EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 9
Issue: 7
01-07
Year: 2022

EVALUATION OF SOME ASPECTS OF HEMATOLOGICAL VALUES AND D-DIMER IN COVID-19 POSITIVE CHILDREN

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Article Received on 25/04/2022 **Article Revised on 15/05/2022** **Article Accepted on 04/06/2022**

ABSTRACT

Background: The current pandemicCOVID-19 was first identified in December 2019 in Wuhan City of China. In Bangladesh COVID-19 cases were first identified on March 8, 2020. With the emergence of SARS-CoV-2 mutants, the number of children infected with SARS-CoV-2 has gradually increased worldwide. It affected the health systems and the routine of the population globally. Several hematological parameters have been reported tobe disturbed in patients with COVID-19, starting from the disease's early phases. So, hematological parameters are of significant importance for diagnosis and treatment decisions in severe COVID-19 patients. D-Dimer is also a specific diagnostic and prognostic bio-marker for COVID 19. It is also used as an inflammatory marker. Papers describing hemocytological and bio-markers like D-dimer in pediatric population of Bangladesh are scarce. **Objective:** The objective of this study is to evaluate blood cells, haemoglobin (Hb), haematocrit (Hct) and D-dimer in COVID-19 positive Children of Bangladesh. **Materials and Methods:** This was a cross-sectional descriptive study conducted in the department of Clinical Pathology, Bangladesh Shishu Hospital and Institute, Dhaka from August 2020 to April 2021. Forty-one COVID-19 positive children were recruited in the study. The measurements of hemoglobin blood cells, haemoglobin(Hb) and haematocrit (Hct) were done from an accredited laboratory. The study was approved by Institutional Ethics Review Board. A questionnaire was prepared and pretested to obtain the data. Statistical analysis was performed by on-line statistics calculator. The results were expressed as mean±SD, frequency and percentage of all variables into three categories: normal, lower than low normal and higher than high normal. **Result:** The mean age of the patients was 4.5 yrs with minimum age 5 days and maximum age 15 years. There were 27 (0.66%) male and 14 (o.44%) female children with a male/female ratio of 1.9:1. The mean±SD of D-dimer was 1.809±2.46 mg/L and 24.39% had higher than normal D-dimer value. The mean±SD of total WBC count was 9.44±5.25 x10^9/L and 14.63% children had leucopenia and 19.51% had leukocytosis. Neutropenia was present in 19.51% and neutrophilia in 34.15% children. Lymphopenia was present in 19.51% and lymphocytosis in 36.58% children. Similar number (12.20%) of patients had thrombocytopenia and thrombocytosis. RBC count was lower in 43.9% and higher in 7.31% children. The mean±SD of Hb was 10.82±2.41 gm/dl and anaemia was present in 56.1% children .60.97%) children had lower than normal Hct level and 4.88% had higher than normal value. **Conclusion:** The mean age of the patients was 4.5 yrs. Male children suffered almost 2 times more than female children from COVID-19. One-fourth of children had more than normal D-dimer level. Both leucopenia and leukocytosis were present in them but leukocytosis (19.51%) was more prevalent than leucopenia (14.63%). Neutrophilia (34.15%) was more prevalent than neutropenia (19.51%) in them. Similarly, lymphocytosis (36.58%) was more prevalent than lymphopenia (19.51%) in them. Equal number (12.20%) of patients suffered from thrombocytopenia and thrombocytosis. Significant number of COVID-19 positive children had less than normal RBC count (43.9%), hemoglobin level (56.1%) and hematocrit level (60.97%).

KEYWORDS: COVID positive children, haematological values, D-dimer.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), a current pandemic with several waves and several varients of viruses, resulting from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in December 2019 in Wuhan City, Hubei

Province, China.[1] SARS-CoV-2 has spread quickly across the world. It has been causing various economic and social impacts, affecting globally the health systems and the routine of the population.[2]

On February 11, 2020, the WHO announced a new name for the epidemic disease caused by 2019-nCoV: 2019Coronavirus Disease (COVID-19). As for the virus itself, the International Committee on Taxonomy of Viruses (ICTV) has renamed the previously provisionally named 2019-nCoV as severe acute respiratory syndrome coronaviruse-2, SARS-CoV-2[3] In Bangladesh COVID-19 cases were first identified on March 8, 2020 and first death occurred on March 21, 2020. On 6 May, cases were confirmed in all districts.[4]

