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REVIEW

SARS-CoV-2 Infection: Differences in Hematological Parameters Between Adults and Children

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Abstract: Since December 2019, corona virus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global pandemic, posing a huge threat to human health, and the current epidemic prevention situation is still severe. Hematological parameters directly reflect the damage of SARS-CoV-2 to human blood cells, which can better assess the severity and prognosis of patients infected with COVID-19, but hematological parameters have some differences between adults and children. This article comprehensively reviews the differences in hematological parameters between adults and children after SARS-CoV-2 infection, and provides a reference for the diagnosis and treatment of COVID-19.

Keywords: SARS-CoV-2, COVID-19, hematology, blood parameters, adults, child

Introduction

Coronavirus disease 2019 is a disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[1] It is a global pandemic and has become a public health emergency of international concern (PHEIC).[2] So far, the epidemic has rapidly spread to 222 countries around the world.[3] As of May 9, 2021, a total of 158,312,868 cases of COVID-19 have been diagnosed globally, with a total of 3,296,591 deaths.[4] With the emergence of SARS-CoV-2 mutants, the number of children infected with SARS-CoV-2 has gradually increased worldwide.[5,6] According to a report issued by the American Academy of Pediatrics (APP) and Children's Hospital Association (CHA) on April 29, 2021, in the United States alone, there are 3,782,724 children were diagnosed with COVID-19, accounting for 13.8% of the total number of COVID-19.[5] The positive rate of SARS-CoV-2 in children in the United States is 5.3–33.4%, 1.2–3.1% of COVID-19 hospitalized patients are children, and 0.00–0.21% of COVID-19 deaths are children.[5] Bolaños analyzed the 54,971 confirmed cases of novel coronavirus pneumonia (NCP) registered by the Colombian National Institute of Health (CNIH) and found that the number of confirmed cases of COVID-19 in children accounted for 9.2% of all cases (5062 cases), and the number of confirmed cases of COVID-19 in Omani children accounted for 6.6% of all cases.[7] According to the analysis of 44,672 confirmed cases of COVID-19 by the China's Center for Disease Control and Prevention (CDC), patients aged 20 to 79 years old accounted for 97.9%, with a mortality rate of 2.3%, and under 20 years old accounted for 2.1%, with a mortality rate of 0.02%.[3] So far, there have been many data showing clinical manifestations in adults and children. However, the

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differences in hematological parameters between children and adults after SARS-CoV-2 infection are still unclear. Therefore, this article summarizes and discusses the differences in hematology-related parameters between adults and children after SARS-CoV-2 infection in order to further improve the understanding of COVID-19.

COVID-19 and White Blood Cells

SARS-CoV-2 can cause changes in the number of white blood cells, especially lymphocytes and neutrophils.[8] Slomka et al reviewed the white blood cells' condition in hematology of COVID-19 patients, around one in four COVID-19 patients were suffered from leukopenia (white blood cell $<4.0\times10^9$/L).[8] There is an article showing that lymphopenia is a common hematological manifestation in many patients with COVID-19 whether they are in China or the United States.[9] Guan[10] analyzed the peripheral blood cells (PBC) of 1099 COVID-19 patients, and the results showed that the number of lymphocytes and white blood cells were decreased (lymphocytes $<1.5\times10^9$/L, white blood cells $<4.0\times10^9$/L), respectively accounted for 83.2% and 33.7% of the studied cases. Qin et al[11] conducted a study on 452 hospitalized COVID-19 patients and found that patients with severe infection are more likely to suffer from lymphopenia, and the white blood cell count and neutrophils to lymphocytes ratio (NLR) are higher than others. In addition, Ferrari et al[12] also found the laboratory examination of 207 suspected COVID-19 patients that there was a significant difference in the number of white blood cells in the two groups of patients with SARS-CoV-2 reverse transcription-polymerase chain reaction positive (rRT-PCR) and rRT-PCR negative, and positive COVID-19 patients have a higher number of neutrophils and a lower number of lymphocytes.

However, the changes in the blood system of children may be different from those of adults. For example, the reduction of white blood cell and lymphocyte counts in children with COVID-19 are rare,[13] and it mostly occurs in the early stages of the disease, and some children may have white blood cell counts in the normal range.[14] The study by Qiu et al[15] also suggested that the number of white blood cells in children is not statistically significant to the severity of the disease.

