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CLINICAL AND HEMATOLOGICAL FINDINGS IN PATIENTS WITH CORONAVIRUS DISEASE (COVID-19): REVIEW

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ABSTRACT Coronavirus Disease 2019 (COVID-19) is a new type of disease that has never been previously identified in humans. The virus that causes COVID-19 is called SARS-CoV-2. In humans, SARS-CoV-2 primarily infects cells and glycoproteins contained in the envelope spike of the virus will bind to the ACE2 cellular receptor. The clinical manifestations of COVID-19 patients have a broad spectrum, ranging from asymptomatic mild to severe. This disease significantly affects the haematological system and hemostasis, so haematological findings play an important role in screening and as a prognostic marker. Lymphopenia, thrombocytopenia, leukocytosis, and neutrophilia are important laboratory findings. In addition, several other haematological and hemostasis parameters were found, including neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and lymphocyte to monocyte (LMR), and absolute lymphocyte count (ALC).

KEYWORDS Covid-19, Hematological finding, Clinical finding

Introduction

Coronaviruses are a large family of viruses that cause illnesses ranging from mild to severe symptoms. There are at least two types of coronavirus known to cause diseases with severe symptoms, such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). Coronavirus Disease 2019 (COVID-19) is a new type of disease that has never been previously identified in humans.[1] The virus that causes COVID-19 is called SARS-CoV-2. Coronaviruses are zoonotic (transmitted between animals and humans). Research states that SARS is transmitted from civet cats to humans and MERS from camels to humans. The animal that is the source of transmission of COVID-19 is still not known with certainty.[2,3] COVID-19 is a respiratory tract infection caused by a newly recognized

coronavirus that first emerged in Wuhan, China, in December 2019. Although most people infected by COVID-19 only experience mild disease or without complications, about 14% suffer from the disease, need hospital care and oxygen support, and 5% need to be admitted to an intensive care unit. In severe cases, COVID-19 can be exacerbated by acute respiratory distress syndrome (ARDS), sepsis and septic shock, multi-organ failure, including kidney failure or acute heart failure.[4] Some patients have severe symptoms of COVID-19 accompanied by coagulation abnormalities resembling coagulopathy associated with severe systemic infection, such as disseminated intravascular coagulopathy (DIC) or thrombotic microangiopathy.[5]

Approximately 80% of SARS-CoV-2 resembles SARS-CoV and invades host cells by binding to angiotensin-converting enzyme 2 (ACE2) receptors. Although the documentation regarding COVID-19 manifests primarily as a respiratory tract infection, emergency case data indicate systemic disease related to organ systems including cardiovascular, respiratory, gastrointestinal, neurological, hematological and immune systems.[6] The mortality rate for COVID-19 is lower than SARS and MERS; however, COVID-19 is more deadly than seasonal flu. Elderly people and those with comorbid increase the risk of death in COVID-19, but young people without major underlying diseases also have the potential for death, such as fulminant myocarditis

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and (DIC).[7,8] In this reference, the haematological features of COVID-19 will be discussed.

Pathogenesis of Covid-19

The pathogenesis of SARS-CoV-2 is still not widely known, but it is thought that it is not that different from the more widely known SARS-CoV. SARS-CoV-2 primarily infects cells in the airways that line the alveoli in humans. SARS-CoV-2 will bind to the receptors and make a way into the cell. Glycoproteins contained in the envelope spike of the SARS-CoV-2 virus will bind to the ACE2 cellular receptor. Inside the cell, SARS-CoV-2 duplicates genetic material and synthesizes the required proteins, then forms new virions that appear on the cell surface. Similar to SARS-CoV, in SARS-CoV-2, it is suspected that after the virus enters the cell, the viral RNA genome will be released into the cell cytoplasm and translated into two polyproteins and structural proteins. Subsequently, the viral genome will begin to replicate. The glycoproteins in the newly formed viral envelope enter the membrane of the endoplasmic reticulum or Golgi cells. There is the formation of nucleocapsid composed of the RNA genome and nucleocapsid proteins. Viral particles will grow into the endoplasmic reticulum and

