Academic Science Journal

Association of Blood Indices Changes with Parvovirus B19 Infection in Thalassemia Patients

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Received: 13 June 2024 **Accepted: 1 August 2024**

Published: 30 April 2025

DOI: https://dx.doi.org/10.24237/ASJ.03.02.896D

Abstract

Parvovirus B19 is responsible for several clinical conditions, such as infectious erythematosus, joint inflammation, fetal hydrops, and chronic hemolytic anemia resembling thalassemia syndrome, as well as transient aplastic crises. B19 can be transferred via respiratory secretions, as well as through the use of blood products and blood transfusions. This research aims to study the association of Parvovirus B19 infection on some blood indices in thalassemia patients. The results of the present study showed that the overall positivity rate of the anti-Parvo B19 IgM marker was 28(31.1%) among thalassemia patients. The results of the association of anti-Parvo B19 IgM with the parameters of blood indices (Total WBCs, Lymphocytes, Granulocytes, Hemoglobin, RBCs, and Platelets count) found that the mean ± SD of the total WBC count, total lymphocytes count, total granulocytes count, hemoglobin concentration, total RBC count and platelets count in thalassemia patients who were positive for anti-Parvo B19 IgM were 13.93 ± 13.08 cells/ cu.mm, 9.24 ± 12.01 cells/ cu.mm, 4.69 ± 2.46 cell/ cu.mm, 7.59 ± 1.30 gm/dl, 2.79 ± 0.54 corpuscle/ cu. Mm and 469.4 ± 284.8 platelet/ cu.mm, respectively. This study concluded the seroprevalence of human parvovirus antibodies B19 IgM was found to be (31.1%) positive in patients with thalassemia. In

addition, this study shows no association between patients with positive B19 IgM and negative B19 IgM with total WBC, lymphocyte count, granulocytes, hemoglobin, and RBC.

Key words: Thalassemia, Parvovirus B19, blood indices and ELISA.

Introduction

The term "parvovirus" originates from the Greek word "parvus," which signifies a diminutive virus measuring approximately 25 nanometers in diameter (nm). This virus lacks an envelope and possesses a straight as well as one-stranded DNA (ssDNA) genomic ranging from 4 to 7 kilobase pairs (kb). It is characterized by the presence of two terminations called hairpins [1]. Adeno-associated viruses that are not pathogenic are among the initial parvoviruses detected in people. The two dangerous parvoviruses that are commonly encountered in people of all ages are human parvovirus B19 (HB19V) and human bocavirus 1 (HBoV1). The discovery of B19V was made in 1975 by Cossart et al. In individuals who appear to have a healthy immune system, parvovirus infection can manifest as either an asymptomatic condition or lead to erythema infectious in children and acute arthropathy in adults. Parvovirus B19 infection can persist in persons with weakened immune systems, causing pure red cell aplasia, and, less commonly, thrombocytopenia, and neutropenia [2]. Patients with blood problems, particularly those with chronic hemolytic anemia, such as sickle cell anemia, thalassemia, and hereditary spherocytosis. In these individuals, there is an elevated rate of production of immature red blood cell precursors to counterbalance the destruction of mature red blood cells. Parvovirus B19 infection can inhibit the production of red blood cells and cause a sudden decrease in the number of immature red blood cells, a condition known as transitory aplastic crisis. The temporary cessation of red blood cell production is exclusive to individuals with chronic hemolytic anemia as a result of the limited lifespan of red blood cells. There is an elevated risk of B19 transmission in these patients [3, 4].

Serological confirmation of recently acquired infection and occasional recognition of a virus in cells and bones have established a connection between B19V and various other disorders of the blood. However, the exact role of B19V in causing these illnesses is not as well-defined as its role in transitory. According to Kerr *et al.*,[5]. Hemphagocytosis is a widespread, often

severe, and usually life-threatening condition characterized by a failure of the bone marrow and a decrease in white blood cell count, accompanied by warmth as well as a significant increase in blood levels of inflammatory mediators and factors assert [6].

