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Role of Haematology Laboratory in Covid 19 Infections

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Abstract
Coronavirus disease 2019 (COVID-19) is an infectious illness caused by the SARS-CoV-2 virus. The infections can be transmitted through droplets of different sizes: when the droplet particles are >5-10 μm in diameter they are referred to as respiratory droplets, and when then are <5μm in diameter, they are referred to as droplet nuclei. Symptoms include fever, coughing, headaches, exhaustion, breathing issues, loss of smell, and loss of taste. Haematology is the study of the physiology and pathology of the cellular elements of blood. The three major cellular components of blood are red blood cells (erythrocytes), white blood cells (leukocytes) and platelets (thrombocytes). Haematology laboratory is one of the essential laboratories found in hospitals that performs a wide variety of basic and advanced hematology testing on whole blood, plasma, bone marrow and other body fluids. Haematology plays a crucial role in the diagnosis of COVID-19. Blood tests, such as Full blood counts and coagulation profiles, can provide valuable information about the patient's immune response, inflammation, and potential complications associated with the virus. While these tests are not definitive for COVID-19 diagnosis on their own, they are an essential component of the overall diagnostic process when used in conjunction with other clinical and laboratory findings, including molecular tests like PCR. Haematology, therefore, contributes to a comprehensive assessment of COVID-19 patients, aiding in their management and treatment.

Keywords: *Role, Haematology Laboratory, Covid 19 Infection*

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious illness caused by the SARS-CoV-2 virus. Authorities discovered the first recorded case In Wuhan, China, in December 2019 (1). The illness soon spread throughout the world, causing the COVID-19 pandemic. Although COVID-19 symptoms might vary, they frequently include fever, coughing, headaches, exhaustion, breathing issues, loss of smell, and loss of taste (2). One to fourteen days after viral exposure, symptoms

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may appear. At least one-third of infected individuals don't have any symptoms at all. (3). The majority (81%) of individuals who experience symptoms that are noticeable enough to be categorized as patients do so in the mild to moderate range (up to mild pneumonia), 14% in the severe range (dyspnea, hypoxia, or more than 50% lung involvement on imaging), and 5% in the critical range (respiratory failure, shock, or multiorgan dysfunction). Older people are at a higher risk of developing severe symptoms. Some people continue to experience a range of effects (long COVID) for years after infection, and damage to organs has been observed (4).

Transmission of Covid 19

Respiratory infections can be transmitted through droplets of different sizes: when the droplet particles are >5-10 μm in diameter they are referred to as respiratory droplets, and when then are <5μm in diameter, they are referred to as droplet nuclei (5). According to current evidence, COVID-19 virus is primarily transmitted between people through respiratory droplets and contact routes (6).

Airborne transmission via aerosols formation is suspected to be the main mode of transmission. Aerosols are particles under 100 μm in diameter thus their minute size and suspension in the air may ease direct contraction of the virus (7). Aerosols may be formed during various surgical and dental procedures or may be formed as droplet nuclei while talking, coughing, and sneezing by an infected patient. Droplet formation serves as a potent mode for human-to-human transmission. In the same study, cough training (respiratory exercise), which is done postoperatively, produces a large number of droplets and aerosols in a surrounding space (8). This increases the amount of exposure and, thus, the risk of virus transmission. Dentists are at a higher risk of exposure as dental patients are required to spit or gargle after oral procedures like extraction, drilling, and drainage of dental abscess. Thus, these aerosol-producing procedures must be performed using appropriate protective equipment (8).

Symptoms of Covid-19

- Continuous cough
- High temperature, fever or chills
- Loss of or change in, your normal sense of taste or smell
- Shortness of breath
- Unexplained tiredness, lack of energy
- Muscle aches or pains that are not due to exercise
- Not wanting to eat or not feeling hungry
- Headache that is unusual or longer lasting than usual
- Sore throat, stuffy or runny nose
- Diarrhoea

- Feeling sick or being sick (9).

What is Haematology Laboratory?