Golgi cells. In the final stage, vesicles containing virus particles will combine with the plasma membrane to release new viral components.[12] In SARS-CoV, Protein S was reported as a significant determinant of virus entry into host cells. It is known that the entry of SARS-CoV into the cell begins with the fusion of the viral membrane with the plasma membrane of the cell. In this process, the S2 protein plays an important role in the proteolytic cleavage process, mediating the membrane fusion process. Apart from membrane fusion, clathrin-dependent and clathrin-independent endocytosis mediate the entry of SARS-CoV into host cells.[14]

Viral and host factors play a role in SARS-CoV infection.[15] The cytopathic effect of the virus and its ability to overpower the immune response determines the severity of the infection. Immune system dysregulation then plays a role in tissue damage in SARS-CoV-2 infection. Inadequate immune response results in viral replication and tissue damage. On the other hand, an excessive immune response can cause tissue damage.[15]

The immune response caused by SARS-CoV-2 is not fully understood but can be studied from the mechanisms found in SARS-CoV and MERS-CoV. When the virus enters the cell, the viral antigen will be presented to antigen presentation cells (APCs). Viral antigen presentation mainly depends on the major histocompatibility complex (MHC) class I molecules. However, MHC class II also contributes.[9] The antigen presentation further stimulates the body's humoral and cellular immune response mediated by virus-specific T and B cells. In the humoral immune response, IgM and IgG are formed against SARS-CoV. Immunoglobulin M against SARS-CoV is lost at the end of week 12, and IgG can last long.[9] The results of a study on patients who had recovered from SARS showed that after 4.

There could be found CD4+ and CD8+ memory T cells specific to SARS-CoV, but the number decreased gradually in the absence of an antigen.[17] Viruses have mechanisms to evade the host immune response. SARS-CoV can induce the production of double-membrane vesicles that do not have pattern recognition receptors (PRRs) and replicate in these vesicles so that the host cannot recognize them. SARS-CoV and MERS-CoV also inhibited the IFN-I line. Antigen presentation is also inhibited in MERS-CoV infection.[9]

a. Immune Response to Hosts in COVID-19 with Clinical Mild

The immune response that occurs in patients with manifestations of COVID-19 that is not severe is illustrated in a case report in Australia. In these patients, there was an increase in CD38+ HLA-DR+ T cells (activated T cells), especially CD8 T cells, on days 7-9. In addition, there was an increase in antibody-secreting cells (ASCs) and follicular helper T cells in the blood on day 7, three days before symptom resolution. A progressive increase in IgM/ IgG SARS-CoV-2 was also found from day 7 to day 20. These immunological changes persist for up to 7 days after the resolution of symptoms. There was also a decrease in CD16+ CD14+ monocytes compared to healthy controls. Activated natural killer (NK) cells HLA-DR+CD3-CD56+ and monocyte chemoattractant protein-1 (MCP-1; CCL2) were also increased, but levels were the same as in healthy controls. In patients with mild manifestations of COVID-19, no increase in proinflammatory chemokines and cytokines was found, even when symptomatic.[18]

b. Immune Response to Hosts in COVID-19 with Clinically Serious Weight

The difference in the immunological profile between mild and severe cases of COVID-19 can be seen in a study in China. The study found lower lymphocyte counts, higher leucocyte and neutrophil-lymphocyte ratio, and lower percentages of monocytes, eosinophils and basophils in severe cases of COVID-19. Proinflammatory cytokines, namely TNF- α , IL-1 and IL-6 and IL-8 and markers of infection such as procalcitonin, ferritin and C-reactive protein, were also higher in severe clinical cases. Helper, T suppressor, and regulatory T cells were decreased in COVID-19 patients with lower levels of T helper and regulatory T in severe cases. Another case report in a COVID-19 patient with ARDS showed decreased CD4 and CD8 T lymphocytes. The CD4 and CD8 lymphocytes were in a hyperactivation state, indicated by the high proportion of the HLA-DR + CD38 + fraction. CD8 T lymphocytes contained cytotoxic granules in high concentrations (31.6% positive for perforin, 64.2% positive for granulysin, and 30.5% positive for granulysin and perforin). In addition, it was also found an increase in the concentration of Th17/CR6+, which was proinflammatory.[19]