According to Mayama *et al*.,[7], hem phagocytosis can occur as a result of B19V disease in pregnant individuals and in the bone marrow of individuals experiencing transient shock. While anemia is commonly associated with symptoms of hematological illness caused by B19V infection, it is worth noting that a mild form of thrombocytopenia often coexists with TAC[5]. According to Ganaie and qiur (2018), B19V is responsible for various disorders, which are characterized by distinct stem cell appearance. B19V disease commonly manifests as a fifth illness and brief aplastic emergency in both healthy and hematological people[8].

In pregnancy, the disease can lead to hydration, while B19V may remain in the bone marrow, resulting in pure aplasia of red cells in a host with a compromised immune system[9]. B19V infection has been associated with liver disease, heart disease, autoimmune, and syndrome of chronic fatigue. The majority of B19V diseases are probably without symptoms, as developing seroconversion happens without any noticeable sickness[10]. The occurrence of thrombocytopenia is observed exclusively in cases of B19V disease, potentially resulting in recognition of idiopathic thrombocytopenic purpura (ITP), characterized by immune destruction of platelets, characterized by the absence of platelet production in the bone marrow[11].

B19V disease can lead to neutropenia due to immune-triggered death of granulocytes or a failure of the bone marrow to create white blood cells (agranulocytosis). Prolonged B19V disease was found to be correlated with recurring agranulocytosis[12]. In Iraq, especially in Basra city showed the seroprevalence of human parvovirus antibodies for B19V IgG and B19 IgM were (89.4%) and (9.6%), respectively in thalassemia patients [13]. Therefore this study aimed to detect the prevalence of Human parvovirus B19 antibodies in thalassemia patients in Diyala, Iraq. Then study the associassion between positive and negative B19 IgM and hematological parameters.

Materials and Methods

Study group and Blood specimens' collection

The current study was done in Diyala province for the period from January 2023 to January 2024. Ninety Patients with thalassemia were randomly selected from the Center of Hematological Diseases of the Diyala Directorate of Health in Baqubah as they regularly attend that center. These patients were clinically diagnosed as thalassemia patients and enrolled in this study as a study group. The ages ranged from 1 to 60 years. They consisted of 47 males and 43 females. A special questionnaire was pre-constructed to collect information regarding age, gender, type of thalassemia, duration of thalassemia (Years), HBV, HCV and HIV infection, and blood indices (Total WBCs, Lymphocytes, Granulocytes, Hemoglobin, RBCs and Platelets count). The data was collected via brief individual interviews with the participants. Each participant donated a venous blood sample of 5 milliliters using sterile disposable plastic syringes. The collected samples were then prepared and stored at a temperature of -20°C until they were used.

Detection of serological marker anti-Parvo B19 IgM

The test was done using a commercially available kit (Dia. PRO, Italy anti-Parvo B19 antibody IgM ELISA).

Determination of complete blood counts:

The hematological Parameters of the thalassemia patients infected with parvovirus B19 were performed and statistically analyzed. Full parameters of CBC were determined using the Urit 3000 plus automated system. Blood samples were collected in EDTA tubes and then quickly placed on a roller mixer for 5-10 minutes. The samples were processed individually by removing the cover of the EDTA tube and immersing the tip of the aspiration pipe into the blood; the equipment then produced a whistling sound as a signal of complete aspiration. The blood tube was removed away. The results were displayed on the equipment screen within 3-5 minutes. The results report was printed on A4 paper by a companion printer.

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Results and Discussion

Positivity rate of anti- parvivirus B19 IgM

The positivity rate of anti-parvivirus B19 IgM among 90 thalassemia patients is shown in Table 1. Twenty-eight (31.1 %) of the study group were anti-parvivirus B19 IgM positive. Meanwhile, 62 (68.9 %) were anti-parvivirus B19 IgM negative.

Table 1: Positivity rate of anti- parvivirus B19 IgM.

Viral markers		**Patients group No.(%)**	***P value***
Parvo B19 IgM	Positive	28 (31.1)	0.0001*
	Negative	62 (68.9)	

*A statistically significant difference between the percentages at a significance level of 0.05.

