Original Article

Assessment of relevant hematological and biochemical parameters associated with toxoplasmosis in children with multi-transfusion for β-thalassemia major and sickle cell anemia

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ABSTRACT

Background: Due to frequent blood transfusions and associated immune deficiency, children with β-thalassemia major and sickle cell anemia, are highly exposed to the opportunistic parasite, *T. gondii*. Notably some biomarkers may reflect the systemic inflammatory response and organ involvement during toxoplasmosis, hence guide the clinical management and treatment strategies.

Objective: The study aimed to investigate the detection rate of toxoplasmosis in children with multi-transfused hemolytic anemias and estimate the potential association with relevant hematological and biochemical parameters.

Subjects and Methods: In a case control study, 150 anemic children (110 β-thalassemia, and 40 sickle cell anemia), and 150 non-anemic controls were investigated for the positivity of anti-*Toxoplasma* IgG and IgM antibodies. Complete blood count, serum ferritin, alanine aminotransferase (ALT), aspartate transaminase (AST), urea, creatinine, and C-reactive protein (CRP) were investigated.

Results: Respectively, the seroprevalence of *Toxoplasma* IgG (29.3%, and 4%), and IgM (10.7% and 0%) was significantly (P<0.001) higher in anemic children than the controls. *Toxoplasma* IgG and IgM seropositivity was insignificantly higher in children with β-thalassemia than those with sickle cell anemia. In anemic cases, total leucocytic count, ALT, AST activities, CRP were significantly increased (P<0.05) in *Toxoplasma* seropositive than seronegative children. Hemoglobin and other CBC parameters, ferritin, urea and creatinine concentration were stable when compared to seronegative ones.

Conclusion: Prior to administering blood transfusion to β-thalassemia major and sickle cell anemia affected children, it is critically necessary to screen donor's blood for anti-*T. gondii* antibodies.

Keywords: β-thalassemia; blood transfusion; CRP; ferritin; kidney functions; liver functions; seroprevalence; sickle cell anemia; toxoplasmosis.

Received: 12 December, 2024; **Accepted:** 1 February, 2025.

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Print ISSN: 1687-7942, **Online ISSN:** 2090-2646, **Vol. 18, No. 1, April, 2025.**

INTRODUCTION

Thalassemias are a diverse group of genetic disorders marked by reduced synthesis of alpha or beta chains of hemoglobin (Hb)[1]. β-thalassemia is an inherited autosomal recessive blood disorder resulting from point mutations or, less commonly, deletions in the beta globin gene on chromosome 11. This leads to decreased (beta^{+}) or absent (beta^{0}) synthesis of the beta chains of Hb with subsequent severe anemia[2]. The cornerstone therapy in improving the life span and the existence of thalassemic patients is blood transfusions with regular iron chelation[3]. Sickle cell disease is a common monogenic disorder resulting from the inheritance of two abnormal Hb (beta globin) genes leading to consequent erythrocyte rigidity, vaso-occlusion, hemolysis, chronic anemia with progressive impairment to most organs[4]. Regular blood transfusions can reduce the likelihood of vaso-occlusion and stroke by diluting the proportion of sickled cells in the circulation[5].

Toxoplasmosis, which ranks among the top five neglected parasitic diseases, usually affects one-third of the global population, particularly those living in low-income and developing nations. In immunocompetent individuals, toxoplasmosis is mostly asymptomatic but can have devastating consequences, potentially resulting in fatal illness in immune-compromised patients[6]. Humans can acquire toxoplasmosis through diverse routes, one of which is blood transfusion, where acutely infected blood donors can transmit the infection to blood recipients[7]. Being mostly asymptomatic, diagnosis of toxoplasmosis should be verified by further parasitological or

 DOI: 10.21608/puj.2025.344090.1280

serological testing rather than depending absolutely on clinical manifestations. Several serological tests are considered to distinguish *Toxoplasma*-specific antibodies where IgA and/or, IgM and IgG antibodies help to differentiate between acutely acquired and chronic infections[8]. Several investigations revealed higher frequency of *Toxoplasma* antibodies in healthy blood donors, in Egypt, where over 50% of them proved to be seropositive for toxoplasmosis[7,9].

Children with β-thalassemia and sickle cell anemia are subjected to regular, and frequent blood transfusion with subsequent exposure to transfusion-transmitted infections such as toxoplasmosis. Moreover, both thalassemia and sickle cell anemia are associated with the persistent stimulation of the immune system by recurrent blood transfusions, overload of iron, splenectomy and immunological deficiencies[10]. Such immune defects render those patients susceptible to opportunistic toxoplasmosis[11].

