https://doi.org/10.37939/jrmc.v28i1.2424

Frequency Of Hematological Abnormalities in Children (Age 1 Month To 12 Years) Presenting With Sars-Cov-2 Infection At Shifa International Hospital

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Abstract

Objective: To determine the frequency of haematological abnormalities in pediatric patients presenting with COVID-19 infection.

Methods: A Cross-Sectional analytical study was conducted at the paediatric department of Shifa International Hospital Islamabad, over a period of six months from December 2021 to June 2022. A total of 325 pediatric patients of 1 month to 12 years of age who presented with symptoms of COVID-19 having positive reverse transcription polymerase chain reaction results were included in this study. Effect modifiers such as age and gender were controlled through stratification. Post-stratification Chi-square test was applied to determine the association of these effect modifiers with haematological abnormalities. A p-value equal to or less than 0.05 was considered significant. Data analysis was done using SPSS version 24.0.

Results: The mean age of patients included in this study was 5.62±2.70 years. The majority were males with a male to female were 187(57.54%) and 138 (42.46%) respectively. Low WBC count was found in 58 (17.8%), leukocytosis in 20 (6.2%), thrombocytopenia in 43(13.2%), thrombocytosis in 06(1.8%), neutropenia in 69 (21.2%), lymphopenia in 17 (5.2%), lymphocytosis in 59 (18.2%), monocytopenia in 10 (3.1%), deranged fibrinogen levels in 07 (2.2%), deranged D-Dimers in 154 (47.4%) and deranged INR in 166 (51.1%) patients.

Conclusion: Hematological abnormalities are common in children presenting with COVID-19 infection. Deranged INR, D-Dimers, low WBC count, thrombocytopenia and neutropenia were commonly found in haematological abnormalities in children with COVID-19 infection.

Keywords: COVID-19, Hematological abnormalities, Neutropenia, SARS-COV-2 infection.

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Cite this Article: Muntaha ST, Ayaz H, Mahmood H, Kulsoom A, Tayyab M, Farooq A. The Frequency Of Hematological Abnormalities in Children (Age 1 Month To 12 Years) Presenting With Sars-Cov-2 Infection At Shifa International Hospital. JRMC. 2024 Mar. 29;28(1). https://doi.org/10.37939/jrmc.v28i1.2424.

Received January 19, 2023; accepted July 31, 2023; published online March 15, 2024

1. Introduction

SARS-COV-2 led to the outbreak of COVID-19 that was first epi centred in Hubei Wuhan China in December 2019. The SARS-CoV-2 is a highly contagious virus that spreads between people through respiratory droplets. It spreads globally within a short period.[1,2] The risk of getting COVID-19 infection and its progression to severe disease is associated with age and comorbidities.[3,4] People of all ages and both genders are at equal risk of getting infection. Reported cases of COVID-19 in the paediatric population are less when compared to the adult population with a prevalence of around 2.2% globally.[5,6] The paediatric population usually has a milder course of illness with either asymptomatic carriers or mild symptoms of disease and rarely develops the severe disease. Children with comorbidities are at more risk of developing complications of the disease.[7] Infected children can either be asymptomatic with an estimate of around 45% or may develop symptoms of fever, fatigue, respiratory symptoms like cough, dyspnea and gastrointestinal symptoms like vomiting, diarrhoea and abdominal pain. The vast majority of the paediatric population diagnosed with COVID-19 who has mild or moderate disease does not progress to severe disease and is managed with supportive care. Supportive care includes prevention & treatment of disease complications. Children with comorbid medical conditions like neuro metabolic disorders, bronchial asthma, immune compromised state, congenital heart defects and obesity are at higher risk of developing severe disease.[8]