Blood indices in study groups:

Table (2) contains some essential blood indices in both study groups. Starting with the total WBC count, the results found that the mean ± SD of total WBC count was 14.33 ± 12.24 cells/cu.mm with a range of 2.31-52.05 cells/cu.mm. The difference was statistically significant (*P*= 0.0001). Concerning the lymphocyte count, the results found that the mean ± SD of lymphocyte count in thalassemia patients was 8.62 ± 9.95 cells/ Cu.mm with a range of 1.00-45.73 cells/ Cu.mm. The difference was statistically significant (*P*= 0.0001). Furthermore, the mean ± SD of the granulocyte count in the thalassemia patients was 5.71 ± 4.22 cells/ Cu.mm with a range of 1.30-18.78 cells/ Cu.mm. Therefore, the difference between groups was statistically significant (*P*= 0.0001). The results also found that the mean ± SD of the hemoglobin concentration in thalassemia patients was 7.75 ± 1.31 gm/dl with a range of 4.4-10.7 gm/dl. The mean ± SD of the total RBC counts in the thalassemia group was 2.84 ± 0.51 corpora/cu.mm with a range of 1.75-3.91 corpuscles/cu.mm. Additionally, the results in Table (2) showed that the mean ± SD of the platelets count in the thalassemia group was 472.6 ± 261.41 platelets/ cu.mm. With a range of 92-987 platelets/ cu.mm. Thus, the difference was statistically significant (*P*= 0.0001).

Table 2: Mean ± SD and range of some blood indices in study group

Blood indices	Patients group Mean ±SD (Range)	*P* value
Total WBCs (x10^3)	14.33 ± 12.24 (2.31-52.05)	0.0001*
Lymphocytes (x10^3)	8.62 ± 9.95 (1.00-45.73)	0.0001*
Granulocytes (x10^3)	5.71 ± 4.22 (1.30-18.78)	0.0001*
Hemoglobin (g/dL)	7.75 ± 1.31 (4.4-10.7)	0.0001*
RBCs (x10^6)	2.84 ± 0.51 (1.75-3.91)	0.0001*
Platelets count (x10^3)	472.6 ± 261.41 (92-987)	0.0001*

*A statistically significant difference between two independent at a significance level of 0.05.

Association of parvovirus B19 IgM with blood indices:

1. Total WBC count:

Results presented in Table (3) showed the association of anti-Parvo B19 IgM with the parameters of blood indices. The mean ± SD of the total WBC count in thalassemia patients who were positive for anti-Parvo B19 IgM was 13.93 ± 13.08 cells/ cu.mm. While the mean ± SD of the total WBC count in thalassemia patients who were negative for anti-Parvo B19 IgM was 14.51 ± 11.94 cells/cu.mm. The results indicated that there were statistically insignificant differences at (*P*= 0.835).

Table 3: Association of parvo B19 IgM with Total WBC count in study group**.**

Blood indices	Thalassemia patients Anti-parvovirus B19 IgM	
	Positive	Negative
Total WBCs (x10^3)	13.93 ± 13.08	14.51 ± 11.94
***P* value**	0.835	0.764

2. Total lymphocytes count:

Table (4) revealed that the mean ± SD of the total lymphocyte count in thalassemia patients who were positive for anti-Parvo B19 IgM was 9.24 ± 12.01 cells/ cu.mm and that of the negative anti-Parvo B19 IgM was 8.34 ± 8.96 cells / cu.mm. The results indicated that there were statistically insignificant differences at (*P*= 0.693).

Table 4: Association of parvo B19 IgM with Lymphocytes count in study group

Blood indices	Thalassemia patients	
	Anti-parvovirusB19 IgM	
	Positive	Negative
Lymphocytes count (x10^3)	9.24 ± 12.01	8.34 ± 8.96
P value	0.693	0.810

3. Total granulocytes count

The mean ± SD of the total granulocyte count in thalassemia patients who were positive and negative for anti-Parvo B19 IgM were 4.69 ± 2.46 cell/ cu.mm and 6.17 ± 4.76 cell/ cu.mm, respectively. The results indicated that there were statistically insignificant differences at (*P* = 0.123). All data are shown in Table (5).