Haematology is the study of the physiology and pathology of the cellular elements of blood. The three major cellular components of blood are red blood cells (erythrocytes), white blood cells (leukocytes) and platelets (thrombocytes) (10). Haematology laboratory is one of the essential laboratories found in hospitals that performs a wide variety of basic and advanced hematology testing on whole blood, plasma, bone marrow and other body fluids. Additionally, advanced hematological tests are performed using a variety of techniques including flow cytometry, electrophoresis and microscopy and many other methods. Routine hematology testing including Full blood count, blood differential, smear morphology and bone marrow staining, routine coagulation testing (Prothrombin time and Prothrombin thromboplastin time) and Hemoglobin electrophoresis (11)

Red Blood Cells

Erythrocytes, red blood cells (RBC), are the functional component of blood responsible for the transportation of gases and nutrients throughout the human body. Their unique shape and composition allow for these specialized cells to carry out their essential functions. The role of the erythrocyte is critical in investigating many disease processes in a variety of body systems. The mature erythrocyte has a biconcave, discoid shape and is anucleated. This design allows for the flexibility needed to navigate the cardiovascular system and for an increased surface area which supports sufficient gas exchange and permits the cell to carry out its function (12).

White Blood Cells

White blood cells, also called leukocytes or immune cells also called immunocytes, are cells of the immune system that are involved in protecting the body against both infectious disease and foreign invaders. White blood cells include three main subtypes; granulocytes, lymphocytes and monocytes (12). White blood cells are part of the body's immune system. They help the body fight infection and other diseases. Types of white blood cells are granulocytes (neutrophils, eosinophils, and basophils), and agranulocytes (monocytes, and lymphocytes (T cells and B cells)). Myeloid cells (myelocytes) include neutrophils, eosinophils, mast cells, basophils, and monocytes. Monocytes are further subdivided into dendritic cells and macrophages. Monocytes, macrophages, and neutrophils are phagocytic. Lymphoid cells (lymphocytes) include T cells (subdivided into helper T cells, memory T cells, cytotoxic T cells), B cells (subdivided into plasma cells and memory B cells), and natural killer cells (12).

Platelets

Platelets are small blood cells with several physiological purposes; the best studied is thrombosis activation. Through their clotting activity and activation of the coagulation cascade, they are crucial to maintaining adequate blood volume in those with vascular injury. The initiation of this activity begins with tissue injury and results in the release and binding of several glycoproteins, growth factors, and clotting factors (13).

Haematological Tests In Covid 19

Platelet (PLT) count

Platelets count is an important parameter included in numerous classification systems that evaluate disease severity, such as in multi organ dysfunction syndrome. In COVID-19 infection, the

presence of thrombocytopenia correlates with the severity of the disease and indicates the presence of a consumption coagulopathy. Platelet number was found to be lower in patients with either more severe illness or poor outcomes and even lower in non-survivors. Thrombocytopenia tends to reach a significant level in the late clinical stage of COVID-19 (14). The mechanism by which the coronavirus interferes with the haematopoietic system is still unclear. Three mechanisms of a cascade can be assumed to explain thrombocytopenia in SARS-CoV-2 infections: 1) direct infection of bone marrow cells by the virus with inhibition of Platelet synthesis; 2) destruction of Platelets by the immune system; 3) aggregation of Platelets in the lungs with the formation of microthrombi and further consumption of Platelets. Viruses can interact with megakaryocytes and reduce PLT synthesis (15). It has been assumed that the SARS-CoV-2 inhibits bone marrow haematopoiesis through specific receptors to depress the primary formation of PLTs and resulting thrombocytopenia (16). Viral infection and inflammation result in pulmonary capillary damage. Damaged lung tissues and pulmonary endothelial cells may cause a process of megakaryocyte rupture and increased PLT consumption (17). Also, SARS-CoV-2 can boost autoantibodies and immune complexes, resulting in the specific destruction of PLTs by the immune system (18). While PLTs contribute to the basal barrier integrity of the alveolar capillaries, they may also contribute to lung injury in a variety of pulmonary disorders and syndromes. PLT-leukocyte aggregates and PLT-endothelial interactions appear to play a role in the pathogenesis of acute lung injury (19). In Covid-19 infection, the damage of the lung tissues and lung endothelial cells can cause PLT aggregations with the formation of micro thrombi and further consumption of PLTs (20). In fact, most patients with thrombocytopenia have high concentrations of D-dimers with alteration of the coagulation parameters that confirm the hypothesis of triggering intravascular coagulation (20).