COVID-19 and Lymphocytes

Like many viruses, SARS-CoV-2 can destroy the immune function of $CD4^+$T cells and weaken their ability to secrete cytokines against pathogens, thereby reducing the ability of $CD4^+$T cells to kill pathogens, so we think SARS-CoV-2 infection is related to immune response, and the number of lymphocytes is positively correlated with immunity.[16,17] In severe SARS-CoV-2 infection, the virus enters the human body and releases a large amount of toxins, causing viremia and infecting the entire body, stimulating the human body to produce a large number of inflammatory cytokines, and the continuous disorder of inflammatory cytokines may lead lymphocytes to occur apoptosis, and some cytokines can also induce lymphocyte deficiency.[18] Therefore, severe cases are more likely to have a lower lymphocyte count, and the decrease of $CD4^+$T cell count is more pronounced than other T lymphocytes.[11] In addition, $CD8^+$ T cells can attack pathogens, but due to the reduction of $CD4^+$T cells, their ability is weakened.[19] Thereby, as the disease progresses, lymphocytes in COVID-19 patients may continue to decline or even die.[19] This is consistent with Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV).[20] Diao et al[21] retrospectively analyzed the lymphocytes of 522 patients diagnosed with COVID-19, and found that in elderly patients (≥60 years old) and intensive care unit (ICU) patients, the total number of T cells, $CD4^+$T cells and $CD8^+$T cells were significantly reduced, lower than 800/μL, 300/μL and 400/μL, and they were negatively correlated with the survival rate of patients. They also further analyzed the expression of T cell failure marker (PD-1) in the peripheral blood of 14 COVID-19 patients, compared with non-ICU patients and healthy groups, the expression of PD1 in ICU patients were increased, showing that as the severity of COVID-19 patients increases, their T cell population will continue to be consumed and exhausted.[21] Similarly, someone analyzed the clinical data of 99 COVID-19 adult hospitalized patients and found that the lymphocytes, $CD4^+$T cells and $CD8^+$T cells in the peripheral blood of COVID-19 patients were gradually decreased, and the count of $CD4^+$T cells and $CD8^+$T cells can detect and identify critically ill patients earlier.[22] Consequently, the lymphocyte count of COVID-19 patients shows a downward trend, especially in critical patients, which is of great significance for assessing the severity of patients.[10,19,20,23,24]

However, there are some differences between children and adults infected with SARS-CoV-2. In the acute phase of COVID-19 in children, $CD4^+$T cells are slightly elevated, while $CD4^+$Treg is suppressed, and these children with COVID-19 have not obvious severe symptoms,

which is different from adults.[25] Among 68 children with SARS-COV-2 in Marrakech, Morocco, 5 cases (7%) were found to have neutropenia, while only 2 cases (3%) had lymphopenia.[26] Compared with adults, fewer children are suffered from COVID-19 with lymphopenia.[13] This may be related to the higher levels of natural killer (NK) cells in the blood of children than in adults,[27] but it may be also related to the effective innate immune system and the maturity of ACE2,[14] which is also the reasons for a symptom of children infected with COVID-19 lighter than adults. In a survey of 171 children, only 3.5% of them had lymphopenia,[28] and it is a sharp contrast with the study of Guan et al.[10,15] Although the decrease of lymphocyte count is not common in COVID-19 children, the number of lymphocytes in moderately infected people is less than that in mildly infected people ($P = 0.0083 < 0.01$), and the lymphocyte count of the deaths is lower than that of survivors,[15] this is common with adults.[29] Therefore, although the decrease in the lymphocyte count of children with COVID-19 are not as obvious as those in adults, it cannot be ruled out that the lymphocyte count can be used as an indicator of the severity of childhood diseases.

COVID-19 and Neutrophils

When SARS-CoV-2 invades the human body, it releases toxic substances or destroys related cells, and cause inflammation, which chemotactically stimulates the aggregation of neutrophils and releases a large number of inflammatory mediators and cytokines, such as IL-1, IL-8, etc.[30,31] Therefore, the number of neutrophils in severe COVID-19 patients can increase.[29] Studies have shown that plasma cytokines such as IL-7, IL-10, G-CSF and TNF-F in patients with severe COVID-19 are higher than those in non-ICU patients.[23] In addition, neutrophils can release a large amount of elastase, induce cell damage, and exert corresponding cytotoxic effects. Although the clinical features of COVID-19 pneumonia are similar to other pneumonia, the increase in neutrophils is more pronounced in patients with COVID-19 pneumonia.[32] Wang et al[20] found that the number of neutrophils in patients with severe COVID-19 infection was higher than that in mild patients, especially in the dead patients, the increase in neutrophils was significantly higher than that in survivors. It is related to the mechanism by which neutrophils attack SARS-CoV-2 and the severe COVID-19 patients are combined with other bacterial infections which increases the number of neutrophils.[33] Therefore, in adult patients with severe COVID-19, the number of neutrophils is significantly higher than that of mild patients (Table 1).

For children with COVID-19, for example, in the study of Yarali et al,[34] 7 COVID-19 patients (23.3%) had a decrease in the number of neutrophils, which was the same as the analysis result of Gizem.[35] However, in children diagnosed with COVID-19 with multi-system inflammatory syndrome (MIS-C), the number of neutrophils has increased,[36] and many cases can be diagnosed with neutrophilia.[37–40] The study by Shahin et al[41] is consistent with the above. They conducted a comprehensive analysis of the laboratory examinations of 88 children with COVID-19 and showed that the absolute neutrophil count is positively correlated with the severity of the disease and the length of stay in the hospital, and the neutrophil count of children with severe illness was significantly increased.[41] In summary, in ordinary children with SARS-CoV-2 infection, the number of neutrophils can be reduced, but it is significantly higher in severe children (Table 2), which is consistent with the results of adult studies.