Table 5: Association of parvo B19 IgM with Granulocytes count in study group.

Blood indices	Thalassemia patients	
	Anti-parvovirus B19 IgM	
	Positive	Negative
Granulocytes count (x10^3)	4.69 ± 2.46	6.17 ± 4.76
P value	0.123	0.601

*A statistically significant difference between two independent groups at a significance level of 0.05.

4. Hemoglobin concentration:

The mean ± SD of the hemoglobin concentration in thalassemia patients who were positive and negative for anti-Parvo B19 IgM were 7.59 ± 1.30 gm/dl and 7.82 ± 1.32 gm/dl respectively. The results indicated that there were statistically insignificant differences at (*P*= 0.433).

Table 6: Association of parvo B19 IgM with hemoglobin concentration in study group.

Blood indices	Thalassemia patients	
	Anti-Parvo B19 IgM	
	Positive	Negative
Hemoglobin conc. (x10^3)	7.59 ± 1.30	7.82 ± 1.32
P value	0.433	0.666

5. Total RBC count

The mean ± SD of the total RBC count in thalassemia patients who were positive and negative for anti-Parvo B19 IgM were 2.79 ± 0.54 corpuscle/ cu. mm and 2.87 ± 0.49 corpuscle/ cu. Mm respectively. The results indicated that there were statistically insignificant differences at (*P*= 0.474). All data are presented in Table (7).

Table 7: Association of parvo B19 IgM with TRBC count in study group.

Blood indices	Thalassemia patients	
	Anti-Parvo B19 IgM	
	Positive	Negative
TRBC count ($x10^6$)	2.79 ± 0.54	2.87 ± 0.49
P value	0.474	0.311

**A statistically significant difference between two independent groups at a significance level of 0.05.

6. Platelets count

Table (8). revealed that the mean ± SD of the platelets count in thalassemia patients who were positive and negative for anti-Parvo B19 IgM were 469.4 ± 284.8 platelet/ cu.mm and 474.1 ± 252.6 platelet/ cu.mm respectively. The results indicated that there were statistically insignificant differences at (*P*= 0.937).

Table 8: Association of parvo B19 IgM with platelets count in study group.

Blood indices	Thalassemia patients	
	Anti-parvovirus B19 IgM	
	Positive	Negative
Platelets count ($x10^3$)	469.4 ± 284.8	474.1 ± 252.6
P value	0.937	0.369

*A statistically significant difference between two independent groups at a significance level of 0.05.

The current results, which included 90 thalassemia patients, showed that 31.1% were infected by parvovirus B19 as they were positive for anti-parvovirus B19 IgM. Worldwide studies have found higher infection rates by parvovirus B19 among thalassemia patients, as studies revealed that the anti-parvovirus B19 IgG and IgM ranged from 18.2–81% and 14.5–41.1%, respectively [14]. In a survey conducted in Iraq, 34% of thalassemia were found positive for anti-parvovirus B19 IgM [15]. In another study, the anti-parvovirus B19 IgG and IgM were 74.7% and 3.3% respectively[16].In India, reported 81% of thalassemia patients were positive for anti-B19V IgG, and 41.1% were positive for anti-B19V IgM[17]. The high incidence of parvovirus B19 in thalassemia patients can be attributed to its resistance to most physicochemical factors and its primary mode of transmission through respiratory secretions, especially during childhood[18]. Additionally, it can be transferred by blood and blood products [19, 20]. Consequently, individuals with β-thalassemia who frequently have blood transfusions or receive blood products are very susceptible to parvovirus B19 infection[21]. It is important to note that in Iraq, donated blood pints were only screened for hepatitis B,

