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Hematological profile of hospitalized children in post-COVID-19 infection state

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Abstract

Coronavirus Disease 19 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the first global pandemic of the 21-th century. Even though the COVID-19 public health emergency ended, COVID-19 continues to be a health risk. COVID-19 in children appeared early in the pandemic. Children were less affected or suffered from milder disease than adults, however soon after multisystem inflammatory syndrome emerged. This study aims to explore hematological findings in hospitalized children presented in post SARS CoV-2 infection state. Of the 87 children included in the study 55% had leukocytosis, 58% had thrombocytosis, 66% had elevated CRP, 62% had elevated Fibrinogen, 37% had elevated Ferritin, and 32% had elevated D-dimer. The hemostatic system is mostly affected by the Multisystem Inflammatory Syndrome in children that follows SARS CoV-2 infection, leukocytosis, elevated CRP, Fibrinogen, Ferritin, and D-dimer are the most common findings. A careful monitoring of hematological and inflammatory parameters is recommended while evaluating children with MIS-C.

Keywords: COVID-19; MIS-C; Hematological; Inflammatory; Marker.

1. Introduction

Coronavirus Disease 19 (COVID-19), is the acronym which defines an illness caused a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It emerged in late 2019 in Wuhan, Hubei province in China, where were reported a cluster of atypical pneumonia arising from unknown causes [1]. COVID-19 rapidly spread all over the world, and on March 11, 2020, the World Health Organization (WHO) declared COVID-19 a global pandemic. On May 11, 2023 the COVID-19 public health emergency ended, however COVID-19 continues to be a health risk. COVID-19 continues to be a health risk. On April 5, 2023, WHO estimated confirmed COVID-19 infections numbered over 762 million individuals worldwide and have resulted in nearly 7 million deaths [2].

Coronaviruses are a large family of positive-sense single stranded RNA viruses. There are described four genera of coronaviruses, but only six species of them are known to cause diseases in humans. The way of transmission is between humans mainly through close contact with the infected individual or through contaminated surfaces by dispersing droplets when coughing or sneezing. The virus enters in the cells by binding to the angiotensin-converting enzyme 2 (ACE2), which is highly expressed in lung cells, alveolar cells, cardiac myocytes, the vascular endothelium, and a small subset of immune cells [3, 4]. ACE2 promotes the release of several vasoactive anti-inflammatory peptides, thus SARS-CoV-2 limits the activity of ACE2 mediated metabolic pathway, causing so the development of inflammation in the lungs and myocardium [5, 6, 7]. The clinical presentation in adults ranges from mild illness to severe pneumonia, the most

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severe cases suffer complications including acute respiratory distress syndrome, acute cardiac injury, and thromboembolic complications.

COVID-19 in children appeared early in the pandemic. The first case was a ten year old boy from China, reported on January 20, 2020 [8]. Since the beginning of the pandemic it was evident that children were less affected or suffered from milder disease than adults, the number of severe cases that needed hospitalization was small with rare cases of fatalities. Different factors were accused for this age distinction in COVID-19 burden and severity between children and adults. The minor ACE2 lung expression in children is associated with less viral entry in cells and consequently minor respiratory symptoms. The more robust innate immune response in children, mandatory vaccination and frequent viral respiratory tract infections, fewer comorbidities and stronger pulmonary regenerative potential are some other factors that protect children from SARS-CoV-2 infection [9, 10, 11, 12]. However in late spring 2020 UK National Health Service issued an alert on an emerging pediatric inflammatory multisystem disorder. After that a case definition for multisystem inflammatory syndrome in children (MIS-C) was proposed, and sever countries reported their cases. The clinical features of this emerging syndrome were similar with other well-known inflammatory syndromes in children including Kawasaki disease and Toxic shock syndrome, and it showed life-threating risk. The time in which MIS-C emerged and its serological profile suggested that this inflammatory syndrome was not mediated by direct viral invasion but was associated with the development of acquired immune response to SARS CoV-2 [13, 14].