Neutrophil-lymphocyte and platelet-lymphocyte ratio

Neutrophil-lymphocyte ratio is elevated in the bloodstream of COVID-19 infected patients; Zhang *et al* (21) reported that NLR combined with IgG might be a better predictor than neutrophil count alone in predicting the severity of COVID-19 (22). Levels of NLR and PLR correlate with COVID-19 disease severity. Patients with severe disease had higher NLR and PLR values compared to non-severe diseases (23). Neutrophil-lymphocyte ratio and PLR have been considered independent factors associated with COVID-19 progression; however, the mechanisms behind this are not understood (24). At the early stage of COVID-19, the total number of leukocytes in peripheral blood is normal or decreases, while the lymphocyte count decreases (25). The initial and peak value of NLR in deceased patients were higher than in survivors (26). The increase of NLR means the progressive increase of neutrophils, and/or the decrease of lymphocytes. Due to the rapid involvement of inflammatory processes in COVID-19, severe COVID-19 patients have demonstrated elevated PLR levels, this suggests the potential use of this inflammatory marker to determine the prognosis of COVID-19 patients, especially in resource-limited settings, the increase of neutrophils often suggests an underlying bacterial infection, while the decrease of lymphocytes means a compromised system (24).

Neutrophilia

Neutrophilia, except for patients with bacterial infections or superinfections, correlates with hyperinflammatory state and cytokine storm, an integral part of the pathogenic mechanism of

COVID-19. Neutrophils are involved in many viral respiratory diseases associated with ARDS (27). A minority of patients present leucocytosis, supported by neutrophilia: this finding seems to correlate with a more severe course. As COVID-19 progresses, the number of circulating neutrophils gradually increases; thus, neutrophilia has been identified as a marker of severe respiratory disease and a poor outcome. Leukocytes and neutrophils were significantly higher in severe than in non-severe COVID-19 infected patients. Further, along with COVID-19 disease progression, both leukocyte and neutrophil counts increased in the severe groups (28). In peripheral blood smear, morphological alterations in circulating neutrophils, such as the reduction of nuclear lobularity and the presence of heavy cytoplasmic granulations, have been described. These morphological changes were transient and reversible preceding the appearance of the large reactive atypical lymphocytes, characteristic of viral infections (29).The increase of neutrophils has been reported not only in the bloodstream but also in the lung tissue (30). The increased infiltration of immature and/or dysfunctional neutrophil contributes to the abnormal lungs' immune response in severe patients. Similar to other viral infections, SARS-CoV-2 infection promotes neutrophil extracellular traps release, which can contribute to tissue damage. Aberrant activation of neutrophils might exacerbate host response in COVID-19. Lung autopsies revealed the presence of neutrophils in lung capillaries and their extravasation into alveolar space (31). Neutrophils have a crucial role as drivers of hyperinflammation associated with COVID-19 disease via enhanced degranulation and cytokine production (32).

Coagulation profile

Measuring parameters such as prothrombin time (PT) and activated partial thromboplastin time (aPTT) can help assess a patient's blood clotting ability. Coagulation abnormalities have been observed in some COVID-19 patients. Abnormal blood coagulation often occurs in critically ill COVID-19 patients, which seriously affects their prognosis. This retrospective study investigated the implications of changes in blood coagulation in patients with coronavirus disease 2019 (COVID-19) (33).

D-dimer test

Elevated levels of D-dimer, a product of blood clot breakdown, can be associated with blood clotting disorders, which have been observed in some severe cases of COVID-19. D-dimer, thus is a commonly tested parameter in hospitalized patients with COVID-19. The rise in the D-dimer level reflects the degradation product of fibrin accumulating in the alveoli, coming to the blood. Thus, it is understood that D-dimer is associated with the degree and prognosis of lung injury (34).