Early identification of toxoplasmosis in β-thalassemia and sickle cell anemia patients is crucial for controlling and subsequent efficient treatment of the disease. Therefore, our study aimed to detect acute and chronic toxoplasmosis among these children who undergo frequent blood transfusions. Estimating the correlation between toxoplasmosis with some relevant hematological and biochemical parameters was also another goal.

SUBJECTS AND METHODS

This case-control study was conducted in Hematology and Pediatric Clinics of Beni-Suef University Hospital during the period from February 2023 to June 2024.

Study design: Two groups of multi-transfused children (β-thalassemia major and sickle cell anemia), and a control group were enrolled. To achieve our objective, hematological and biochemical parameters were evaluated along with serological estimation of toxoplasmosis for all participants.

Study population and data collection: In a hospital-based case-control study a total of 300 children were equally divided into 2 groups. The case group included children with β-thalassemia major (No.=110), or sickle cell anemia (No.=40) referred to Hematology Clinic of Beni-Suef University Hospital. The control group included sex and age matched-non anemic children referred to Pediatric Outpatient Clinic of Beni-Suef University Hospital.

Children aged from 1 year up to 18 years and of both sexes were included. Inclusion criteria for cases were children with diagnostic assurance of β-thalassemia major or sickle cell anemia as regards the patient's history, blood tests, medical records, and Hb electrophoresis and those who received blood regularly. Exclusion criteria included children under 1 year old, and over 18 years, children receiving immunosuppressive drugs, children with primary liver or kidney disease, kidney transplantation, malignancy, children with agammaglobulinemia, and or history of any immunosuppressive disease.

All children were subjected to history-recording demographic data and risk factors associated with *Toxoplasma* infection in addition to clinical data related to β-thalassemia major, sickle cell anemia, and toxoplasmosis. General examination included abdominal, chest, and cardiac examination with high stress on β-thalassemia major and sickle cell anemia signs.

Sample collection and preparation: Sterile venipunctures were used to withdraw 5 ml of venous blood samples. Two ml of each blood sample were added to vacutainers containing EDTA, to perform the hematological tests. The remaining 3 ml of the sample was centrifuged at 3000 rpm for 20 min to separate the serum. Serum samples were transferred to labelled Eppendorf tubes and stored at (-80°C) until the required biochemical and serological tests were conducted.

Hematological parameters: These included a complete blood count (CBC) to calculate the Hb concentration, RBCs, platelets, mean corpuscular volume (MCV), total and differential leucocytic cells.

Biochemical parameters: Activity of AST and ALT was estimated in accordance with the instructions provided by commercially available diagnostic kits (LifeSpan Biosciences, Seattle, WA, USA). Kidney function tests were measured by the estimation of serum urea and creatinine by the enzymatic methods (Kit: BioMerieux, France). The CRP value was estimated by the automated Cobas CRP test following the manufacturer's recommendations of the kit supplier. Serum ferritin level was estimated using ELISA technique following the instructions mentioned in the assay kit (Sigma-Aldrich. USA).

Serological assessment of *T. gondii* infection: Serum samples for each participant were screened for anti-*Toxoplasma* IgM and IgG antibodies using commercially available ELISA kits (Precheck co. USA) guided by the manufacturer's instructions[11]. Each plate's optical density (OD) was measured at a wavelength of 450 nm. The cut-off value was calculated according to the equation mentioned by the manufacturer supplier.

Statistical analysis: The collected data was revised for accuracy and completeness, then coded, entered, and analyzed by Statistical package for Social Science (SPSS version 25) program. For descriptive statistics,

numbers and percentages proportions were used to present qualitative data. Mean and standard deviation were used for presenting quantitative data. The normality of distribution was verified by Shapiro-Wilk test, and the Mann Whitney test was used to compare between two studied groups for abnormally distributed quantitative variables. The Chi square test was used for categorical variables to compare between different groups. For analytical statistics, differences were considered significant at $P \leq 0.05$.

Ethical considerations: Informed written consents were obtained from parents of all children before participating in the study. The Research Ethics Committee of the Faculty of Medicine at Beni-Suef University, Egypt (FM-BSU REC) approved the study. The certificate of ethical approval is listed under number 04012023.

