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Prevalence and risk factors of severe bacterial infections in thalassemia patients

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Abstract

Background: Thalassemia is an inherited disease, and it is considered as one of the most common monogenic disorders that lead to chronic hemolytic anemia. Thalassemia is newly classified into non–transfusion-dependent thalassemia (NTDT), and transfusion-dependent thalassemia (TDT) based on the necessity of regular blood transfusions. Thalassemia major patients may need a chronic blood transfusion, iron chelation medication, and splenectomy as a part of their treatment. One of the most common causes of death in thalassemia patients is a bacterial infection. The predisposing factors of the infections are either related to the disease itself (e.g. anemia and reticuloendothelial system dysfunction) or to the treatment (e.g. splenectomy, transfusion-related infections, and iron chelation).

Aim: To determine the prevalence and risk factors of severe bacterial infections in NTDT and TDT thalassemia patients at a tertiary hospital

Method: A retrospective study was conducted on patients with NTDT & TDT. Records were scanned from 2014 to 2018 from the hematology department of a tertiary hospital, Jeddah, Saudi Arabia. Patients of all ages who had severe bacterial infection were included in this study.

Results: This study was applied to a total of 231 thalassemia patients at a tertiary hospital in Jeddah, Saudi Arabia. 119 (51.5%) of them were females, and 112 (48.5%) were males; the mean age was 22 years (± SD 13.3). The majority of the patients were TDT 214 (92.6%), and 17 (7.4%) were NTDT. A total of 38 (16.5%) thalassemic patients admitted due to bacterial infection. Most of the patients get infected by *Escherichia coli, Staphylococcus aureus,* and *Klebsiella pneumoniae* with the percentage of (24.1%, 13.8%, 13.8%), respectively.

Conclusion: In conclusion, Patients undergone splenectomies are not susceptible to bacterial infection. Deferoxamine or iron-chelating drugs does not increase the risk of bacterial infection in patients with thalassemia. Finally, a prophylactic antibiotic is not useful in decreasing bacterial infection in thalassemic patients.

Keywords: Thalasemia, Bacterial infections, Pediatrics

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Introduction

Thalassemia is an inherited disease, and it is considered one of the most common monogenic disorders that lead to chronic hemolytic anemia. The pathophysiology of thalassemia in general is imbalance between the α/β-globin [1]. It mainly defects in genes result in diminished synthesis of one or more of the globin subunits [2]. They classified according to the severity of clinical presentation into thalassemia major, thalassemia intermediate, and thalassemia minor [3]. Thalassemia newly classifies into non–transfusion-dependent thalassemia (NTDT), and transfusion-dependent thalassemia (TDT) based on the necessity of regular blood transfusions [4]. The symptoms and severity of thalassemia vary according to how many globins is affected and which type of thalassemia present. From asymptomatic or mild till severe symptoms [5]. Clinical features of the disease develop in the first year of life, Firstly, presents as pallor, accompanied by splenomegaly depend on the severity, fever, and failure to grow [6,7]. High prevalence of the thalassemia was present in the Mediterranean region, Southeast Asia, and Africa population [8].

Thalassemia major patients may need a chronic blood transfusion, iron chelation medication, and splenectomy as a part of their treatment [9]. Transfusion is considered as a primary lifesaver therapy for thalassemia, but it contains significant risk including transfusion reactions, hemosiderosis, infections, and alloimmunization [10]. Hemosiderosis was the commonest complication in chronically transfused patients [11]. One of the most common causes of death in thalassemia patients is a bacterial infection [12-14]. The predisposing factors of the infections are either related to the disease itself (e.g. anemia and reticuloendothelial system dysfunction) or the treatment (e.g. splenectomy, transfusion-related infections, and iron chelation) [15].

There were multiple studies showed that severe complications are still frequent due to iron overload. Regardless of heart failure, infection in patients with thalassemia considered as a common cause of death accounted for 12% to 26% of patient deaths [12,13]. A previous study had estimated that the prevalence of infection ranges from 22.5% to 66% in TM patients [16-19]. Another previous study conducted between (2011-2015) showed that Saudi Arabia has one of the highest prevalence rates of β –thalassemia and Sickle Cell Disease comparing to other countries in the Middle East [20]. Moreover a study conducted in 2015 in Khon Kaen University, Thailand they select 211

thalassemia patients, severe bacterial infections were found in 11 patients of them [3]. Also, there are many risk factors which will make the thalassemia patient more vulnerable to the infection like the duration of the disease, treatment with deferoxamine and if the patient had a splenectomy [15]. Other studies have been done on non-transfusion dependent thalassemia patients (NTDT) to know the prevalence of bacterial infection among them, and the result was moderate. Also, they found that iron overload, deferoxamine therapy, duration after splenectomy for more than ten years considered as a risk factor for severe bacterial infection [3].