With the emergence of SARS-CoV-2 mutants, the number of children infected with SARS-CoV-2 has gradually increased worldwide.[5] 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] Bolanos 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.[6] 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%.[7] So far, there have been manydata showing clinical manifestations in adults and children.It appears to affect children less severely than adults, with majority of benign forms and asymptomatic cases[1] and reports of death are scarce.[8,9] However, the pediatric population may play a major role in the community spread of SARS-CoV-2. In addition to viral shedding in nasal secretions, there is evidence of fecal shedding for several weeks after diagnosis, which poses a challenge for infection control.[10] The COVID-19 clinical features can include various symptoms, such as fever, myalgia, dry cough, dyspnea, fatigue, radiological evidence of ground glass lung opacities compatible with atypical pneumonia, diarrhea, and neurological manifestations. Furthermore, its severity is extremely variable,and for this reason, this disease can be classified as asymptomatic, mild,moderate, or severe.[2]

According to a review article of de Souza et al (2020) the clinical features of COVID-19 positive children include fever (47.5%), cough (41.5%), pneumonia (36.9%), pharyngeal erythema (20.6%), tachycardia (18.6%), tachypnea (13.4%), nasal symptoms (11.2%), upper airway infections (10.9%), diarrhea (8.1%), nausea/vomiting 28 (7.1%), fatigue (5.0%), respiratory distress (3.5%), sore throat 10 (2.5%), respiratory failure (1.8%), creptations (1.5%), sputum (1.5%), hypoxemia (1.3%), abdominal pain (0.5%), sneezing (0.5%), cyanosis (0.5%), and lymphadenopathy (0.2%),[11] Although the majority of patients withCOVID-19 have a mild influenza-like illness or may be asymptomatic, a small proportion of patients develop severe pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure, and can even die.[12] Several international guidelines describe that suspectedSARS-CoV-2 infection shows abnormalities inhemocytometry, particularly in severe cases. In January2020, diagnostic criteria that were published by Chinese authorities state that one of the two following criteria should be met: fever or respiratory symptoms; or normal or decreased white blood cell counts/decreased lymphocyte counts. In addition, computerized tomography-based pneumonia should be present as well as a travel history or contact with a patient with fever or respiratory symptoms from Hubei Province or with a confirmed case within 2 weeks.[13] Guidelines for Australia and New Zealand, released in March 2020, identified lymphopenia and neutrophilia as prognostic markers for severe disease in COVID-19 cases.[14] The Centers for Disease Control and Prevention in the United States also released guidance that stressed that leukopenia (9–25%), leukocytosis (24–30%), and lymphopenia(63%) were among the most common laboratory abnormalities reported in hospitalized COVID-19patients with pneumonia.[15] The reason why some individuals become critically ill, while others donot, remains an unsolved puzzle. Comorbidities and laboratory markers have been proposed for risk stratification.[16] Hematological parameters, including peripheral blood counts and coagulation tests, have become prominent in predicting the severity of the COVID-19 from the outset. Moreover, disseminated intravascular coagulation (DIC)was common among non-survived COVID-19 patients.[17] Thus, hematological parameters are of significant importance for treatment decisions in severe COVID-19 patients. Several hematological parameters have been reported to be disturbed in patients with COVID-19, starting from the disease's early phases.[18,29,20,21] There is mounting evidence that in critically ill patients, there are characteristics of hyperinflammation, which consist of elevated serum C-reactive protein (CRP), procalcitonin(PCT), D-dimer, and hyperferritinemia. These findings suggest a possibly crucial role of a cytokine storm in COVID-19 pathophysiology.[22]

There is mounting evidence that in critically ill patients, there are characteristics of hyper inflammation, which consist of elevated serum C-reactive protein (CRP), procalciton in(PCT), D-dimer, and hyperferritinemia. These findings suggest a possibly crucial role of a cytokine storm in COVID-19 pathophysiology.[22] D-

Dimer is a specific bio-marker for patients with venous thromboembolism, and is also used as an inflammatory marker.[23] As a prognostic marker, D-dimer should be considered in the management of hospitalized COVID-19 patients. The elevated values among the older patients demonstrate their vulnerability to develop thrombotic complications.[24] More availability of different diagnostic tools for COVID-19 infection would help to control the disease. Molecular techniques to detect the virus have been developed, but healthcare workers have limited access to these tests as they require specialized equipment and expertise. Serology tests, which are even more limited, are still being evaluated and their use is more appropriate for epidemiological purpose. In daily practice, indirect indicators ofCOVID-19, such as increases in C-reactive protein (CRP),D-dimer, albumin, ferritin and LDH levels, are also used and have proven to be of value, especially to estimate the severity of infection. Also, hemocytometric changes have been identified as supporting evidence of aCOVID-19 infection and as possible indicators of severe disease.[25] Complete blood count is the most commonly performed hematological laboratory test worldwide and most routine laboratories are equipped with a hematology analyzer. They often provide results within a short time. Although many papers describing hemocytometric changes inCOVID-19 patients are available at online and printed journals, data regarding this issue in pediatric population of Bangladesh are lacking. so, the primary objective of this stiudy is to describe hemocytometric changes and ddimerstsatus in pediatric patients with COVID-19.