RESULTS

The age of enrolled children ranged from 2 to 17 years, with a mean of 9.19±4.478 in case and 9.54±4.263 in control groups. Most of the anemic cases and controls were boys (62% and 70.7%, respectively) and from rural areas (89.3%, and 78.0% respectively). No significant difference was detected between cases and controls in relation to age, gender, and education. Positive statistical significance ($P<0.001$) for consanguinity was recorded in 54.4% of cases versus 22.7% in controls (Table 1).

Out of the total 150 samples tested for toxoplasmosis in β-thalassemia and sickle cell anemia group, 29.3% and 4% were seropositive for IgG and IgM anti-*Toxoplasma* antibodies, respectively. While in the control group, the seroprevalence was 10.7% and 0% for IgG and IgM antibodies, respectively. A significant statistical difference was recorded between cases and control groups in reference to the seroprevalence of IgG (OR=3.476) and IgM antibodies. *Toxoplasma* seropositivity was higher in β-thalassemia group than sickle cell anemia group regarding IgG (30.9% versus 25%, respectively) and IgM antibodies (4.5% versus 2.5%, respectively) with non-statistical difference (Table 2).

The possible association between different risk factors and IgG seropositivity in anemic cases (Table 3) was statistically significantly different regarding *Toxoplasma* IgG seropositivity for mean age. The seroprevalence of *T. gondii* IgG was higher in anemic children who had contact with soil with statistically significant association ($P=0.019$). Regarding gender, boys in both groups had greater frequencies of anti-*T. gondii* IgG antibodies than girls, although the difference was not statistically significant. Other assessed risk factors showed no significant correlation with toxoplasmosis.

Table 1. Sociodemographic data among anemic and non-anemic children.

Variables	Anemic children (no.=150)	Non-anemic controls (no.=150)	Statistical analysis	
			Test of significance	*P* value
Age				
Min. – Max.	2.0 - 17.0	3.0 - 17.0	$U = 10699$	0.462
Mean ± SD	9.19 ± 4.478	9.54 ± 4.263		
Gender				
Boys	93 (62.0%)	106 (70.7%)	$X^2 = 2.523$	0.142
Girls	57 (38.0%)	44 (29.3%)		
Residence				
Urban	16 (10.7%)	33 (22.0%)	$X^2 = 7.049$	0.012*
Rural	134 (89.3%)	117 (78.0%)		
Education				
Yes	101 (67.3%)	106 (70.7%)	$X^2 = 0.390$	0.618
No	49 (32.7%)	44 (29.3%)		
Positive consanguinity	81 (54.4%)	34 (22.7%)	$X^2 = 31.727$	<0.001*
Positive family history@	80 (53.3%)	0 (0%)	$X^2 = 109.1$	< 0.0001*

U: Mann Whitney test; ***X*²:** Chi square; **@:** For anemia; ***:** Significance ($P<0.05$).

Table 2. Frequency of *Toxoplasma* infection among children with anemia compared to non-anemic controls.

	Anemic children (n=150)			Non-anemic controls (no.=150)
	β-thalassemia (no.=110)	Sickle cell anemia (no.=40)	Total (no.=150)	
Positive IgG	34 (30.9%)	10 (25.0%)	44 (29.3%)	16 (10.7%)
Statistical analysis	$X^2 1 = 0.264$, $P1 = 0.686$		$X^2 2 = 16.333$, $P2<0.0010$* OR= 3.476	
Positive IgM	5 (4.5%)	1 (2.5%)	6 (4.0%)	0 (0.0%)
Statistical analysis	$X^2 1 = 1.123$, $P1 = 0.364$		$X^2 2 = 1.123$, $P2 = 0.030$*	

***X*²:** Chi square; ***:** Significance ($P<0.05$). ***P*1:** Comparison between β-thalassemia and sickle cell anemia; ***P*2:** Comparison between cases and controls.

Table 3. Demographic data and risk factors in relation to *Toxoplasma* IgG among seropositive and seronegative anemic children.