ARDS is the leading cause of death in COVID-19 patients. The cause of ARDS in SARS-CoV-2 infection is cytokine storm, which is an uncontrolled systemic inflammatory response due to the release of large amounts of proinflammatory cytokines (IFN- α , IFN- γ , IL-1 β , IL-2, IL-6, IL-7, IL-10, IL-12, IL-18, IL-33, TNF- α , and TGF β) and large amounts of chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, and CXCL10).[9,20] Granulocyte-colony stimulating factor, interferon- γ -inducible protein 10, monocyte chemoattractant protein 1, and macrophage inflammatory protein 1 alpha were also seen. This excessive immune response can lead to lung damage and fibrosis, resulting in functional disability.[21]

III. Clinic manifestations

The clinical manifestations of COVID-19 patients have a broad spectrum, ranging from asymptomatic, mild symptoms, pneumonia, severe pneumonia, ARDS, sepsis, to septic shock. About 80% of cases were classified as mild or moderate, 13.8% were seriously ill, and 6.1% of the patients fell into a critical condition. The proportion of asymptomatic infections is unknown.[22]

Viremia, and high viral load from nasopharyngeal swabs in asymptomatic patients have been reported.[14] Mild symptoms are defined as a patient with an acute uncomplicated upper respiratory tract infection, which may present with fever, fatigue, cough (with or without sputum), anorexia, malaise, sore throat, nasal congestion, or headache. The patient does not need oxygen supplementation. In some cases, the patient also complained of diarrhoea and vomiting.[14,20] COVID-23 patients with severe pneumonia are characterized by a fever plus one of the following symptoms: (1) respiratory rate $>30x/$ minute, (2) severe respiratory distress, or (3) 93% oxygen saturation without oxygen assistance. In geriatric patients, there may be atypical symptoms.[14]

Most patients infected with SARS-CoV-2 show respiratory symptoms such as fever, coughing, sneezing, and shortness of breath. The most common symptoms are fever, dry cough and fatigue. Other symptoms found are productive cough, shortness of breath, sore throat, headache, myalgia/ arthralgia, chills, nausea/ vomiting, nasal congestion, diarrhoea, abdominal pain, hemoptysis, and conjunctival congestion. More than 40% of the fever of COVID-19 patients had a peak temperature between 38.1-39°C, while 34% had a fever over 39°C.[2,14,22]

The course of the disease begins with an incubation period of about 3-14 days (median 5 days). The leukocytes and lymphocytes are still normal or slightly decreased, and the patient is asymptomatic. In the next phase (early symptoms), the virus spreads through the bloodstream, presumably mainly in tissues that express ACE2, such as the lungs, gastrointestinal tract and heart. Symptoms in this phase are generally mild. The second attack occurs four to seven days after the initial symptoms appear. The patient still has a fever and begins to have tightness, the lesions worsen, and the lymphocytes decrease. The markers of inflammation begin to increase, and hypercoagulation begins. If not resolved, the next phase of inflammation gets out of control, and a cytokine storm occurs, which results in ARDS, sepsis, and other complications.[6,14]

IV Hematology of patients with covid-19 infection

Based on research conducted in China and elsewhere, clinical haematology laboratories play an important role as a prognostic marker. Although the information in some cases is based on results from a limited amount of data and must be validated by additional studies, the available findings establish clinical haematology laboratory as an important element in triage and patient management. Apart from RT-PCR testing for organisms, laboratory tests have never been assessed for the sensitivity or specificity of COVID-19 diagnosis, although values as prognostic indicators have been stated.[23]