SARS-CoV-2 virus affects vital organs of the body and shows clinical heterogeneity with involvement of respiratory, gastrointestinal and haematological systems. Decreased lymphocyte count and hypercoagulability with derangements in fibrinogen and D Diamers have been commonly noted in patients with COVID-19 and are considered indicators of poor disease outcome.[9] After getting a COVID-19 infection, triggering of the immune system results in

the unrestrained inflammatory response that plays an important role in disease pathogenesis, clinical manifestations and complications. This results in haematological derangements like lymphopenia, lymphocytosis and disturbances in granulocytes and monocytes. [10] These haematological derangements lead to superimposed bacterial infection, septic shock and multiorgan failure. Patients with comorbid conditions like diabetes, hypertension and obesity are at more risk of developing complications. Researchers found a correlation between obesity & comorbidities of COVID-19.[11]

A study by Siddiqui et al on the effect of COVID-19 infection on haematological findings in pediatric patients reported low white blood cell count in 8.5% of patients, thrombocytopenia in 5.6% of patients, neutropenia in 15.5% patients, and lymphopenia in 26.8% patients.[12] Another study by Tiwari et al reported neutrophilia in 36.3% of patients, lymphopenia in 27.3% of patients, monocytosis in 18.2% of patients, and thrombocytopenia in 18.2% of patients.[13]

The objective of our study was to find out the frequency of haematological abnormalities in children infected with COVID-19 presenting in a tertiary care hospital. The rationale of the study is that children who develop severe diseases can experience breathing difficulty, hypoxia, acidosis, shock, acute respiratory distress syndrome, respiratory failure & haematological derangements with rapid progression, which ultimately ends in mortality. Significant haematological derangements like thrombocytopenia, neutropenia, lymphopenia, and the ratio of neutrophils to lymphocytes and platelets to lymphocytes are being observed in severe forms of disease and considered poor prognostic factors. Early detection of haematological derangements can help in assessing the severity of the disease and early management. Currently, treatment of severe disease comprises maintaining oxygenation either with oxygen therapy, non-invasive or invasive ventilation, steroids, anti-viral drugs and correction of haematological disturbances like deranged D Diamers, fibrinogen, and severe thrombocytopenia. Most critically sick patients don't respond well to current treatment strategies. Therefore, proper knowledge of the pathophysiology and development of haematological disturbances will not only help in the early detection of disease severity but will also be helpful to start early treatment. This will help to determine prognosis and patient outcome. Early detection of haematological derangements can help to protect patients from severe disease. It will help in the early recovery of patients.

2. Materials & Methods

It was a cross-sectional study with a non-probability consecutive sampling technique carried out at the paediatric department, Shifa International Hospital Islamabad from 13th Dec 2021 to 12th June 2022. A total of 325 patients were included in the study. Sample size calculation was done with the formula; N= Z,2 X P(100-P) / e2 Where P is the estimated frequency of Low Platelet Count =5.6%9 And e is the desired margin of error of 2.5%. Children diagnosed with COVID-19 infection confirmed positive for reverse transcription polymerase chain reaction with age one month to twelve years of age of both genders were included in the study. Children with known haematological disorders such as haemophilia, thalassemia, lymphoma and leukaemia were excluded from the research. Approval by hospital IRB and ethical committee via letter No 371-21/13/10/2021 was taken. A written informed consent was taken from the parents by explaining to them the objectives of the study. Data on baseline study variables like age and gender was collected at the time of inclusion in the study. Venous blood samples were obtained from each patient for confirmation of the diagnosis of haematological abnormalities as per operational definitions.

Relevant data was written on a structured Performa. Data was entered and analyzed using SPSS version 24.0. For quantitative variables e.g. age mean & standard deviation were used. For qualitative variables e.g. hematological derangements and gender, frequency and percentages were used. Effect modifiers such as age and gender were controlled through stratification. Post-stratification Chi-square test was applied to determine the association of these effect modifiers with haematological abnormalities. P-value ≤ 0.05 was considered as significant.

3. Results

A total of 325 children were included in the study with a mean age of 5.62±2.70 years with males & females were 57.54% & 42.46% respectively. Descriptive statistics of age are shown in Table 1.

Table 1: Descriptive statistics of age.