Variables	Anemic children (n.=150)		Statistical analysis	
	Seropositive (no.=44)	Seronegative (no.=106)	Test of significance	*P* value
Age (Mean±SD)	10.727 ± 4.131	8.552 ± 4.4796	*U* = 1659.0	0.005*
Gender				
Boys	26 (59.1%)	67 (63.2%)	X^2 = 0.224	0.713
Girls	18 (40.9%)	39 (36.8%)		
Residence				
Urban	3 (6.8%)	13 (12.3%)	X^2 = 0.968	0.398
Rural	41 (93.2%)	93 (87.7%)		
Education				
Yes	35 (79.5%)	66 (62.3%)	X^2 = 4.222	0.055
No	9 (20.5%)	40 (37.7%)		
Positive cognition	21 (47.7%)	60 (57.1%)	X^2 = 1.108	0.368
Contact with cats	10 (22.7%)	20 (18.9%)	X^2 =0.289	0.655
Eating under cooked meat	20 (45.5%)	41 (38.7%)	X^2 =0.592	0.469
Eating unwashed vegetables	9 (20.5%)	26 (24.5%)	X^2 =0.288	0.675
Contact with soil	29 (65.9%)	46 (43.4%)	X^2 =6.304	0.019*
Source of water				
Safe	39 (88.6%)	93 (87.7%)	X^2 =0.024	1.00
Unsafe	5 (11.4%)	13 (12.3%)		

U: Mann Whitney test; ***X*²:** Chi square; ***:** Significance (*P*<0.05).

The association of frequent blood transfusions with *Toxoplasma* IgG and IgM seroprevalence varied between anemic cases. Both IgG and IgM were higher in children receiving blood transfusion every ≤3 m (79.5% and 66.7%, respectively) than those receiving blood every 4-6 m (20.5% and 33.3%, respectively) with statistical significance (*P*<0.001) (Table 4).

No significant difference was recorded between *Toxoplasma* IgG seropositive and seronegative anemic children regarding symptoms and signs except for presence of enlarged lymph nodes which was significantly (*P*=0.007) more frequent among IgG seropositive anemic children than seronegative ones (Table 5).

Concerning laboratory data of anemic children, higher mean levels of total leucocytic count (TLC), ALT, AST and CRP were recorded in seropositive anemic children with statistically significant difference (*P*=0.018, 0.039, 0.043, and 0.035, respectively). Other laboratory data showed no significant relationship with toxoplasmosis (Table 6).

Table 4. Association between *Toxoplasma* IgG and IgM seropositive anemic cases with frequency of blood transfusion.

Frequency of blood transfusion	IgG seropositive anemic children (no.=44)	*P* value	IgM seropositive anemic children (no.=6)	*P* value
≤ 3 m	34 (79.5%)	<0.001*	4 (66.7%)	<0.001*
4 - 6 m	10 (20.5%)		2 (33.3%)	

***:** Significance (*P*<0.05).

Table 5. Symptoms and signs related to *Toxoplasma* IgG among seropositive and seronegative anemic children.

Variables	Anemic children (n.=150)		Statistical analysis	
	Seropositive (no.=44)	Seronegative (no.=106)	Chi square test	*P* value
Fever	5 (11.4%)	26 (24.5%)	3.287	0.079
Hepatomegaly	31 (70.5%)	73 (68.9%)	0.037	1.00
Splenomegaly	29 (65.9%)	57 (53.8%)	1.872	0.206
Enlarged lymph nodes	12 (27.3%)	10 (9.5%)	7.761	0.007*
Pallor	44 (100.0%)	105 (99.1%)	0.418	1.00
Cardiac disorder	12 (27.3%)	17 (16.0%)	2.517	0.172
Facial features	18 (40.9%)	29 (7.4%)	2.654	0.123
Jaundice	11 (25.0%)	19 (17.9%)	0.973	0.372
Respiratory symptoms	13 (29.5%)	34 (32.1%)	0.093	0.848
Short stature	18 (40.9%)	49 (46.2%)	0.356	0.592

***:** Significance (*P*<0.05).

Table 6. Laboratory data among *Toxoplasma* IgG seropositive and seronegative anemic patients.