Ferritin levels

Ferritin is a protein that stores iron. Elevated ferritin levels can indicate inflammation and are associated with a more severe course of COVID-19. Ferritin level has been strongly correlated with COVID-19 disease severity (35). Hyperferritinemia has been observed as an independent factor associated with high mortality rates in COVID-19 infections (36). Studies have reported hyperferritinemia as a poor prognostic predictor in COVID-19 patients (37).

Importance of Haematology in the Diagnosis of Covid 19

Blood tests have an important role in early diagnosis of the disease, considering the information they provide to physicians regarding the inflammatory process. This information includes leukocyte count and characteristics such as neutrophil- or lymphocyte-dominance, inflammation (CRP), collateral organ damage (acute renal failure, acute liver failure) and the severity of the

disease. Furthermore, biomarkers provide information regarding the nature of pneumonia, meaning that physicians can determine whether a disease is bacterial or due to other etiologies by analyzing blood test results (38). Full blood counts are values such as white blood count, neutrophil, lymphocyte and platelet count (PLT), mean platelet volume and certain ratios of these values. These can be used as inflammatory markers. Neutrophils are the most characteristic cell type among the white blood cells and are an important component of the immune system. Regulated by mast cells, epithelial cells and macrophages, neutrophils also take part in inflammatory processes. The role of lymphocytes in both inflammation and infections is evident. Additionally, thrombocytes also have importance in the regulation of various inflammatory processes. While these parameters may be used as inflammatory markers by themselves, their ratios to one another may also be indicators of early inflammation (39) Circulating leukocytes respond to stress by increasing neutrophils and reducing lymphocytes; the ratio of these two parameters is also used as an inflammatory marker (40). Considering previous research, the use of circulating biomarkers representing inflammation and the immune system have been considered as a prognostic indicator in COVID-19-positive patients. However, their utility in terms of diagnosis has not been explored (41).

Haematological Management of Covid-19

Convalescent plasma: is a passive antibody therapy that has been used to prevent or treat infectious diseases for more than a century (42). The CP is obtained using apheresis in survivors with prior infections caused by pathogens of interest in whom antibodies against the causal agent of disease are developed. The major target is to neutralize the pathogen for its eradication (43) Composition of CP is variable and include a wide variety of blood derive components. Plasma contains a mixture of inorganic salts, organic compounds, water, and more than 1000 proteins. In the latter we found albumin, immunoglobulins, complement, coagulation and antithrombotic factors among other (44). In the absence of effective countermeasures, human convalescent plasma has been widely used to treat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of novel coronavirus disease 19 (COVID-19). Convalescent plasma has received full or conditional regulatory authorization in the United States and many other countries for therapeutic use in adults and children hospitalized with suspected or laboratory-confirmed SARS-CoV-2 positive COVID-19 (45). The evidence supporting the use of convalescent plasma to treat patients with COVID-19 is not definitive (46). There is evidence that supports the therapeutic use of convalescent plasma among patients with COVID-19 who are treated earlier in the disease course using plasma with sufficient antibody levels (47). In contrast, however, several large clinical trials that transfused severely ill patients later in the disease course have suggested there is no mortality benefit conferred from COVID-19 convalescent plasma (48). Although there are many studies evaluating the clinical efficacy of convalescent plasma in otherwise immunocompetent patients, there is a paucity of studies evaluating the use of convalescent plasma in COVID-19 patients with immunosuppression or immunodeficiency. Patients with immunosuppression or immunodeficiency have been disproportionately affected by the COVID-19 pandemic, (49) and often present with persistent SARS-CoV-2 infection and may shed viable SARS-CoV-2 for months (50).

RED BLOOD CELLS TRANSFUSION: red blood cell exchange is a new therapeutic approach as adjunctive treatment in some patients with severe COVID-19. This treatment helps oxygenation

by physical removal of non-functional RBCs and substitutes them with new RBCs. Early administration of erythropoietin or blood transfusion is recommended to treat hypoxemia in patients with COVID-19 (51).