MATERIALS AND METHODS

Study design

This cross-sectional comparative study was conducted in the Department of Clinical Pathology, Bangladesh Shishu Hospital and Institute, Dhaka from August 2020 to April 2021. Forty-one COVID-19 positive children who attended in Out Patient Department (OPD) or got admitted in Bangladesh Shishu (Children) Hospital, Dhaka during the study period were recruited for the study. The study was approved by Institutional Ethics Review Board. A questionnaire was prepared and pretested to obtain the data including age, sex, heamatological variables, and D dimer level of the children. Children suffering from COVID-19 were suspected by observing symptoms and signs and confirmed by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR).

Laboratory analysis

Two milliliter peripheral venous blood samples were collected under sterile conditions into EDTA tubes. The measurements of hemoglobin (Hb), haematocrit (Hct), the RBCcount, total and differential count of WBC and platelet count were obtained by haematology analyser: Mythic -22 using reagent kits (Diluent, cleaner, lytic) and recheck manually by an expert pathologist from an accredited laboratory.

Statistical analysis

Statistical analysis was performed by using online statistical calculator. The concentration of Hb, HCT, the RBC count, total and differential count of WBC and platelet count were expressed as mean±SD and range (lower value –upper value). Three categories of frequency and percentage: normal range, lower than low normal values and higher than high normal values, were calculated.

RESULT

Table I: Distribution of Demographic variables of COVID positive children.

Demographic variables of the patients	
Age (Mean, range)	4.5yrs (5 days to 15 years)
Gender (m/f)	17/14 (ratio= 1.9:1)

The mean age of the patients was 4.5 yrs. The minimum of the patients were 5 days to and the maximum age was 15 years. There were 27 (0.66%) male and 14 (o.44%) female children with a male/female ratio of 1.9:1.

Table- II: Distribution D-dimer, Platelet count and total WBC count, Neutrophil and lymphocyte count of COVID-19 positive children.

Variables	Mean±SD (range)	Normal f(%)	Below normal f(%)	Above normal f(%)	Normal range
D-dimer	1.809±2.46(0.05-9.20)	13(31.70%)	18(43.90%)	10(24.39%)	0.4-2.27mg/l
WBC	9.44±5.25(2-22.1)	27(65.85%)	6(14.63%)	8(19.51%)	4.5-13.5
Neutrophil	50.85±18.0980(2-82)	19(46.34%)	8(19.51%)	14(34.15%)	33-61
Lymphocyte	41.975609±17.49(12-94)	18(43.90%)	8(19.51%)	15(36.58%)	28-48
Platelet	325.78±142.133(30-671)	31(75.61%)	5(12.20%)	5(12.20%)	150-450

f, frequency

The mean±SD of D-dimer was 1.809±2.46 with a range of 0.05 to 9.20mg/L. Almost one-third of the children (31.70%) had normal D-dimer level. 18(43.90%) children had lower than low normal value (<0.4mg/L) and 10(24.39%) had higher than high normal value (>2.27mg/L). The mean±SD of total WBC count was 9.44±5.25 x10^9/L with a range of 2-22.1x10^9/L. Slightly less than two-thirds of the children (65.85%) had normal total WBC count. 6(14.63%) children had total WBC count lower than low normal value (<4.5x10^9/L x10^9/L) and 8(19.51%)8(19.51%) had higher than high normal value (>13.5x10^9/L). The mean±SD of Neutrophil % was

50.85±18.10% with a range of 2-82%. Nineteen (46.34%) children had normal neutrophil count. 8(19.51%) children had PNL% lower than low normal value (<33%) and 14(34.15%) had higher than high normal value (>61%). The mean±SD of lymphocyte% was 41.98±17.49% with a range of 12-94%. Eighteen (43.90%) children had normal lymphocyte count. 8(19.51%) children had lymphocyte% lower than low normal value (<28%) and 15(36.58%) had higher than high normal value (>48%).The mean±SD of total platelet count was 325.78±142.13 x10^9/L with a range of 30-671 x10^9/L. Three quarters of the children (75.61%) had normal platelet value. 5(12.20%) children had total platelet count lower than low normal value 150x10^9/L) and 5(12.20%) had higher than high normal value (>450x10^9/L).