Variables	Anemic children (n.=150)		Statistical analysis	
	Seropositive (n.=44)	Seronegative (n.=106)	Mann Whitney test	*P* value
RBCs	3.78±0.54	3.83±0.65	2298	0.888
Hb(g/dl)	7.62±1.56	8.07±5.03	2259	0.763
MCV (fl/cell)	61.58±12.81	62.77±11.64	2116	0.372
TLC	12.24±8.03	9.69±6.09	1757	0.018*
Neutrophils	57.87±12.24	56.74±9.96	2173.5	0.512
Monocytes	4.37±2.49	4.14±1.74	2288	0.852
Lymphocytes	36.20±10.55	38.19±10.19	2101	0.340
Platelets	435.06±220.49	510.64±240.15	1920	0.089
Ferritin	921.87± 959.16	1007.81±742.27	1909	0.081
ALT	39.52±25.38	30.78±22.89	2309	0.039*
AST	38.10±21.01	32.81±26.17	2968.5	0.043*
Urea	26.59±8.05	24.93±8.38	1967	0.131
Creatinine	0.60±0.84	0.59±0.58	2096.5	0.321
CRP	32.44±1.57	12.28±1.13	3159.5	0.035*

***:** Significance (P<0.05).

DISCUSSION

The present study sheds light on one of the transfusion-transmissible infections, toxoplasmosis, in a category of children with β-thalassemia and sickle cell anemia. Anemic children are in a state of immune deficiency and in continuous need for frequent blood transfusion as a life-threatening intervention[12]. Comparable seroprevalence rates to our results in anemic children (29.3%, and 4% for IgG and IgM, respectively) were previously recorded in Iran[13] and Iraq[14]. In the latter report on thalassemia patients, anti-*T. gondii* IgG was detected in 30.76%, and 32%, while anti-*T. gondii* IgM was detected by 1.70% and 4%, respectively (P<0.05). Several studies recorded higher seroprevalences of toxoplasmosis among thalassemia patients for each of anti-*Toxoplasma* IgG and IgM antibodies in Iran (51.9%, and 3.4%)[15], and in Egypt (53.6%, and 23.2%)[16] with statistically significant difference between thalassemia and control groups. The investigators attributed the higher prevalence in thalassemia major to the frequent need for blood transfusions.

Our results conflicted with Moghimi *et al*.[17] who found no significant difference in Yazd city in Iran between β-thalassemia major patients and control group in respect to anti-*Toxoplasma* antibodies. The investigators suggested that the smaller population in this city, along with its residents' higher income and better hygiene conditions contributed to the lower seroprevalence in the area.

In agreement with our results, Ferreira *et al*.[18] observed that seropositivity for *Toxoplasma* IgG and IgM antibodies was higher in the β-thalassemia group compared to the sickle cell anemia group. The study compared three groups: sickle cell anemia, homozygous β-thalassemia, and heterozygous β-thalassemia. This may be explained by the fact that individuals having β-thalassemia major typically need regular blood transfusions to manage their chronic anemia and prevent complications of organ damage. In contrast, sickle cell anemia, primarily causes intermittent episodes of pain, and organ damage due to the sickled RBCs with less frequent transfusions needed except during acute crises. Studies have highlighted that patients with thalassemia major usually require transfusions every 2-4 w, while sickle cell anemia patients generally require transfusions less often[19,20].

Risk factors associated with *T. gondii* infection were estimated in our study. Contact with soil showed a statistically significant difference between *Toxoplasma* seropositive and seronegative anemic children, a finding consistent with the study by Cong *et al*.[21]. Children are often more vulnerable to this mode of transmission, as they tend to play outdoors particularly in agricultural areas added to poor sanitation in these areas. No statistically significant differences were recorded for *Toxoplasma* seropositivity between both genders, aligning with the findings of two studies[18,22], but conflicting with another study[15]. That study reported a significantly higher prevalence of *Toxoplasma* IgG antibodies in women. The authors suggested that women's higher susceptibility to infection could be linked to cleaning meat and vegetables at home. However, in our study, it makes sense that no gender difference was observed, as the participants were children. Other risk factors investigated in our study were not statistically significant among seropositive children, a finding also reported by several studies[13,14,22]. However, there are reports of a statistically significant association between *Toxoplasma* seropositivity and less educated patients[15], contact with cats[15], eating undercooked meat[15,16,23], and drinking unpurified water[14].

The highest rates of IgG and IgM seropositivity were observed in individuals receiving blood transfusions more frequently, particularly those transfused every three months or less, with statistical significance compared to those transfused less frequently, aligning with the findings of El-Tantawy *et al*.[16]. In fact, frequent blood transfusions are crucial for children with β-thalassemia major and sickle cell anemia. However, since *T. gondii* can survive in citrated blood at 5°C for up to fifty days or longer, it can remain viable in stored blood for several weeks, making transfusions of blood, platelets, or leukocytes potential transmission route[24,25]. Confirming this concept, several studies carried out in Egypt displayed higher seroprevalence of *Toxoplasma* antibodies in healthy volunteer blood donors ranging from 33.7% to 67.4%[7,9,26,27]. Unfortunately, according to national and international guidelines, screening for *T. gondii* antibodies in blood packs has not yet been implemented in blood banks before donation.