A. Lymphopenia

Lymphopenia is a common finding in patients with COVID-19 infection, and is believed to represent an adaptive immune response to the virus. In several early studies of 41 adults with RT-PCR confirmed COVID-19 infection, Huang et al emphasized that lymphopenia (defined as absolute lymphocyte count $<1.0 \times 10^9/$ L) was present in 26 (63%) patients.[20] In a study of 67 COVID-19 patients from Singapore, Fan et al identified a lymphocyte count $<0.6 \times 10^9/$ L for intensive room care indication.[24]

The exact cause is unclear. However, functional studies suggest that SARS-CoV-2 might impair the function of T helper

(CD4 +) cells and Treg cells and promote early hyperactivity followed by rapid cytotoxic (CD8 +) T cells fatigue.

B. Thrombocytopenia

Thrombocytopenia is an important indicator of a COVID-19 patient, as highlighted by recent reviews. This is not surprising since platelet counts are used in scoring systems such as Multiple Organ and Dysfunction Score (MODS), Simplified Acute Physiology Score (SAPS) II, and Acute Physiology and Chronic Health Evaluation (APACHE) II and thrombocytopenia is an indicator of severe disease in the scoring system. The [26] Nine meta-analysis studies showed that thrombocytopenia was reported in most patients.[27] This is similar to the SARS outbreak case data, in which thrombocytopenia was reported in 55% of cases and correlated with an increased risk of serious disease.[23] In patients with severe infection, thrombocytopenia was identified in up to 57.7% of patients vs 31.6% of patients with non-severe COVID-19 symptoms.[23]

The use of platelet counts in conjunction with other factors associated with severe disease has not been reported in COVID-19 patients, although it has been used in SARS. For example, Zou et al reported that the platelet count, in conjunction with hypoxemia, was used as a prognostic model of SARS disease severity with an accuracy of 96.2%.[29]

It has been reported that platelet-specific receptors are known to interact with viruses. Viruses can directly interact with platelets, thereby changing the number and function of platelets. Various mechanisms are described and depend on the type of virus. One of them: triggering systemic inflammation and clearing activated platelets through the spleen/ liver macrophages and / or phagocytosis by neutrophils as in the case of influenza and rhinovirus, suppressing platelet production or increasing platelet destruction as in the case of herpes and simian viruses, and cross-reaction of anti-viral antibodies with a platelet integrin surface as in the case of adenovirus.[29] For thrombocytopenia associated with COVID-19, several suspected mechanisms include development of autoantibodies or immune complexes mediating clearance, direct infection of hematopoietic cells or progenitor cells and megakaryocytic strains via CCR13 or CD66a resulting in decreased platelet production, increased thrombomodulin leading to activation of the pathological coagulation pathway and consumption. platelets and increased plasma tissue-plasminogen activator concentrations resulting in fibrinolysis.[29]

C. Leukocytosis

Leukocytosis, regardless of describing neutrophilia, lymphocytosis, or both, was noted for little in patients infected with COVID-19, and a sign of bacterial infection or superinfection. Metanalysis of the literature identified 84% of patients with severe disease compared with 4.8% of patients with mild to moderate disease.[23] A study by Takayuki Yamada, et al. regarding fever, leucocytosis, and elevated CRP associated with severe COVID-19 suggest that leukocytosis and elevated CRP at initial hospital admission can be biomarkers for predicting severe COVID-19.[24]

D. Neutrophilia

Neutrophilia data sources are incomplete and have not been widely discussed in the literature. Available data suggest that the expression of cytokine storms and the hyperinflammatory

state play an important role in COVID-19 and related infections such as SARS. Cytoplasmic and nuclear morphological anomalies, from hyposegmental nuclei to apoptosis may be associated with hyperinflammatory state with cytokine storms. Neutrophils usually precede an increase in reactive lymphocytes. Neutrophilia is also indicated with bacterial infection.[23,25] For example, Faruqi et al. noted that neutrophilia was common in ICU patients.[25] The neutrophil to lymphocyte ratio (NLR), easily calculated from routine blood tests by dividing the number of neutrophils by lymphocytes, has been reported to be of value in indicating the patient's overall inflammatory status.