ANTICOAGULANT THERAPY**:** Since the beginning of the COVID-19 pandemic, disease severity has been linked to markers of coagulation disturbances such as prothrombin time prolongation, elevated fibrin degradation products, reduced platelet count, and especially to elevated D dimer (52). Higher levels of D dimer and the presence of other coagulation disturbances have been independently associated with development of respiratory failure and death in patients with COVID-19 (53). The use of heparin, particularly in those patients with more pronounced elevations of D-dimer and in those with elevated sepsis induced coagulopathy (SIC) score, has been associated with a better prognosis (54). Main protease (Mpro) is a key enzyme of coronavirus that plays an essential role in concerning viral replication and transcription. Li *et al* (55) demonstrated that heparin binds to SARS-CoV-2 Mpro, inhibiting its proteolytic activity in vitro. Therefore, heparin might inhibit SARS-CoV-2 replication and transcription by inhibiting the activity of the SARS-CoV-2 Mpro protein. Potje et al (56) showed that plasma from hospitalized COVID-19 patients contained increased levels of glycocalyx components and increased heparanase activity, indicating glycocalyx disruption. Moreover, plasma from COVID-19 patients also resulted in glycocalyx shedding and disturbed redox balance in healthy ECs of the umbilical veins cells. Low-molecular-weight heparins (LMWH) inhibited glycocalyx perturbation induced by plasma from COVID-19 patients (56).

Another intriguing potential therapeutic role of heparin in COVID-19 seems to be the inhibition of heparanase, an endothelial glycocalyx-degrading enzyme that contributes to vascular leakage and inflammation. The activity of heparanase was associated with disease severity in COVID-19 patients, and Buijsers et al. demonstrated that LMWH could reduce its activity (57). Diabetic patients, whose levels of D dimer are greater than those of non-diabetic patients, have also been shown to have a worse prognosis regarding COVID-19 (58). Moreover, hypercoagulative features can differentiate severe COVID-19 associated pneumonia from that caused by other viruses (59). Over the last months it has been consistently shown that SARS-Cov-2 causes a cytokine storm, endothelial and epithelial dysfunction, which ultimately lead to the activation of the coagulation cascade, causing thrombotic phenomena (53). Similarly to what happens in severe sepsis, the widespread deposition of intravascular clots compromises adequate blood supply, contributing to organ failure (60).

Conclusion

Haematology plays a crucial role in the diagnosis of COVID-19. Blood tests, such as Full blood counts and coagulation profiles, can provide valuable information about the patient's immune response, inflammation, and potential complications associated with the virus. While these tests are not definitive for COVID-19 diagnosis on their own, they are an essential component of the overall diagnostic process when used in conjunction with other clinical and laboratory findings, including molecular tests like PCR. Haematology, therefore, contributes to a comprehensive assessment of COVID-19 patients, aiding in their management and treatment.

Future Directions

1. Biomarker Identification: Hematology plays a crucial role in identifying specific biomarkers associated with COVID-19. In the future, more precise markers may be discovered, aiding in quicker and more accurate diagnosis.
2. Hematological Abnormalities: Continued research on COVID-19's impact on blood cells may reveal further insights into hematological abnormalities. Monitoring these abnormalities could help diagnose and manage the disease.
3. Point-of-Care Testing: There may be a shift towards developing point-of-care hematological tests that can quickly detect COVID-19-related blood abnormalities, making diagnosis more accessible and rapid.
4. AI and Machine Learning: Integration of AI and machine learning algorithms may assist in analyzing hematological data to identify COVID-19 cases. These technologies can provide faster and more accurate results.
5. Comorbidity Assessment: Hematology can aid in assessing comorbidities and complications in COVID-19 patients, which can inform treatment decisions and patient management.
6. Monitoring Long COVID: As the understanding of long COVID (post-acute sequelae of SARS-CoV-2 infection) grows, hematology may play a role in monitoring and diagnosing the hematological aspects of this condition.
7. Therapeutic Monitoring: Hematological tests can help monitor patients receiving COVID-19 treatments, ensuring they are responding appropriately and not experiencing adverse effects.
8. Population Screening: Hematological markers may be used in population screening efforts to identify asymptomatic or pre-symptomatic carriers of the virus.

Conflict of Interest: The authors have declared no conflict of interest.

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