hepatitis C, and immunodeficiency viruses, starting in the late 1980s. However, screening for parvovirus B19 virus was not conducted. The current results reported that blood indices, including total WBC count, total granulocyte count, and total lymphocyte count, were all significantly increased in thalassemia patients. However, none of these parameters were significantly associated with anti-parvovirus B19 IgM. White blood cells, also known as leukocytes, are integral components of the immune system. They play a crucial role in safeguarding the body from infectious diseases and external intruders. White blood cells (WBCs) consist of three primary subtypes: granulocytes, lymphocytes, and monocytes. Every single white blood cell is generated and derived from a hematopoietic stem cell located in the bone marrow[22]. White blood cells, namely granulocytes such as neutrophils, eosinophils, and basophils, as well as agranulocytes like monocytes and lymphocytes, are critical components of the body's immune system [23]. Lymphocytes play a crucial role in the immune system. Lymphocytes consist of T cells, which play a vital role in cell-mediated and cytotoxic adaptive immunity, and B cells, which are responsible for humoral immunity [24]. Increased lymphocyte counts (lymphocytosis) suggest viral or intracellular bacterial infections[25]. Granulocytosis typically indicates the presence of bacterial or parasite diseases or allergic inflammation[26]. Thalassemia often leads to frequent occurrences of infections. The vulnerability to infections in thalassemia is caused by a wide range of immunological disorders and exposure to infectious agents[27]. Thalassemic patients exhibit immunological abnormalities that affect both the innate and adaptive immune systems. The CD4/CD8 ratio is below the average range, and there is a decrease in neutrophil and macrophage phagocytosis, neutrophil chemotaxis, and natural killer activity. Additionally, there is a reduction in C3 and C4 levels. Elevated levels of immunoglobulins were seen, and a rise in B lymphocytes was noted, along with poor differentiation and activation[28, 29]. Factors that increase the likelihood of infections in thalassaemic individuals include severe anaemia, excessive iron levels, removal of the spleen, and various immunological disorders. The primary bacterial infections are caused by *S. aureus, Streptococcus viridance, Enterococci, Pseudomonas fluorescens, Salmonella enteritidis, Citrobacter freundii, Serratia marcescens, Enterobacter cloacae,* and *Coliform bacteria*[30].

Parasitic infections include Toxoplasma gondii and Leishmania donovani. Viral infection includes HIV, HHV-6, HHV-8, HBV, HCV, HGV, parvo B19 and TTV[29, 31, 32]. These infections induce the proliferation and activation of leucocytes, lymphocytosis and granulocytosis in the blood circulation of thalassemia patients.

Hemoglobin (Hb) is an iron-containing protein that aids in the transportation of oxygen in red blood cells (RBCs). Hemoglobin in the bloodstream transports oxygen from the lungs to the various tissues in the body, where it is released to facilitate aerobic respiration. An average individual possesses a quantity of 12 to 20 grams of haemoglobin per 100 millilitres of blood[33]. The primary kind of haemoglobin in adults, known as haemoglobin A, is encoded by the genes HBA1, HBA2, and HBB in humans. The alpha 1 and alpha 2 subunits are encoded by the HBA1 and HBA2 genes, which are located in close proximity to each other on chromosome 16. On the other hand, the beta subunit is encoded by the HBB gene, which is located on chromosome 11[34]. Thalassaemia is a hereditary disorder that affects the production of globin chains in haemoglobin. Thalassaemia is caused by an imbalance in the creation of globin chains, which results in the ineffective formation of red blood cells, accelerated destruction of red blood cells, and disrupted regulation of iron levels. The clinical presentation has a wide range of variability, spanning from nearly normal without any sequelae to severe cases that necessitate lifetime transfusion assistance[35]. β-thalassemia, the most severe form, occurs when both β-globin genes are damaged or mutated, leading to a marked reduction in Hb production, which is presented clinically as chronic anemia[35]. Furthermore, thalassemia patients with parvo B19 infection are under double effect of Hb reduction. This virus infects and replicates in its target cells, erythrocyte progenitor cells, in the bone marrow, causing cessation of erythropoiesis and, consequently, reduction in both RBCs and Hb concentration[36]. Therefore, B19V is considered to be a potentially life-threatening pathogen in individuals with a high rate of red blood cell production[14, 37].