COVID-19 and the Ratio of Neutrophils to Lymphocytes (NLR)

In peripheral blood, the ratio of neutrophils to lymphocytes (NLR) is a marker of inflammation, and it has become one of the recognized effective indicators of systemic inflammation.[42]

In the early stage of COVID-19, the number of T lymphocytes are decreased, but the number of neutrophils are normal or slightly decreased.[11,19] At this time, the NLR is increased relatively. However, in the later stages of the disease, as the infection worsens and other bacterial infections occur, the number of neutrophils are increased significantly, while the lymphocyte count is still decreasing.[19,32,33] Therefore, the NLR is increased significantly, that is, the more severe the patients are, the NLR is higher, this also indicates a poor prognosis.[32] Xu conducted a study on 187 patients who diagnosed with COVID-19 and found that inflammation can stimulate the production of neutrophils and accelerate the apoptosis of lymphocytes, which is closely related to the risk of death in the hospital.[43] For every increase in NLR, the risk of death in hospital is increased by 8%, that is, patients with elevated NLR have a higher risk of death during hospitalization, and the risk of death in men is greater than that in women.[43] Tan compared the severity

Table 1 The Hematological Parameters of Adults with COVID-19 Between Severe Patients and Non-Severe Patients

Reference	Leucocytes,×10^9/L, Median (IQR)		Lymphocytes, ×10^9/L, Median (IQR)		Neutrophils, ×10^9/L, Median (IQR)		Neutrophil to Lymphocyte Ratio, Median (IQR)		D-Dimer, μg/L, Median (IQR)	
	Non-Severe	Severe	Non-Severe	Severe	Non-Severe	Severe	Non-Severe	Severe	Non-Severe	Severe
[11]	NR	NR	1.0 (0.7–1.3)	0.8 (0.6–1.1)	3.2 (2.1–4.4)	4.3 (2.9–7.0)	3.2 (1.8–4.9)	5.5 (3.3–10.0)	NR	NR
[20]	NR	NR	0.9 (0.6–1.2)	0.8 (0.5–0.9)	2.7 (1.9–3.9)	4.6 (2.6–7.9)	NR	NR	106.0 (101.0–285.0)	414.0 (191.0–1324.0)
[23]	5.7 (3.1–7.6)	11.3 (5.8–12.1)	1.0 (0.7–1.1)	0.4 (0.2–0.8)	4.4 (2.0–6.1)	10.6 (5.0–11.8)	NR	NR	500.0 (300.0–800.0)	2400.0 (600.0–14,400.0)
[42]	5.0 (3.8–6.0)	7.0 (4.5–11.3)	1.2 (0.9–1.6)	0.5 (0.3–0.9)	3.1 (2.1–4.2)	6.1 (3.3–10.1)	NR	NR	420.0 (340.0–850.0)	1220.0 (550.0–11,540.0)
[57]	4.9 (4.0–5.6)	5.2 (4.7–6.8)	1.4 (1.0–1.8)	0.9 (0.7–1.3)	2.8 (2.1–3.5)	3.3 (3.0–5.8)	NR	NR	NR	NR
[68]	4.4 (3.6–5.7)	7.4 (4.2–8.6)	1.2 (0.9–1.5)	0.6 (0.4–0.9)	NR	NR	2.9 (1.7–3.5)	8.7 (3.7–14.4)	NR	NR

Notes: Presentation for median (IQR); p value<0.05.
Abbreviations: NR, Not Report; IQR, interquartile range.

of NLR and CT of patients, and found that NLR was positively correlated with CT severity score, while the number of lymphocytes was negatively correlated with CT severity score.[44] Hakan Keski found that the number of neutrophils were increased significantly in 8.2% (25/304) deaths, and the NLR was significantly higher than that of survivors.[29] And NLR was used as a reference standard for all patients infected with COVID-19 in the study for grouping, with NLR = 3.07 as the boundary, the mortality rate of patients with a value which was greater than 3.07 was significantly higher than that of other patients.[29]

In short, NLR can be used as an easy-to-measure biological indicator of the severity of COVID-19 in adults, which can help us determine more clearly for the severity of SARS-CoV-2 infection in patients. Therefore, NLR can be used as an independent risk factor for disease severity and prognosis.[45–47]

In addition, are the NLR different between children with COVID-19 and adults? A retrospective study analyzed the clinical manifestations and laboratory examinations of 39 patients with COVID-19 under the age of 18, and found that there were no significant changes in the laboratory examinations of patients in ordinary cases, but the NLR was significantly increased in severe children,[48] which is consistent with adult's data. Garcia-Salido conducted a statistical analysis of children with multiple system inflammatory syndrome secondary to COVID-19 (MIS-C), the neutrophils and NLR in the MIS-C group were both higher than non-MIS-C group.[49] Since MIS-C is a more serious clinical manifestation in the course of COVID-19 in children, NLR can also be used as one of the indicators to assess the severity of the disease in children with SARS-CoV-2 infection.[49]