V. Hematology parameters in covid-19 patients

Apart from those described above, there are several components of blood tests that can be used as a monitoring tool and predictor of COVID-19, including:

A. Neutrophil to Lymphocyte Ratio (NLR)

The ratio of neutrophils to lymphocytes (NLR) is easily calculated from the results of routine blood tests by dividing absolute neutrophils by absolute lymphocytes. NLR has been reported to have value in indicating inflammatory status of patients.[32]

From the results of a retrospective cohort study by Yuwei Liu, et al. The 245 COVID-19 patients found that patients with increased NLR had a higher risk of death during hospitalization. A study conducted by Yang Ai-Ping reported that an NLR > 3.3 was associated with more severe COVID-19.[32]

NLR has been proposed as a new biomarker of systemic inflammation. A high NLR is obtained from an increase in neutrophil value and a decrease in the lymphocyte value. The inflammatory response can stimulate neutrophil production and the rate of lymphocyte apoptosis. Dysregulation of immune cell responses and consequent immunological abnormalities are believed to play an important role in the severity of disease caused by viruses. When there is dysregulation of the immune response, this condition causes excessive inflammation and can even lead to death.[34,35]

B. Platelet to Lymphocyte Ratio (PLR)

Inflammation plays an important role in the pathophysiology of COVID-19. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) can indirectly indicate the inflammatory status of the patient. PLR is calculated by dividing absolute platelets by absolute lymphocytes. In recent years, the platelet to lymphocyte ratio (PLR) has been validated as a prognostic marker in various diseases, such as heart disease, solid tumors, sepsis, pneumonia, and acute respiratory distress syndrome (ARDS).[32] A literature study conducted by Abigail, et al. obtained a correlation between PLR levels and the severity of COVID-19. There was a higher PLR value in patients with severe COVID-19 than in mild ones. Research conducted by Yang Ai-Ping reported a PLR cut-off >180 associated with COVID-19.[32]

Severe COVID-19 patients showed increased leukocytosis, neutrophilia, lymphopenia, and thrombocytopenia compared to mild COVID-19 patients. Patients have a greater likelihood of occurring ARDS and require care in the intensive care unit (ICU). The mechanism of lymphopenia in COVID-19 is associated with the ability of the virus to infect T cells via the angiotensin-converting enzyme 2 (ACE2) receptor and the spike protein CD147. The end result is decreased levels of CD3+, CD4+, CD8+,

T lymphocytes, and an increase in T reg cells. The increase in proinflammatory cytokines and T cell lymphopenia causes severe COVID-19 patients to experience a cytokine storm, resulting in more lymphocytic apoptosis and multiorgan failure. Overall, decreased levels of CD4+ and CD8+ T lymphocytes correlated with the degree of disease severity, which can lead to an increase in NLR or PLR.[32,35]

C. Lymphocyte to Monocyte Ratio (LMR)

A very high neutrophil to lymphocyte ratio (NLR) predicts a poorer prognosis in patients with ARDS. However, the lymphocyte to monocyte ratio (LMR) has been shown to be a more adequate prognostic biomarker than NLR in most chronic inflammatory diseases, including metastatic and pathological autoimmune cancers.[36] Research conducted by Zhang Ting reported an LMR cut-off value of 3.0 associated with COVID-19.[41]