The aim of this study is to explore hematological findings in hospitalized children presented in post SARS CoV-2 infection state.

2. Material and Method

This study is retrospective. There are enrolled 87 children, 0-14 years, hospitalized during January 2022- December 2022, in University Hospital Center "Mother Teresa", Tirana, Albania.

Diagnosis on admission were: Fever without a focus or Fever of unknown origin.

All cases were Negative for Nasopharyngeal Reverse Transcription-polymerase Chain Reaction (RT-PCR) Test and Positive for Serological Test (IgM, IgG).

All children fulfilled clinical and laboratory criteria for MIS-C.

Data were extracted from the clinical records. The parameters studied are: hematological parameters; white blood cells, red blood cells, hemoglobin, platelets, C reactive protein, fibrinogen, d-Dimer, ferritin.

3. Results

From the 87 children included in the study blood examination revealed:

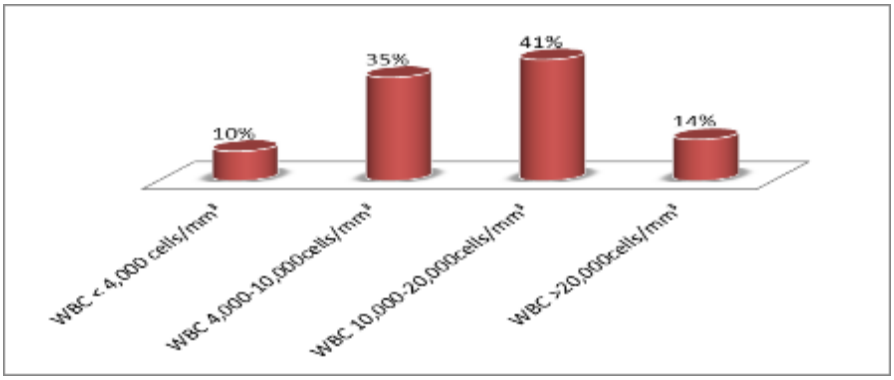

Figure 1 Leukocyte values

96% of the children had antibodies of the IgG class for SARS CoV-2, and 4% of the children had both antibodies of class IgM and IgG for SARS CoV-2.

Leukopenia (WBV < 4,000 cells/ml) in 10% of cases. Normal leukocytes (WBC 4,000-10,000 cells/ml) in 35% of children, moderate leukocytosis (WBC 10,000-20,000 cells/ml) in 41% of cases, and high leukocytosis (WBC >20,000 cells/ml) in 14% of children. (Fig.1)

Deep neutropenia (Neutrophils <500 cells/ml) were found in 7% of cases, mild to moderate neutropenia (Neutrophils 500-1,500 cells/ml) were found in 21% of children, normal values of neutrophils (Neutrophils 1,500-8,000 cells/ml) were found in 45% of cases, and Neutrophilia (Neutrophils >8,000 cells/ml) were found in 14% of cases. (Fig.2)

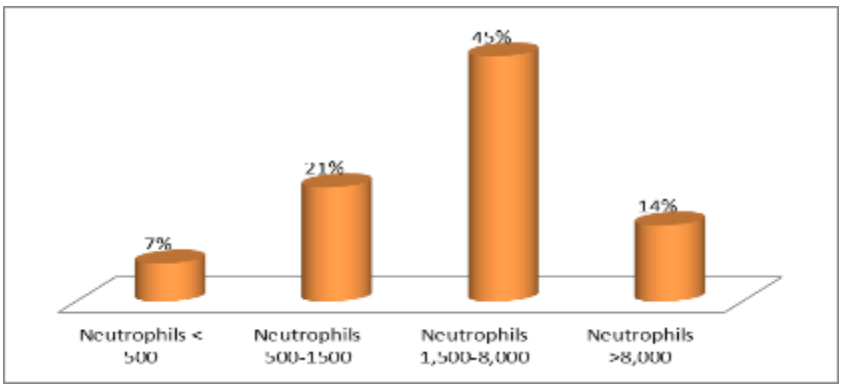

Figure 2 Neutrophils values

Lymphopenia (Lymphocytes <2,000 cells/ml) were found in 22% of children, normal values of lymphocytes (Lymphocytes 2,000-10,000 cells/ml) were found in 71% of cases, and lymphocytosis (Lymphocytes >10,000 cells/ml) were found in 7% of cases. (Fig.3)