COVID-19 and Eosinophils

As one of the important cells in allergies, 50% of patients have decreased eosinophils between the ages of 20 and 100 who were infected with SARS-CoV-2.[50]

A researcher's clinical hematology analysis of 140 COVID-19 patients found that 52.9% of patients had eosinophilia.[51] In addition, the number of eosinophils in COVID-19 patients is negatively correlated with the severity of the disease.[52] Comparing to moderate to severe patients, the number of eosinophils in severe patients was decreased significantly, and under the condition of controlling the influencing factors, the decrease level was positively correlated with the prognosis.[52,53] At the same time, the number of eosinophils was also correlated with platelet count and D-dime in the study, and which makes the patients with fewer eosinophils have a higher risk of death.[54] But at present, the cause and mechanism of eosinophilia are not fully understood. It may be related to the large secretion of adrenal corticosteroids to enhance the body's anti-infection ability, or the use of glucocorticoids during treatment to reduce

Table 2 The Ratio of Hematological Value in Adults and Children with COVID-19

	Adults								Children							
Reference	[10]	[23]	[29]	[45]	[51]	[69]	[70]	[81]	[15]	[26]	[34]	[35]	[37]	[41]	[63]	[89]
Region	China	China	Turkey	China	China	China	China	China	China	Morocco	Turkey	Turkey	United States	Saudi Arabia	United Arab Emirates	Oman
Total patients	1099	41	302	582	138	149	135	161	36	68	40	251	288 (MIS-C)	88	288	56
Severe	173	13	25	116	56	NR	40	30	NR	NR	NR	NR	148	5	NR	5
Non-severe	926	28	277	466	82	NR	95	131	NR	NR	NR	NR	140	83	NR	51
Leucopenia(%)	33.7	25.0	12.9	NR	19.6	24.2	20.7	41.0	31.0	8.3	13.3	NR	NR	18.0	NR	21.0
Neutropenia(%)	NR	NR	8.3	NR	NR	22.8	NR	NR	NR	13.9	23.3	14.3	<40.0	7.2	10.4	NR
Lymphopenia(%)	83.2	63.0	19.2	51.6	75.4	35.6	50.4	26.1	31.0	2.8	30.0	25.9	>75.0	21.7	NR	39.0
Anemia(%)	NR	NR	40.4	8.7	NR	NR	NR	8.1	NR	5.9	NR	NR	>40.0	NR	NR	NR
Thrombocytopenia (%)	36.2	5.0	14.2	16.7	NR	13.4	17.0	6.8	NR	5.6	NR	4.40	>50.0	NR	72.0	NR
D-dimer>500μg/L(%)	46.4	NR	66.6	66.7	43.2	14.1	NR	NR	8.3	33.5	NR	NR	NR	38.7	NR	NR

Notes: Leucopenia means leucocytes are less than 4.0×10^9/L; Neutropenia means neutrophils are less than 1.5×10^9/L; Lymphopenia means lymphocytes are less than 1.5×10^9/L; Anemia means hemoglobin are less than 120g/L; Thrombocytopenia means platelets are less than 150×10^9/L; The normal value of D-dimer is less than 500μg/L.

Abbreviations: NR, Not Report; MIS-C, Multisystem Inflammatory Syndrome of COVID-19.

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eosinophils and this may be also related to the direct effect of SARS-CoV-2 on the general immune system.[53] During studying the therapeutic effect of lopinavir, it was also found that the eosinophil level in the COVID-19 study cases was lower than normal range in the early stage, especially during the first week of hospitalization; however, it cannot be solely attributed to glucocorticoid exposure.[55] Because none of the patients in the experimental group received glucocorticoid treatment at the beginning of hospitalization.[55] Therefore, in the case of acute lung injury caused by SARS-CoV-2, the reduction of eosinophils may be related to the stress response mechanism, and the eosinophils are on the rise during the treatment process, and the granulocytes of eosinophils was continued to improve keeping with the imaging and virological improvement of all discharged patients.[55] Thus, eosinophils may be one of the signs of the progress and recovery of COVID-19.[55] But there are few data on the changes in the number of eosinophils in children with COVID-19, so its role is not clear.