Age (Years)	
Mean	5.62
S.D.	2.70
Minimum	02
Maximum	12

The frequency of Gender is shown in Figure 1.

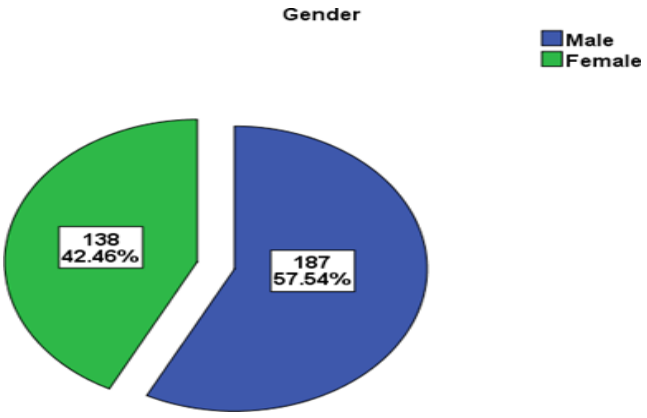

Figure 1: Frequency of gender.

The frequency of the presence of haematological abnormalities is shown in Table 2.

Table 2: Frequency of presence of hematological abnormalities.

Hematological Abnormalities	Frequency	Percentage (%)
Low WBC Count	58	17.8%
Leukocytosis	20	6.2%
Thrombocy topenia	43	13.2%
Thrombocytosis	06	1.8%
Neutropenia	69	21.2%
Lymphopenia	17	5.2%
Lymphocytosis	59	18.2%
Monocytopenia	10	3.1%
Deranged Fibrinogen Levels	07	2.2%
Deranged D-Dimers	154	47.4%
Deranged INR	166	51.1%

Stratification of age to determine the association of age with haematological abnormalities is shown in Table 3.

Table 3: Stratification of age to determine the association of age with hematological abnormalities.

Hematological Abnormalities		Age Groups		P-value
		02-04 Years	**05-12 Years**	
Low WBC Count	Yes	25 (18.2%)	33 (17.6%)	0.87
	No	112 (81.8%)	155 (82.4%)	
Leukocytosis	Yes	11 (8.0%)	09 (4.8%)	0.23
	No	126 (92.0%)	179 (95.2%)	
Thrombocytopenia	Yes	18 (13.1%)	25 (13.3%)	0.97
	No	119 (86.9%)	163 (86.7%)	
Thrombocytosis	Yes	03 (2.2%)	03 (1.6%)	0.69
	No	134 (97.8%)	185 (98.4%)	
Neutropenia	Yes	31 (22.6%)	38 (20.2%)	0.60
	No	106 (77.4%)	150 (79.8%)	
Lymphopenia	Yes	04 (2.9%)	13 (6.9%)	0.11
	No	133 (97.1%)	175 (93.1%)	
Lymphocytosis	Yes	24 (17.5%)	35 (18.6%)	0.80
	No	113 (82.5%)	153 (81.4%)	
Monocytopenia	Yes	03 (2.2%)	07 (3.7%)	0.43
	No	134 (97.8%)	181 (96.3%)	
Deranged Fibrinogen Levels	Yes	04 (2.9%)	03 (1.6%)	0.42
	No	133 (97.1%)	185 (98.4%)	
Deranged D-Dimers	Yes	66 (48.2%)	88 (46.8%)	0.81
	No	71 (51.8%)	100 (53.2%)	
	Yes	73 (53.3%)	93 (49.5%)	
Deranged INR	No	64 (46.7%)	95 (50.5%)	0.50

Table 4: Stratification of gender to determine the association of gender with hematological abnormalities.