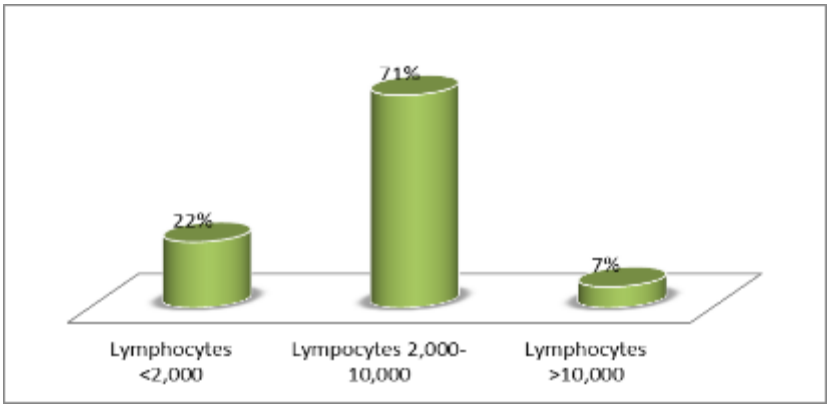

Figure 3 Lymphocytes values

Thrombocytopenia (PLT <150,000 cells/ml) were found in 2% of children, normal thrombocytes (PLT 150,000-400,000 cells/ml) were found in 40% of children, moderate thrombocytosis (PLT 400,000-700,000 cells/ml) were found in 45% of children, high thrombocytosis (PLT 700,000-1,000,000 cells/ml) were found in 11% of children, and extreme thrombocytosis (PLT >1,000,000 cells/ml) were found in 2% of children. (Fig.4)

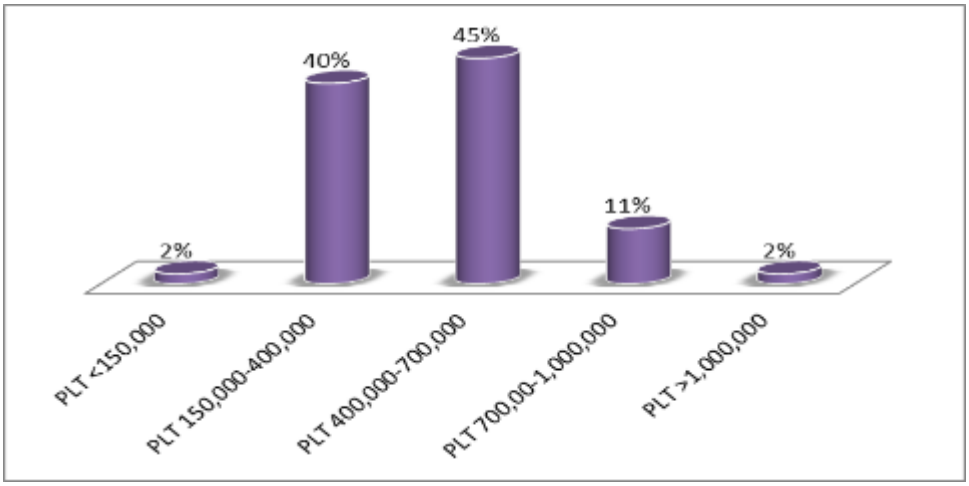

Figure 4 Thrombocytes values

Erythrocytes (RBC >3,000,000 cells/ml) were normal in 100% of cases. Normal hemoglobin (Hgb >12g/dl) was found in 70% of children, mild anemia (Hgb 10-12g/dl) was found in 27% of children and moderate anemia (Hgb <10g/dl) was found in 3% of cases. (Fig.5)