In the study, Paolo Lissoni et al., Concluded that evaluating the LMR value can be a simple and less expensive biomarker for monitoring the development of COVID-19 infection and respiratory complications. A study showed that the decrease in lymphocytes that occurs in patients with respiratory distress in COVID-19 is associated with a concomitant increase in the number of monocytes, followed by a decrease in the LMR value. In addition, it is possible that the lymphocytopenia associated with COVID-19 is caused by the release of lymphocytes from the blood circulation then infiltrating the lung tissue and causing respiratory distress due to lung damage, rather than reduced lymphocyte production. Therefore, decreased LMR is a more adequate clinical biomarker for monitoring the progression of COVID-19 infection and its prognosis for other, less specific parameters, such as NLR and PLR.[36]

D. Absolute Lymphocyte Count (ALC)

It is known that lymphocytopenia, defined as an absolute lymphocyte count (ALC) <1000 cells/ μ L, occurs in COVID-19 and correlates with disease severity. It is known that lymphocytopenia is a common systemic manifestation of viral diseases, particularly coronaviruses such as SARS-CoV and MERS-CoV, which have been shown to cause lymphocytopenia.[37]

A retrospective cohort study on COVID-19 patients conducted by Jason Wagner et al. found evidence of association between lymphocytopenia and disease severity. COVID-19 patients admitted to the ICU had a higher lymphocytopenia rate than patients who were not admitted to the ICU. Patients with persistent lymphocytopenia during treatment with COVID-19 have a likely poor prognosis. Persistent lymphocytopenia is associated with a poor prognosis after diagnosis with sepsis. Drewery et al. (2014) hypothesized that this could be due to an anti-inflammatory response in the later stages of sepsis. Thus, there is a possibility that lymphocytopenia causes an immunosuppressive condition, causes more severe conditions in COVID-19 and requires ICU care.[37]

Coagulation factor interference in covid-19 patients

Thrombotic complications appear to be an important problem in patients with COVID-19. Initial reports on the COVID-19 pandemic indicated that infected patients generally had thrombocytopenia (64.2%) and increased D-Dimer (46.4%), while these rates were higher in patients with severe COVID-19 disease (each 57.7% and 59.6%). In addition, one of the common laboratory findings recorded in COVID-19 patients who require

hospitalization is an increase in D-Dimer. It has been established that elderly individuals and comorbid individuals (both groups tended to have higher D-Dimers) were more likely to die from COVID-19. Other supporting data shows that patients infected with this new type of coronavirus are at risk of developing DIC.[38, 40]

Thrombocytopenia and increased D-Dimer can be explained by excessive activation of the coagulation cascade and platelets. Viral infection elicits a systemic inflammatory response and causes an imbalance between procoagulant and anticoagulant homeostatic mechanisms. Various pathologic mechanisms are involved, including endothelial dysfunction, increased von Willebrand factor, activation of the Toll-like receptor (TLR), and activation of the tissue factor pathway. Platelets, after the introduction of the antigen, become active and interact with leukocytes to facilitate pathogen clearance through activation of the leukocytes and clot formation. Platelets are the main mediator of inflammation and sensors of infectious agents through the interaction of cell surface receptors and pathogens (pathogen pattern recognition receptors) or immune system derivatives (immunoglobulin Fc receptors and complement receptors).[39, 40]

Summary

Coronavirus Disease 2019 (COVID-19) is a new type of disease that manifests primarily as respiratory tract infections and in systemic diseases related to organ systems, including cardiovascular, respiratory, gastrointestinal, neurological, haematological and immune systems. This disease has a significant effect on the haematological system and hemostasis. Lymphopenia is an important laboratory finding. In addition, thrombocytopenia, leukocytosis, and neutrophilia were also found. Several other haematological parameters were found, including neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), lymphocyte to monocyte (LMR), and absolute lymphocyte count (ALC).

Blood hypercoagulability is common in COVID-19 patients who are hospitalized. In addition, d-Dimer enhancement, PT and aPTT elongation, and fibrin product degradation have been reported. Therefore, the occurrence of disseminated intravascular coagulation (DIC) requires continued vigilance and early prevention.

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Conflict of interest

There are no conflicts of interest to declare by any of the authors of this study.

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