The results showed that thalassemic patients had a significant decrease in the RBC count and Hb%. Erythrocytes, are the main blood cells that provide oxygen to human tissues via blood circulation. A red blood cell (RBC)'s cytoplasm includes a lot of haemoglobin, an iron-oxygen biomolecule. Each red blood cell in humans has around 270 million haemoglobin

molecules[38]. In a healthy individual, mature red blood cells circulate in the blood for approximately 100 to 120 days [39].

The findings revealed a statistically significant increase in platelet count among patients with thalassemia. Platelets, also known as thrombocytes, are a vital component of blood that, together with coagulation factors, respond to blood artery injuries by aggregating and initiating the formation of a blood clot. Platelets are cytoplasmic particles that originate from megakaryocytes in the bone marrow or lung and then enter the bloodstream. Platelets are exclusively present in mammals[40]. Platelets play a significant role in hemostasis, which is the process of halting bleeding by forming a clot at the point where the endothelium is damaged. Furthermore, platelets possess cytokines and growth factors that can facilitate wound healing and the restoration of injured tissues[41]. Thrombocytopenia is a medical disorder where the number of platelets in the blood is lower than the usual range of 150,000 to 450,000 platelets/microliter. Insufficient platelet levels might result in protracted or severe bleeding. What is the most prevalent coagulation disorder.

Thrombocythemia, also known as thrombocytosis, is a medical disorder characterized by an elevated platelet count in the blood[42]. β-thalassemia is characterized by both inadequate erythropoiesis and peripheral hemolysis, resulting in a persistent condition of chronic anemia[43]. Ineffective erythropoiesis results in the enlargement of the bone marrow, which is accompanied by alterations in the bones. As a consequence, the production of blood cells may be stimulated in the spleen and liver, leading to the enlargement of these organs (hepato-splenomegaly). Peripheral hemolysis in β-thalassemia results in red blood cells (RBCs) displaying prothrombotic markers. This leads to a state of increased blood clotting, known as a hypercoagulable state. Platelet activation and other coagulation factors further contribute to this condition.

Clinically, it presents as the formation of blood clots in veins and arteries, as well as complications such as pulmonary hypertension and cerebrovascular events[44]. The Parvovirus B19, commonly known as erythrovirus, exhibits a strong and nearly exclusive affinity for erythroid progenitors, leading to apoptosis. Individuals with conditions characterized by increased production of red blood cells, such as thalassemia, may experience

a significant decrease in the number of immature red blood cells, known as reticulocytes, leading to the development of severe anemia[27]. Hemophagocytosis typically results in severe and often fatal bone marrow failure and pancytopenia. This condition is characterized by a significant increase in inflammatory markers and cytokines[6]. Thalassemia caused by B19V infection typically presents anaemia as its main characteristic. However, it is also expected to observe moderate thrombocytopenia, often accompanied by other symptoms. Thrombocytopenia can arise as a result of parvo B19 infection. This can lead to a diagnosis of idiopathic thrombocytopenic purpura, where the immune system destroys platelets, or occasionally megakaryocytic thrombocytopenic purpura, where the bone marrow fails to manufacture platelets[11]. All this evidence denotes lowering the platelet count in thalassemia patients, contrary to what is found in the current results. This could be due to the fact that blood samples from thalassemia patients are usually collected after a blood transfusion. Furthermore, bacterial or viral infection in those patients indeed elevated all blood cells and platelets.

Conclusion

In this study, Parvovirus B19 infection was observed in patients with hematologic diseases, specifically thalassemia patients, and this had an impact on their blood indices. Implementing screening measures for people with a heightened risk of parvovirus B19 infection can significantly decrease the occurrence and prevalence of parvovirus B19 infection.

Source of funding: The researchers relied on their personal funding.

Conflict of interest: The authors declared no conflicting interests.

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