Table III: Distribution RBC, Haemoglobin, haematocrit and red cell indices in COVID-19 positive children.

Red cell variables	Mean±SD (range)	Normal f(%)	Below normal f(%)	Above normal f(%)	Normal range
RBC(X10^6/µL)(Mean±SD)	4.105±0.757(1.99-5.56)	20(48.78%)	18(43.9%)	3(7.31%)	4-5.2
Hb(gm/dl) Mean±SD	10.82±2.41(5.7-18.1)	16(39.02%)	23(56.1%)	2(4.88%)	11.5-15.5
Hct(%)	32.32±6.70(17.3-51.8)	14(34.15%)	25(60.97%)	2(4.88%)	35-45

f, frequency

The mean±SD of RBC count 4.105±0.757X10^6/µL with a range of 1.99-5.56X10^6/µL. Almost half of the children (48.78%) had normal RBC count. 18(43.9%) children had RBC count lower than low normal value (<4X10^6/µL) and 3(7.31%) had higher than high normal RBC count (>5.2X10^6/µLX10^6/µL). The mean±SD of Hb was 10.82±2.41 gm/dl with a range of 5.7-18.1gm/dl. Slightly more than one-third of the children (39.02%) had normal Hb level. 23(56.1%) children had Hb level lower than low normal value (<11.5 gm/dl) and 3(7.31%) had higher than high normal Hb value (>15.5 gm/dl). The mean±SD of Hct was 32.32±6.70 with a range of 17.3-51.8%. Almost one-third of the children (34.15%) had normal Hct value. 25(60.97%) children had Hct lower than low normal value (<35%) and 2(4.88%) had higher than high normal value (>45%).

DISCUSSION

Since March 2020, the world has declared a global health crisis caused by the coronavirus COVID-19 pandemic. After Asia, Europe, the United States is the most affected. The main features described are pulmonary manifestations, however, this systemic infection seems to have a direct impact on the hematopoietic system. Many publications have documented the clinical, biological and radiological characteristics ofCOVID-19 infection, and several international societies have developed protocols for management and follow-up. In these recommendations, biological analysis and especially the complete blood count, represents amajor tool in the diagnosis, monitoring, detection of severe forms, and hematological complications.[27] Quantitative hematologic abnormalities have been reported since the first papers, all blood cells can be affected during COVID-19, mainly leukocyte and platelet cells.[28]

In our study the mean±SD WBC count was 9.44±5.25 x10^9/L with a range of 2-22.1x10^9/L. 6(14.63%) children had lecopenia and 8(19.51%) children leucocytosis. The mean±SD Neutrophil % was 50.85±18.10% with a range of 2-82%. Neutropenia was present in 8(19.51%) children and neutrophilia was present in 14(34.15%) children. The mean±SD lymphocyte% was 41.98±17.49% with a range of 12-94%. Eight (19.51%) children had lymphopenia and 15(36.58%) children had lymphocytosis. The mean±SD of total platelet count was 325.78±142.13 x10^9/L with a range of 30-671 x10^9/L. Five (12.20%) children had thrombocytopenia and 5(12.20%) children had thrombocytosis.

Our study is supported by the findings of Lee et al (2020) [29] and Zare-Zardini et al (2020)[30]and Qiu et al (2020).[31]

Lee et al (2020)[29] and Zare-Zardini (2020)[30] found the changes in the blood system of children which differ from those of adults. For example, the reduction of white blood cell and lymphocyte counts in children with COVID-19 are rare, and it mostly occurs in the early stages of the disease, and some children may have white blood cell counts in the normal range. The study by Qiu et al (2020)[31] also suggested that the number of white blood cells in children is not statistically significant to the severity of the disease.

Our study is also somewhat consistent with the studies conducted with adult patients by Guan et al (2020)[32], Slomka et al (2020).[33] and Cheung et al (2021).[34]

Guan et al (2020)[32] 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 <1.5×109/L, white blood cells <4.0×109/L), respectively accounted for 83.2% and 33.7% of the studied cases. They also found a predominance of thrombocytopenia (36.2) their series.[32]

Lin Tan et al (2020)[35] explained that lymphopenia is the most common sign, in fact, the coronavirus attack directly and indirectly the lymphocytes by immune and inflammatory mechanisms.. Wang et al (2020)[36] concluded that the analysis of the lymphocyte count is therefore a reliable indicator of the severity, which can be really useful in the monitoring and therapeutic

adaptation, moreover after clinical improvement the lymphocyte count is corrected. Lippi et al (2020)[27] describe d that the pathophysiologic mechanism of thrombocytopenia is multifactorial due mainly to disseminated intravascular coagulation, micro-vascular thrombosis and macrophagic activation syndromes, that can cause bleeding and poor outcome We also found that the mean±SD of D-dimer was 1.809±2.46 with a range of 0.05 to 9.20mg/L. 18(43.90%) children had lower than low normal value (<0.4mg/L) and 10(24.39%) had higher than high normal value (>2.27mg/L). This low incidence of high D-dimer may indicate the fact that children develop less severe symptoms in COVID-19 disease.