COVID-19 and Platelets

COVID-19 and Platelet Count

The decrease of platelet count is not as common as lymphopenia in patients with COVID-19.[9] (Table 2) Guan et al[10] studied 1099 COVID-19 patients, 36.2% of COVID-19 patients had thrombocytopenia ($<150\times10^9$/L), and 36.1% of non-critical patients had thrombocytopenia, but thrombocytopenia is as high as 57.7% in critical patients. Chen et al[56] and Qian et al[57] believe that thrombocytopenia in patients with COVID-19 may be related to SARS-CoV-2's inhibition of bone marrow hematopoiesis and increased levels of auto-antibodies and immune complexes to cause the immune system to specifically destroy platelets. In addition, platelet aggregation and thrombosis can also increase platelet consumption.[58] Cheung et al[9] summarized several mechanisms of thrombocytopenia, including viral infection causing thrombocytopenia directly, cytokine storms damaging bone marrow, lung injury causing platelet destruction indirectly, and immune complex damaging to platelets, ect. A study has shown that the platelet count is related to the severity of the disease and the prognosis, if the platelet count is greater than 135×10^9/L, then patients with COVID-19 are less likely to develop severe cases.[59] And compared with non-severe cases, severe COVID-19 patients' platelet was declined constantly with the disease progresses.[59] Lippi et al[60] meta-analysis of 9 items of 1779 COVID-19 patients showed that low platelet count is related to the increase in severe illness and mortality of COVID-19 patients, so the decrease in platelet count should be used as a clinical indicator of disease deterioration during hospitalization. Raymond systematically reviewed 23 studies with a total of 8963 COVID-19 patients, the incidence of thrombocytopenia was 18%, the incidence of sequelae in patients with thrombocytopenia was 50%, and the incidence of sequelae in patients without thrombocytopenia is 26%.[61] Yang also retrospectively analyzed the platelet counts of 1476 COVID-19 patients and found that 306 (20.7%) had thrombocytopenia, and 238 (16.1%) were died, and the mortality rate was related to the degree of thrombocytopenia, it means the lower the count platelet is, the higher mortality rate .[62] In this study, the mortality rate of platelet counts between (0–50) $\times10^9$/L was 92.1%, while that of platelet count greater than 150×10^9/L was only 4.7%.[62]

Similarly, the platelet count in children with COVID-19 is also mainly reduced, accounting for about 72.2% of the studied cases, which is higher than that adults.[63,64] In addition, thrombocytopenia ($<150\times10^9$/L) is also common in children with severe SARS-CoV-2 infection.[65] A single-center retrospective study in Turkey showed that the average platelet value of children with COVID-19 was significantly lower than others, and platelet reduction was more obvious in severe COVID-19 children, which was closely related to the severity of the disease ($P<0.05$).[35] A study by Davies et al[66] showed that the platelets of children with severe COVID-19 children were significantly less than 150×10^9/L on the first day of admission.

Therefore, although the decrease of platelet count is not as common as lymphopenia in COVID-19, it is one of the important indicators to assess the severity of the patient's disease in both adults and children, we can further study the effect and mechanism of this change.

COVID-19 and Platelet to Lymphocyte Ratio (PLR)

PLR refers to the ratio of platelets to lymphocytes, which can reflect the degree of inflammation in the human body in time.[67] It is related to cytokine storm and is similar to NLR in clinical sense.[67] Sun divided 116 patients with COVID-19 into a general group, an ICU severe group and a non-ICU severe group, and the results showed that the PLR of the ICU severe group reached a peak on the seventh day of treatment and then dropped rapidly, while

the other two group showed a downward trend.[68] It is consistent with the results of Qu et al[67] that 6 elderly critical COVID-19 patients had a significant increase in PLR at the beginning of treatment, with a maximum PLR of 626.27, and then it began to decline. These patients have a longer hospital stay and poor prognosis, indicating that PLR is an independent factor in the treatment of critical patients, and it reminds us that in the clinical treatment process, if the early PLR value is greater than 126.7, the patient's condition may get worse.[67] Therefore, PLR has a certain relationship with the prognosis of the disease, but it is rarely mentioned in children. At present, its mechanism is not fully understood, there should be relevant research carried out about it.