Hematological Abnormalities		Gender		P-value
		Male	Female	
Low WBC Count	Yes	48 (25.7%)	10 (7.2%)	<0.01
	No	139 (74.3%)	128 (92.8%)	
Leukocytosis	Yes	11 (5.9%)	09 (6.5%)	0.81
	No	176 (94.1%)	129 (93.5%)	
Thrombocytopenia	Yes	27 (14.4%)	16 (11.6%)	0.45
	No	160 (85.6%)	122 (88.4%)	
Thrombocytosis	Yes	01 (0.5%)	05 (3.6%)	0.40
	No	186 (99.5%)	133 (96.4%)	
Neutropenia	Yes	45 (24.1%)	24 (17.4%)	0.15
	No	142 (75.9%)	114 (82.6%)	
Lymphopenia	Yes	12 (6.4%)	05 (3.6%)	0.26
	No	175 (93.6%)	133 (96.4%)	
Lymphocytosis	Yes	28 (15.0%)	31 (22.5%)	0.08
	No	159 (85.0%)	107 (77.5%)	
Monocytopenia	Yes	07 (3.7%)	03 (2.2%)	0.42
	No	180 (96.3%)	135 (97.8%)	
Deranged Fibrinogen Levels	Yes	05 (2.7%)	02 (1.4%)	0.45
	No	182 (97.3%)	136 (98.6%)	
Deranged D-Dimers	Yes	91 (48.7%)	63 (45.7%)	0.59
	No	96 (51.3%)	75 (54.3%)	
	Yes	101 (54.0%)	65 (47.1%)	0.22
Deranged INR	No	86 (46.0%)	73 (52.9%)	

Stratification of gender to determine the association of gender with haematological abnormalities is shown in Table 4.

4. Discussion

A total of 325 children were included in the study with a mean age of 5.62±2.70 years with males & females were 57.54% & 42.46% respectively. Among haematological abnormalities, leukopenia, leukocytosis, thrombocytopenia, thrombocytosis, neutropenia, and lymphopenia were 17.8%, 6.2% and 13.2%, 1.8%, 21.2%, 5.2%respectively. Deranged fibrinogen levels in 2.2%, deranged D-Dimers in 47.4% and deranged INR in 51.1% of children.

Karbuz et al conducted research in Turkey on the paediatric population with COVID-19 and results showed a male predominance of 50.3% it's consistent with our study findings which showed male predominance.[14] Alkan G et al researched inflammatory markers and haematological parameters and found that COVID infection leads to systemic involvement with haemostatic involvement and derangements in the haematological system. Common haematological disturbances observed were increased leukocyte and neutrophil count. Decreased lymphocyte count and derangements in D Diamers & fibrinogen levels were also observed. These haematological changes correlated directly with the severity of COVID-19. All these findings were consistent with our study findings which also showed such hematological abnormalities.[15]

Recent systemic review results showed that when patients get infected with sars-cov-2, it stimulates the angiotensin-converting enzyme 2 receptor leading to apoptosis of lymphocytes with resulting lymphopenia. They also observed that in hospitalized patients common covid associated derangements in haematological parameters were lymphopenia, leukopenia, thrombocytosis, neutropenia, and neutrophilia. A study carried out by Yarali et al found lymphopenia, neutropenia, and neutrophilia in their results. Ozenen et al in a study found that children with COVID-19 showed neutropenia, lymphopenia and thrombocytopenia in haematology.[16] There exists a direct relation with worse prognosis of COVID-19 and leukocytosis, neutrophilia, lymphopenia, and thrombocytopenia.[17] All these haematological derangements are consistent with our study results.

Wang et al researched characteristics of patients with Covid-19 and observed that in paediatric patients with mild, moderate or asymptomatic disease lymphopenia is seen in 3% of the infants. The most common derangements in haematology were decreased total lymphocytes, prolongation of prothrombin time, and elevation in lactate dehydrogenase. Derangements in D Diamers & INR along with other hematological parameters were seen in patients having severe disease. It has been observed that 2019-nCoV infection is associated with coagulation activation, cellular immune deficiency and myocardial, renal & hepatic injury. These laboratory derangements were similar to those previously seen in patients with SARS-COV & MERS-CoV infection. A limited number of severe COVID-19 cases in the paediatric population is explained partly by a lack of significant lymphopenia. These findings are consistent with our study results. [18]

Yang et al,[19] researched T cell immunity in Covid infection and results found that lymphopenia was seen in almost 80% of critically sick patients with COVID-19 whereas Chen et al,[20] conducted research on clinical and CT scan features of paediatric patients suffering from Covid and found that children with mild disease have lymphopenia with the prevalence of 25%. They also observed that lymphopenia directly correlates with the severity of the disease. In both MERS & SARS, viral-induced cytoplasmic damage & cell apoptosis leads to lymphopenia. All these findings are consistent with our study results.

