent complication among ICU patients with COVID-19 [40]. Ranucci M et al., noticed a normalised coagulation profile when they commenced anticoagulation regimen with Low Molecular Weight Heparin (LMWH) and suggested that all COVID-19 patients be started on therapeutic anticoagulation [43]. It was noted that COVID-19 patients with elevated levels of D-dimers at high risk of VTE are far clinically better when commenced on heparin [40,45].

Blood Transfusion and COVID-19

As the coronavirus pandemic rages worldwide, social distancing and self-quarantine are measures put in practice to control the spread of the virus. These same measures also keep the donors away from the blood centers thus reducing the number of blood donors at various blood donation centers. Similar trend was also seen during the H1N1 pandemic where donors feared contracting the virus from donation facilities and hence stayed at home [46,47]. Many blood centers may be faced with the problem of blood shortages due to reduction in donation rate. The possibility of transmission of coronavirus via blood transfusion has been put forward but evidence to prove transmission is lacking currently [48-50]. Thus, the uncertainty of COVID-19 transmission though blood transfusion has necessitated a 28 day deferral for donors with history of travel to affected areas or donors that had contact with a COVID-19 patient [50].

The SARS-CoV2 virus is known to attach to the epithelium of cells via the human ACE2 receptors. These ACE2 receptors are also found in the lung, kidney, intestine and the heart. Within 2 to 3 days of showing symptoms of COVID-19, a patient may have RNA copies of SARS-CoV-2 detected in the serum or plasma [48]. This suggests there is a theoretical chance of blood donors transmitting the virus to the recipients. Previous outbreaks of SARs and MERS employed the deferral of cases for 28 days after recovery, and contacts, for 14 days. The AABB (formerly known as American Association of Blood Banks) update on 25th February, 2020 has also as a precautionary measure, stated that blood collections centers may adopt these same measures for blood safety since no infection has been reported to have occurred through blood transfusion [51,52]. Therefore, in order to ameliorate or reduce the pressure of blood shortages on the blood centers and safeguard the blood stock, clinicians must learn to apply good patient blood management [53]. Efforts should be made to prevent or treat those

conditions that will cause anaemia, use of alternatives to blood transfusion and minimising excessive blood loss during surgeries by optimising the haemoglobin level preoperatively and achieving adequate haemostasis intraoperatively.

COVID-19 and Haematological Cancers

Haematological cancers are varied in their clinical and biological features. Majority of them are seen in the elderly population. These cancers are associated with immune dysregulation or immuneparesis. The treatment modalities too including radiation, immunotherapy, targeted therapy and chemotherapy also contribute to the immunosuppression and cytopenias seen in patients with haematological cancers. Thus, patients with haematological cancers are at increased risk of developing severe COVID-19 related complications. It is not surprising then to see a higher incidence of pneumonia, use of ventilators and increased mortality among patients with active cancers who contracted COVID-19 infection [54]. Although the novel coronavirus has been noted amongst patients with haematological cancers, no parameter has so far been found to be a predictor of cancer patients that will go on to develop COVID-19. It was noted that patients with haematological cancers usually develop severe forms of COVID-19 infection. This finding was attributed to the effect of the underlying cancer and to the therapy those patients are receiving [55]. This is seen because of bone marrow suppression of many anticancer regimens. Most of these anticancer regimens induce low haemoglobin, neutrophil and lymphocyte count thus worsening the disease severity.

Severs forms of COVID-19 infection are also seen among patients who have non-haematological cancers alongside COVID-19 infection [13]. The fatality rate for COVID-19 is 2.3% among the general population [13,56] but it rises to a rate of 5.6% [15] to 28.6% among cancer patients with COVID-19 infection [57,58]. This period of pandemic will create huge problems for cancer patients (both haematological and non-haematological cancers). There will be delays in diagnosis because some of these patients will present with COVID-19- like symptoms necessitating initial testing for the coronavirus and time wasting. There will be post-ponement of chemotherapy, shortage of blood products and increased risk of infection due to lack of isolation wards. This has been reported among acute leukemia patients by Gavillet M et al., [59]. Onder G et al., noted that out of 355 COVID-19 deaths in Italy, 20% of them had active cancer [60]. Patients with haematological cancers and those who received stem cell transplants are really the vulnerable group for COVID-19 infection. The burning decisions to make now include how to protect this most vulnerable group of patients from infection: whether or not to withhold chemotherapy while treating COVID-19; the need for attenuation of doses or withholding bone marrow suppressive drugs to avoid inducing cytopenias and immunosuppression; reducing number of hospital visits by use of telemedicine for their protection. All these will be taken on a case by case basis because we are dealing with patients with different cancers at different ages and with none or many co-morbidities.

CONCLUSION(S)

There is a strong relationship between the severity of COVID-19 infection and some haematological parameters. The parameters often become deranged with progressive disease. Marked cytopenias are more commonly seen in severe forms than in mild forms of the infection. The degree of lymphocytopenia and thrombocytopenia could predict the progression to pneumonia and subsequent need for ventilator support due to respiratory failure. The PLR is a better marker of disease severity than isolated lymphocytopenia or thrombocytopenia. There is also elevation of D-dimers and abnormalities of PT and aPTT among hospitalised patients, suggesting the need for prophylactic anticoagulation to prevent VTE. Haematological parameters are therefore important indices that could be used to predict the severity of COVID-19 infection.

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