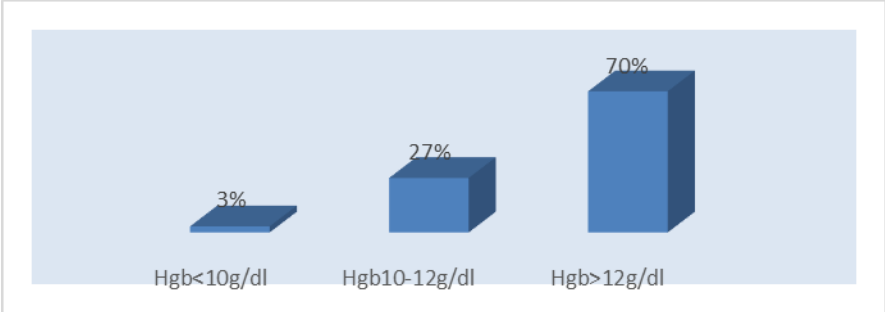

Figure 5 Hemoglobin values

From the measured inflammatory markers C reactive protein (CRP) was found elevated in 66% of cases, Fibrinogen was found elevated in 62% of cases, Ferritin was found elevated in 37% of cases and D-dimer was found elevated in 35% of cases. (Fig.6)

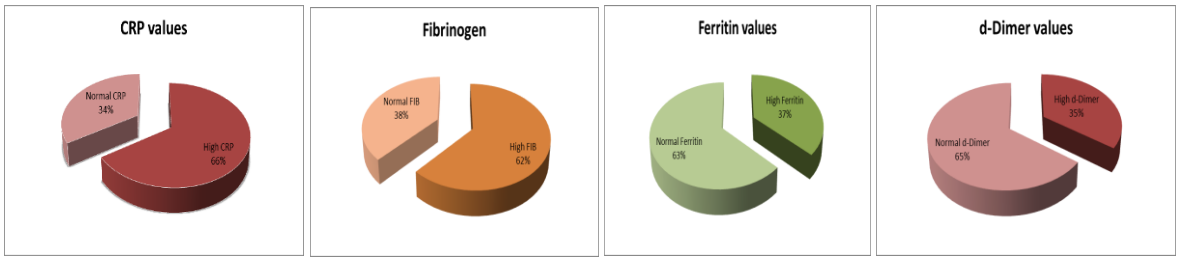

Figure 6 Inflammatory markers

4. Discussion

As the new pandemic greatly impacted the whole world and the threat to life for each of us including medical staff was fearful, the evidence that children were somehow protected was a relief. The emergence of the life-threating inflammatory disorder MIS-C in children dimmed the panorama further. With passing of time, the feverish research on the disease solved some puzzles, growing our knowledge and confidence. Although the COVID-19 public health

emergency ended, it continues to be a health risk. Multisystem Inflammatory Syndrome in children continue to be reported too but appear less severe.

None of the children reported previous SARS CoV-2 infection or contact with infected individual, however their serological test resulted positive for SARS CoV-2 infection. All children had IgG class immunoglobulin for SARS CoV-2, and a small number had both IgM and IgG class immunoglobulin for SARS CoV-2. This indicates that although the infection was asymptomatic it was followed by a delayed immunological reaction which was affected more than two organ-systems and elicited prolonged inflammation. Hemostatic system is the most affected organ-system in children in the post COVID-19 state. Increased white blood cells were found in most of the patients (55%), while leukopenia was found in a minority of them (10%). A considerable number of the patients had normal neutrophil count (45%), 28% had neutropenia and a minority 7% had profound neutropenia (neutrophils <500cells/ml). Most of the children 71% had normal lymphocyte count, whereas 22% showed lymphopenia. Angiotensin-converting enzyme 2 (ACE2) receptors, which are expressed on the surface of lymphocytes, are the way through which SARS-CoV-2 may directly infect lymphocytes. However the lesser expression of ACE2 receptors in children explains the low percentage of cases with lymphopenia in children with acute infection or MIS-C compared to adults [15, 16, 17]. Children with MIS-C are reported to possess neutralizing antibodies against SARS CoV-2, which are associated with Interleukin-18 and Interleukin-16 activation, myeloid chemotaxis and activation of lymphocytes, monocytes, and natural killer cells [18]. The most constant feature in MIS-C is cellular activation affecting multiple hematopoietic lineages. High levels of inflammatory cytokines such as INF-α, INF-γ, IL-1ß, IL-6, IL-8, IL-10, IL-17 have been identified in all studies of MIS-C [19, 20, 21, 22]. NK cells from patients with MIS-C show evidence of enhanced activation, with higher expression of perforin and gran-enzymes [23]. The role of T cells has been investigated in the pathogenesis of MIS-C, and the results revealed lymphopenia as a general feature in the acute phase of the disease [24]. Higher levels of total and neutralizing antibodies against the spike protein have been found in children with MIS-C compared to those with acute COVID-19 [25].