Our data revealed a statistically significant increase in TLC in seropositive anemic children compared to seronegative ones. This finding partially aligns with Mohamed[28], who observed higher TLC in seropositive young pregnant women compared to seronegative controls, though without statistical significance, while also reporting a significant decrease in TLC among older, infected pregnant women in the same study. It is worth mentioning that no statistically significant differences were found in hematological variables, including RBC count, Hb, MCV, MCH, neutrophils, lymphocytes, and platelet count, between *Toxoplasma* seropositive and seronegative anemic children. In contrast, Mousa and Nahab[29] reported a significant increase in RBC count, Hb, MCV, and packed cell volume in thalassemia patients infected with *T. gondii*. They attributed these findings to variations in the immune response of patients with toxoplasmosis.

There was a statistically significant difference in the presence of enlarged lymph nodes between *Toxoplasma* seropositive and seronegative anemic children, a result that partially agrees with El-Tantawy *et al*.[16]. The investigators recorded additional statistical significance with other manifestations like fever, pallor, jaundice, enlarged liver, and splenomegaly between both groups. In acquired toxoplasmosis, lymphadenopathy is classic, common and infrequently a single presenting sign. It is suggested that up to 15% of lymphadenopathies of unknown origin are attributed to toxoplasmosis[30].

Being a multisystem infection, toxoplasmosis significantly impacts the liver, leading to alterations in liver metabolism. It has been shown that liver enzyme levels tend to increase following *Toxoplasma* infection, potentially indicating the extent of liver damage[31]. Hence, serum AST and ALT were assessed as good indicators of hepatocellular injury. In the current study, there was a significant rise in the mean level of serum ALT and AST between *Toxoplasma* seropositive and seronegative anemic children. This agrees with two studies[16,29]. There was no significant difference in serum urea and creatinine levels although these levels were elevated in thalassemia patients compared to control groups in two studies[17,29]. This was attributed to the harmful effects on kidney tissue, resulting in glomerular damage, reduced urea excretion, and urinary abnormalities that ultimately contribute to renal failure.

On the other hand, CRP is regarded as a key immunochemical marker for various medical conditions, with elevated levels observed during infections, inflammation, and tissue damage[32]. Its significant increased level in *Toxoplasma* IgG seropositive anemic children than the seronegative ones agreed with several studies[6,33-36]. Currently, CRP measurements, along with hematological parameters, were proposed as prospective tools for diagnosing acute toxoplasmosis[37].

Ferritin levels were also not statistically associated with toxoplasmosis, a result consistent with Abd El-Latif *et al*.[22]; while another study[38] reported highly significant differences in ferritin levels. The latter study suggested that *T. gondii* reduces the binding affinity between iron and its carrier proteins, releasing free, toxic iron that negatively impacts host cells. The investigators proposed that the presence of *T. gondii* affects biological elements and cellular factors such as iron, transferrin, and ferritin. Additionally, another study[36] recorded higher serum ferritin levels in COVID-19 patients co-infected with *T. gondii* compared to those without toxoplasmosis, across different ages and sexes. In our study, it was suggested that hematological and biochemical laboratory findings can help assess the impact and prognosis of toxoplasmosis on the host, combined with the clinical symptoms.

In conclusion, thalassemia and sickle cell anemia children are more likely to acquire toxoplasmosis after blood transfusion. However, it is essential to broaden screening of blood donors to encompass other important pathogens that are linked to transfusion-transmitted infections.

Acknowledgment: The authors would like to express their sincere gratitude and dedication to all the laboratory personnel of Hematology and Biochemistry Laboratory of Beni-Suef University Hospital.

Author contribution: Abd El Wahab WM, Morgan DS, Hamdy DA, Aboud A, Mohamed YA contributed to study conception and design. Samples collection, and data gathering was performed by Foly SM, Mohamed YA. The original draft was written by Abd El Wahab WM, Hamdy DA, Aboud A, Mohamed YA. All authors contributed to the proposal of the study topic, data analysis, and revising the manuscript. They approved

the authorship and accepted the manuscript final version before publication.

Conflicts of interests: The authors declared that they have no conflict of interest.

Funding statement: No funding.

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