In a retrospective study conducted by Huang et al (2020)[37], the clinical characteristics, treatment and outcome data were collected and analyzed from 676COVID-19 patients stratified into 140 non-survivors and 536 survivors. Moreover, dynamic tracking showed D-dimer kept increasing in non-survivors, while CRP, LDH and PCT remained relatively stable after admission. Guan et al (2020)[32] and Lu et al (2020)[38] supported that in the routine blood test of COVID-19 patients, the occurrence of white blood cells or lymphocyte count decreased were common phenomenon, and the number of white blood cells in both mild and moderate types is mostly decreased.

Zhang et al (2020)[39] found in a study that 5 asymptomatic patients' white blood cells had decreased, while only 1 symptomatic patient's (6.2%) white blood cells had decreased and 2 (12.5%) cases had increased. There was a significant difference in white blood cells between the two groups (p=0.04). The reasonable explanation was that although the 5 asymptomatic patients had no clinical performance, they were infected with SARS-CoV-2 was a pre-exist fact. The erosion of the virus caused excessive destruction of white blood cells, so the number of white blood cells in peripheral blood had decreased. However, the presence of white blood cell count increased inpatients with symptomatic was indicative that the aggravation of the patient's condition. A review by Khartabila et al (2020)[25] indicates that lymphopeniaandan increased NLR are the most consistent abnormal hemocytometric findings and that these alterations may even augment over the course of the disease, especially in those with severe disease.

Slomka et al (2020)[33] found SARS-CoV-2 can cause changes in the number of white blood cells, especially lymphocytes and neutrophils. 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 <4.0×109/L). Cheung et al (2021) showed in their study that lymphopenia is a common hematological manifestation in many patients with COVID-19 whether they are in China or the United States. Ahnach et al (2020)[40] also stated that the blood cells perturbations are seen as a prognosis factors, careful analysis and interpretation of lymphocyte and platelet count, allows not only to evaluate the prognosis, but also helps to adapt therapeutic care.

We also found that the mean±SD of D-dimer was 1.809±2.46 with a range of 0.05 to 9.20mg/L. 18(43.90%) children had lower than low normal value (<0.4mg/L) and 10(24.39%) had higher than high normal value (>2.27mg/L). This low incidence of high D-dimer may indicate the fact that children develop less severe symptoms in COVID-19 disease.

In a retrospective study conducted by Huang et al (2020)[37], the clinical characteristics, treatment and outcome data were collected and analyzed. They found that the levels of Dimerized plasmin fragment D (D-dimer), as well as other markers were significantly higher in non-survivals on admission.

Our study revealed lower RBC count in 43.9% children and higher count in 7.31%, lower Hb in 56.1% children and higher 7.31%, lower Hct in 60.97% children and higher Hct value 4.88%. Detailed discussion of this issue was not possible due to lack of published data addressing red cell status in COVID-19 positive children. However, these lower RBC count, hemoglobin level and hematocrit may not be due to COVID-19 because children without COVID-19 usually suffer from anemia, low RBC count and low hematocrit due to nutritional deficiency and helminthic manifestation among many other causes.

CONCLUSION

The mean age of the patients was 4.5 yrs with minimum age 5 days and maximum age 15 years. There were 27 (0.66%) male and 14 (o.44%) female children with a male/female ratio of 1.9:1. One-fourth of children had more than normal D-dimer level. Both leucopenia and leukocytosis were present in them but leukocytosis (19.51%) was more prevalent than leucopenia (14.63%). Neutrophilia (34.15%) was more prevalent than neutropenia (19.51%) in them. Similarly, lymphocytosis (36.58%) was more prevalent than lymphopenia (19.51%) in them. Similar number (12.20%) of patients suffered from thrombocytopenia and thrombocytosis. Significant number of COVID-19 positive children had less than normal RBC count (43.9%), hemoglobin level (56.1%) and hematocrit level (60.97%).

Conflict of interest: Nothing declared.

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