COVID-19 and D-Dimer and Fibrinogen

In addition to changes about platelet-related counts, D-dimer and fibrinogen, which are related to blood coagulation, also changed during SARS-CoV-2 infection.[20,23,56,69,70] In the study of Gizem,[35] it was found that the average value of fibrinogen in confirmed COVID-19 patients was lower than the average value of suspicious patients. Among inpatients, 71.1% of patients with D-dimer >621μg/L, while outpatients' D-dimer <621μg/L. As the disease progresses, D-dimer levels tend to increase. In a children's hospital in New York, about 93% (25/27) of the children with D-dimer levels at admission were higher than >500μg/L, even up to 5000μg/L, which was higher than that nearly 10 times at admission.[71] Some scholars have also analyzed 6202 COVID-19 patients, during the diagnosis and treatment process, 75.0% of the patients were tested for D-dimer level, and it was found that about 16.8% of patients had D-dimer multiples compared with the normal value, the increase can reach more than 8 times.[72] In Hakan Kesi's[29] analysis about the hematological indicators of SARS-CoV-2 people, it was found that the median value of fibrinogen was 0.1μg/L, which was significantly lower than the lower limit of normal 1.95g/L, even <0.1μg/L, which can reach 69% (P=0.0029<0.05).[23] In addition, D-dimer and fibrinogen can also reflect the severity of the disease. When acute lung injury occurs in severe COVID-19 patients, the body is stimulated to activate blood coagulation, and a large number of thrombin are formed in the body.[73] At this time, too much thrombin will cause platelet consumption, leading to secondary fibrinolysis and DIC.[73] In this study, approximately 71.4% of the patients who were died met the criteria for disseminated intravascular coagulation (DIC) defined by the International Thrombosis and Hemostasis Association.[73] Moreover, the deterioration of coagulation function is positively correlated with the severity of the disease.[74,75] Due to decreased fibrinolysis and elevated D-dimers, thrombus may be formed in the body, even resulting in DIC to happen, and then, the condition of patients will deteriorate soon.[76] In severe cases or death cases, the level of D-dimer is significantly higher than that of other patients, and the content of fibrinogen is significantly reduced, and there are statistics scientific significance,[23,29,48] where D-dimer greater than 1000μg/L is considered to be related to poor prognosis.[10] The rate of COVID-19 suffered by DIC has been reported as 71.4% for deaths.[76] At present, we can use Thrombelastography (TEG) analysis and Rotation Thromboelastometry (ROTEM) test to assess the risk of thrombosis and analyze the blood to provide an overview of hypercoagulable state in severe adult COVID-19 patients to prevent and give the anti-coagulant treatment for thrombosis to avoid death due to thrombosis and DIC.[77] In a study about viscoelastic testing for pediatric patients, they used ROTEM analysis to assess its feasibility in determining thrombosis risk in children, showing that elevated extrinsic thromboelastometry maximal clot firmness (EXTEM MCF) and fibrinogen function thromboelastometry maximal clot firmness (FIBTEM MCF) in ROTEM parameters are evidences for increased clot strength.[78] Al-Ghafry et al[79] also reported that MIS-C patients had a high level of D-dimer with evidence for hypercoagulability on ROTEM, and there was a significant correlation for FIBTEM MCF when D-dimers >1000μg/L.

So, whether in adults or children, D-dimer is significantly increased, which is related to the severity and prognosis of COVID-19 patients, and ROTEM test and TEG may be helpful to analyze the whole blood to assess the risk of thromboprophylaxis, particularly in critically ill patients.[76,78,79]

COVID-19 and Red Blood Cells

With the development of COVID-19, the red blood cell count and hemoglobin are decreased, and the red blood cell count of patients with severe COVID-19 is lower than others, but this is not the main problem in COVID-19 patients.[10,23,24,56,70,80,81] Sun et al studied the hemoglobin changes in the COVID-19 group (116 cases) and the control group (100 cases), and found that the median value of hemoglobin in the COVID-19 group was 132.5g/L, which was significantly lower than the median value of 146.5g/L

in the control group.[68] Among them, there are 27 severe patients in the COVID-19 group, and their hemoglobin concentrations are lower than that of ordinary patients (124g/L vs 134g/L, P=0.013). Henry also stated that compared with patients with mild/moderate COVID-19, patients with severe COVID-19 had significantly lower hemoglobin levels (P<0.001), which was negatively correlated with severity.[82] This study is consistent with the results of Taneri et al.[80] Cen et al[83] also showed that hemoglobin levels below 110g/L are closely related to the progression of COVID-19. Among the severe COVID-19 patients studied by Benoit, the probability of anemia can reach 43.8%, of which mild anemia (110–119g/L) accounts for 18.8%, and moderate anemia (80–109g/L) accounts for 18.8%, severe anemia (<80g/L) accounted for 6.3%, each of which was higher than that of non-severe patients, and there is no severe anemia occurred in non-severe patients.[84] In addition, Lazarian reported that 7 cases of COVID-19 patients developed autoimmune hemolytic anemia (AIHA) during the course of their illness, with an average hemoglobin about 70g/L, and in severe cases, the hemoglobin level decreased by more than 30g/L.[85] Taherifard et al[86] also summarized 94 patients with COVID-19 complicated by autoimmune diseases, of which 22 (22/94) COVID-19 patients were complicated by AIHA, and the maximum hemoglobin decline reached 70g/L, which may be related to the autoimmune function of COVID-19 patients. Of course, the decrease in hemoglobin may be also related to the increase in serum ferritin concentration during the acute reaction period, which reduces the use of iron produced by erythrocytes.[80] At present, the cause of anemia in COVID-19 is not yet fully clear. It has been reported that SARS-CoV-2 can destroy kidney tissue rich in ACE2 receptors, thereby can reduce red blood cell production and increase the destructive effect, which eventually leads to anemia.[87]