In the very young paediatric population immune response when compared to adults, prominent lymphopenia may not be seen due to the differences in their immune response and immaturity of the immune system. Decreased lymphocyte count with severe disease was observed in most of the studies. Total leukocyte count and lymphocyte count depletion are seen in most viral illnesses.[21] In a research conducted among the paediatric population diagnosed with COVID-19, it was observed that 20% of children had increased leukocyte count while 10% had decreased count and 70% cases had normal count.[20] Whereas in this study the leukocyte count was normal in 76% of the cases, low leukocyte count was seen in 17.8% of children and leukocytosis in 6.2% of children. It was also observed that generally in the paediatric population lymphocyte count remains normal. This is due to relatively mild immune suppression.[22] Henry et al reviewed 12 kinds of literature from China which included the paediatric population also and found lymphopenia in 3% of patients and these findings are consistent with our study results.[23]

In 20 children examined by Xia et al studied clinical & CT features and found that in children 70% had normal leukocyte count, 10% had leukocytosis, 20% had leukopenia among which 35% had decreased lymphocytes and 15 % had increased lymphocytes.[20] Lymphocytes to CRP ratio is a newly established inflammatory score that reflects ongoing systemic inflammation in the body. Angel et al carried out a meta-analysis recently and found that in patients with severe COVID-19 disease lymphocyte-to-CRP ratio decreases. They also found that anaemia, thrombocytopenia and rising levels of D Diamers were directly related to mortality in patients with COVID-19.[24] All these are consistent with our study results.

SARS-CoV-2 infection triggers cytokine response resulting in deranged hematological parameters and increased acute phase reactants. In response to proinflammatory cytokines especially interleukin 6, hepatocytes synthesize acute phase reactants like CRP in COVID-19 patients.[25] Bacterial infection results in the release of inflammatory biomarker pro calcitonin, which is the precursor of calcitonin hormone, into blood circulation. Proinflammatory cytokines like tumour necrotic factor, Interleukin-I and Interleukin-6 activate the serum levels of procalcitonin.[26] In the current study major haematological disturbances observed were neutropenia, leukopenia, thrombocytopenia, and lymphocytosis.

The study has some limitations. Haematological disturbances can change over the course of the infection. Moreover, children were hospitalized at different times of disease course for their complaints. It was also noted that correlating disease severity with haematological parameters wasn't done in our study. Research on a large scale is need of time to evaluate haematological parameters to predict hospitalization and correlate the clinical severity of infection in children. Multicenter studies should be done on haematological parameters. Such easily available, reliable and non-expensive diagnostic tools will guide in determining prognosis in

children infected with COVID-19 regardless of clinical condition at the time of presentation.

5. Conclusion

Hematologic abnormalities are common in children presenting with COVID-19 infection. Deranged INR, D-Dimers, low WBC count, thrombocytopenia and neutropenia are common haematological abnormalities found in children with COVID-19 infection.

CONFLICTS OF INTEREST- None
Financial support: None to report.
Potential competing interests: None to report
Contributions:
S.T.M - Conception of study
S.T.M, H.A, H.M, M.T, A.F - Experimentation/Study Conduction
S.T.M - Analysis/Interpretation/Discussion
S.T.M - Manuscript Writing
S.T.M, H.A, H.M, A.K, M.T, A.F - Critical Review
H.A, A.K - Facilitation and Material analysis
All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

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