Mild to moderate decrease in hemoglobin level was found to 27% of the studied children. Inflammatory changes associated with MIS-C could interfere with erythropoiesis, resulting in a decrease in hemoglobin. The low incidence of anemia in MIS-C may relate to the long life span of erythrocyte and the compensatory proliferation of erythrocyte induced by lung inflammation.

In 58% of children were observed elevated levels of platelets, in 2% of them levels were extremely high >1,000,000cells/ml. Thrombocytosis in children are not an unknown phenomenon. It is reactive in nature, particularly common during recovery phase of an infection or inflammation and is usually transient and subsides when the primary stimulus ceases. Reactive thrombocytosis is commonly mediated by increased release of numerous cytokines in response to infections. A wide range of cytokines may participate in the stimulation of platelet production, IL-3, IL-11, granulocyte-macrophage colony-stimulating factor, erythropoietin but the most imported role is plaid by thrombopoietin and IL-6 which are initially elevated in response to infections [26]. The high level of inflammatory cytokines in children with MIS-C serve as stimulus for this exacerbated physiologic reaction of elevated platelets. Despite the strikingly high platelet count, sometimes exceeding 1,000,000 cells/mm3, thrombotic and/or hemorrhagic complications are extremely rare.

C reactive protein (CRP) was found increased in 66% of studied children with MIS-C. CRP is an acute-phase reactant synthesized by the liver in response to cytokines. Its production is controlled by interluekin-6, an inflammatory cytokine that is found increased in MIS-C. CRP is produced by cells in the vascular wall such as endothelial cells, smooth muscle cells too. Fibrinogen was elevated in 62% of cases in the study. Fibrinogen is a soluble protein that is produced in the liver and released into the bloodstream. Fibrinogen is an acute-phase reactant, meaning that elevated fibrinogen levels can be seen in inflammation, tissue damage, infection, cancer, inflammatory conditions [27]. Ferritin was found increased in 37% of children with MIS-C. Ferritin is the cellular storage protein for iron. It is present in small concentrations in blood, and the serum ferritin concentration normally correlates well with total-body iron stores. Ferritin is an acute-phase reactant that coordinates cellular defense against oxidative stress and inflammation [28]. D-dimer was found increased in 35% in the studied children with MIS-C. D-dimer is the degradation product of crosslinked (by factor XIII) fibrin. It reflects ongoing activation of the hemostatic system.

5. Conclusion

Children suffer a less severe acute infection of SARS CoV-2 compared to adults, but the immune dysregulation that follows, pose them at risk of late inflammatory reactions that sometimes may be life-threatening. The hemostatic system is mostly affected by the Multisystem Inflammatory Syndrome in children that follows SARS CoV-2 infection, leukocytosis, elevated CRP, Fibrinogen, Ferritin, and D-dimer are the most common findings. A careful monitoring of hematological and inflammatory parameters is recommended while evaluating children with MIS-C.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed Consent was taken from the parents of the hospitalized child, reported in the study, for using the data of the medical records, providing anonymity.

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