The average hemoglobin of children with COVID-19 was also significantly reduced (P<0.001), children with severe COVID-19 had lower hemoglobin levels than those with non-severe COVID-19, and they had a hemoglobin of 115 ±24g/L, the hemoglobin of non-severe children is 126±20g/L.[35] Kulkarni et al[88] studied 13 infants infected with SARS-CoV-2 and found that the hemoglobin levels of these infants were below the normal range, especially in a patient who was 13-month-old with acute respiratory distress syndrome (ARDS), the hemoglobin level is as low as 22g/L. It is believed that severe anemia is one of the risk factors that affect the outcome of the disease. In a cohort study of 56 children with COVID-19 in Oman, 38% showed signs of anemia, among them, 86% (6/7) of severe children developed anemia, and the probability of anemia was related to age.[89] In addition, Feldstein showed that children with hemoglobin level below 90g/L can reach about 50% in children with multiple system inflammatory syndrome (MIS-C) secondary to COVID-19, it is even more significant in the study of Toubiana, about 95% of these children have a median hemoglobin of 86g/L, which is as low as 53g/L.[37,90]

Consequently, whether it is an adult patient or a child patient with COVID-19, the red blood cell count and hemoglobin may be reduced than normal human, especially in severe patients, and it may be related to cytokine storm and iron metabolism, but it is not yet understood clearly.[91–93]

COVID-19 and Blood Cancer Patients

Due to the low autoimmune function of cancer patients, radiotherapy and chemotherapy will damage normal cells, causing toxicity and side effects. Therefore, cancer patients are more likely to be infected with COVID-19 and may affect the prognosis of cancer patients.[94,95]

According to Yang et al[96] conducted a comprehensive analysis of a total of 63,019 COVID-19 patients in 19 retrospective studies, about 6% of patients had tumor with COVID-19, and the mortality rate was significantly higher than that of non-cancer patients (14.6% vs 3.8%), especially in active tumors. There are many types of tumors. Among patients with tumor infected with SARS-CoV-2, lung cancer is the most common one (22/105), followed by gastrointestinal cancer (13/105), breast cancer (11/105), thyroid cancer (11/105) and hematological malignancies (9/105), and hematological malignancies and lung cancer have a higher probability of serious cases.[97] Among patients with hematological malignancies and COVID-19, lymphoma patients accounted for 11%, followed by leukemia (10%) and multiple myeloma (4%), and for this type of patients, the mortality rate reached 23.5%, and in the changes of hematological indicators, C-reactive protein is significantly increased, which is closely related to mortality.[98] Kim et al also systematically analyzed the clinical characteristics of 33 COVID-19 patients with hematological malignancies, the proportion of chronic lymphocytic leukemia (CLL) patients reached 39.4% (13/33), and multiple myeloma accounted for 33.3% (11/33), acute lymphoblastic leukemia and acute

Table 3 The Main Hematological Parameters in Adults and Children with COVID-19

	Adults								Children							
First author	[10]	[11]	[12]	[20]	[23]	[29]	[68]	[70]	[15]	[26]	[35]	[41]	[63]	[65]	[71]	[89]
Region	China	China	Italy	China	China	Umraniye	China	China	China	Morocco	Turkey	Saudi Arabia	United Arab Emirates	Kuwait and Saudi Arabia	United States	Oman
Total patients	1099	452	105	138	41	302	116	135	36	68	251	88	288	25	27	56
Age, years, median (IQR) or mean±SD	47.0 (35.0–58.0)	58.0 (47.0–67.7)	61.8 ±16.4	56.0 (25.0–87.0)	47.0 (35.0–58.0)	57.1 ±17.6	50.0 (41.0–57.0)	47.0 (36.0–55.0)	8.3 ±3.5	<15.0	8.9 ±6.0	5.7 ±4.7	6.5 (2.0–12.3)	2.8 (0.2–8.5)	<21.0	1.8 (0.2–6.9)
WBC,×10^9/L, median (IQR) or mean±SD	4.7 (3.5–6.0)	5.3 (3.9–7.5)	6.5 ±2.6	4.5 (3.3–6.2)	6.2 (4.1–10.5)	6.8 (0.9–34.3)	4.6 (3.7–6.4)	5.4 (4.1–7.8)	6.1 ±2.1	12.3 (3.8–22.9)	10.0 ±5.8	7.9 ±3.7	7.4 (5.4–9.6)	10.0 ±8.8	20.6 ±12.1	9.4 (5.8–12.9)
NEU, ×10^9/L, median (IQR) or mean±SD	NR	3.9 (2.6–5.8)	4.8 ±2.4	3.0 (2.0–4.9)	5.0 (3.3–8.9)	4.5 (0.6–31.6)	3.1 (2.3–4.3)	3.5 (2.6–4.4)	NR	3.3 (1.0–7.0)	6.3 ±3.9	3.8 ±3.1	2.3 (1.6–3.6)	6.2 ±6.2	15.3 ±10.0	3.8 (1.7–7.5)
LYM, ×10^9/L median (IQR) or mean±SD	1.0 (0.7–1.3)	0.9 (0.6–1.2)	1.1 ±0.8	0.8 (0.6–1.1)	0.8 (0.6–1.1)	1.4 (0.1–4.2)	1.0 (0.7–1.4)	1.1 (0.7–1.5)	2.4 ±0.8	4.3 (1.3–12.5)	2.8 ±2.3	3.3 ±2.0	NR	2.68 ±2.5	1.3 ±1.1	2.7 (1.7–5.0)
NLR median (IQR) or mean±SD	NR	4.2 (2.5–7.7)	NR	NR	NR	3.1 (0.6–50.0)	2.9 (1.8–4.8)	NR	NR	NR	4.7 ±6.3	NR	NR	NR	NR	NR
Hb, g/L median (IQR) or mean±SD	134.0 (119.0–148.0)	NR	NR	NR	126.0 (118.0–140.0)	125.0 (60.0–166.0)	132.5 (122.3–145.8)	133.0 (122.0–147.0)	NR	125.6 (77.0–158.0)	125.0 ±18.4	120.6 ±23.8	125.0 (116.0–133.0)	111.0 ±34.5	94.0 ±29.0	109.0 (93.0–124.0)
PLT, ×10^9/L median (IQR) or mean±SD	168.0 (132.0–207.0)	NR	208.1 ±92.1	163.0 (123.0–189.0)	164.5 (131.5–263.0)	218.0 (34.0–553.0)	180.5 (145.5–229.0)	158.0 (131.0–230.0)	NR	NR	283.6 ±77.4	318.5 ±134.7	87.0 (255.0–372.0)	243.0 ±167.0	175.0 ±173.0	328.0 ±153.0
D-dimer, μg/L median (IQR) or mean±SD	>500 ug/L, 46.4%	NR	NR	NR	500.0 (300.0–1300.0)	793.0 (20.0–19,400.0)	NR	400.0 (200.0–600.0)	290.0 ±200.0	3100.0 (270.0–12,000.)	1434.0 ±1337.0	400.0 (300.0–1370.0)	NR	NR	NR	860.0 (530.0–3080.0)

Notes: Normal value: WBC (4.0–10.0)×10^9/L; NEU (1.8–6.3)×10^9/L; LYM (1.1–3.2)×10^9/L; Hb (110.0–160.0)g/L; PLT (100.0–300.0)×10^9/L; D-dimer <500.0μg/L.

Abbreviations: IQR, interquartile range; NR, Not Report; WBC, White blood cell; NEU, Neutrophil; LYM, Lymphocyte; NLR, Neutrophil to lymphocyte ratio; Hb, Hemoglobin; PLT, Platelet.

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myeloid leukemia accounted for 12.2% (4/33).[99] At the same time, the laboratory tests of 33 patients with hematological malignancies were compared with those of COVID-19 alone.[99] Their white blood cell count and lymphocyte count were both higher than those of COVID-19 patients without hematological malignancies (38.9% VS 9.8%, 45.4% VS 8.2%), and thrombocytopenia was decreased (31.3% VS 11.4%), and the mortality rate was higher than others (40.0% VS 3.6%), both are statistically significant.[99]

The same is true for children with tumors. Madhusoodhan et al[100] analyzed 98 children with tumors and COVID-19. About 62.2% of the children had leukemia, of which 53% had acute lymphoblastic leukemia, and 45.9% of the 98 cases had mild COVID-19, 54.1% are moderate and severe patients.[100] And severe cases in children with malignant tumors combined with COVID-19 show the low lymphocytes, low neutrophils and low platelets, but in children with more severe COVID-19 tumors, the total number of white blood cells tends to increase.[101]

In children with hematological malignancies, such as SARS-CoV-2 infection, most children will postpone anticancer treatment,[102] and be given COVID-19 specific antiviral treatment (lopinavir/ritonavir combine with hydroxychloroquine), and continue to get chemotherapy until the nasopharyngeal swab specimen turns to be negative.[103] However, during the COVID-19 pandemic, there is some controversy as to whether asymptomatic or mild patients with malignant tumors combined with SARS-CoV-2 infection delay chemotherapy.[104]

Conclusion

In general, blood parameters are particularly important in diagnosing COVID-19 and assessing the prognosis of patients. For children, the number of lymphocytes are not as obvious as that of adults (Table 3), and the number of lymphocytes in adults are mostly decreased (Table 2). In addition, leukopenia, neutropenia, thrombocytopenia and increased D-dimer are occurred in both adults and children with COVID-19, and the incidence is higher in adults (Table 2). In addition, whether in adults or children, there are certain differences in hematological parameters between severe and non-severe patients, especially in adult patients, the value of leucocytes, neutrophils, lymphocytes, NLR and D-dimer are more obvious (Table 1).

In short, COVID-19 can lead to abnormal hematological parameters, and there are differences between children and adults, which can provide early clues for COVID-19 diagnosis and treatment. It is suggested that laboratories and clinicians should pay more attention to the dynamic changes of the above conventional hematological parameters, which may have important reference value for dynamically monitoring patients' condition and evaluating the treatment effect.

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Disclosure

The authors report no conflicts of interest in this work.

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