Microorganisms such *Y. enterocolitica, Klebsiella species, E. coli, Streptococcus pneumonia, P. aeruginosa* and Listeria monocytogenes have reported in the state of iron overload [21-23]. Previous studies have found the growth of *Klebsiella* species as major causative bacteria [3,16,24]. One study in Indonesia showed a significant difference in immune response between Splenectomised and non-splenectomized thalassemia significant patients, and they found that the Splenectomised patients are more susceptible to the infection [24,25]. The most important pathogens in splenectomized are *Streptococcus pneumoniae*, *Haemophilus influenza* and *Neisseria meningitides* [26]. A previous study revealed that splenectomy predisposed thalassemia and sickle cell disease patients to severe infections mostly by Gram-negative microorganisms [19]. In other study, iron overload was a result of regular blood transfusions especially in patients who were not under iron chelating therapy, iron presence lead to more susceptibility of gram-negative bacterial infections in thalassemia patients [27].

However, thalassemia is a common congenital disease, but still, there is no enough data about the risk factors in SA. Also, there are limited recent studies about the prevalence of severe bacterial infection in thalassemia patients. So, we aimed in this study to determine the prevalence and risk factors of severe bacterial infections in NTDT and TDT thalassemia patients. Also, to investigate the spectrum of a causal organisms with thalassemia.

Research Methodology

The study was approved by the unit of biomedical ethics of a tertiary hospital Jeddah, Saudi Arabia. A retrospective study was conducted in 2019. The patient's records were scanned from 2014 to 2018 from the Hematology Department of a Tertiary Hospital, Jeddah, Saudi Arabia. Transfusion dependent and non-transfusion independent thalassemia patients of all ages who had severe bacterial infection were included in this study. Severe bacterial infection was defined as a bacterial infection necessitating hospitalization. The clinical presentations and laboratory data, including those of potential risk factors for bacterial infection indicated in the literature, were collected. Bacterial infection was confirmed by the isolation of pathogens from blood, pus, stool, cerebrospinal fluid (CSF), and other body fluids. Data entered by excel, and statistical analysis was performed by SPSS 25. Categorical variables, including primary variables, will be described using frequencies. Continuous variables for customarily distributed will be described using mean and Std. The bivariate analysis was conducted for categorical variables using a Chi-square test to check for all the possible risk factors. Experiment with a P-value <0.05 will be considered significant.

Results

In this study, we aimed to determine the prevalence and risk factors of severe bacterial infections in NTDT and TDT thalassemia patients. This study was applied to a total of 231 thalassemia patients at a tertiary hospital in Jeddah, Saudi Arabia. Table 1 shows 119 (51.5%) of them were females and 112 (48.5%) were males; the mean age was 22 years (± SD 13.3), There were 16 different nationalities, the majority were Pakistani patients 71 (30.7%), 66 (28.6%) were Saudi patients, Most of the patients have O+ blood group 91 (39.2%). The majority of the patients were TDT 214 (92.6%), and 17 (7.4) were NTDT, 79.2% of the patients were non-splenectomized, and 20.8% underwent splenectomy, A total of 38 (16.5%) thalassemia patients admitted to a tertiary hospital Jeddah, Saudi Arabia due to bacterial infection, 25 (65.8%) of infected thalassemia patients had positive cultures, Twenty Two (88%) of the infected patients used antibiotics to treat the infection, The mean hospital stay duration for the admitted patients due to infection was 28 days (± SD 42.06) all are summarized in Table 2.

Table 1. *Demographic data***.**

Variables	N	%
Gender		
Female	119	51.5
Male	112	48.5
Nationality		
Afghanistan	1	.4
Bangladesh	8	3.5
Burma	10	4.3
Chadian	3	1.3
Egyptian	6	2.6
Indian	4	1.7
Indonesia	2	.9
Jordanian	3	1.3
Malaysia	1	.4
Myanmar	9	3.9
Pakistani	71	30.7
Palestinian	11	4.8
Saudi	66	28.6
Somalian	1	.4
Sudanese	3	1.3
Syrian	9	3.9
Blood groups		
A-	3	1.3
A+	67	28.9
AB+	12	5.2
B-	3	1.3
B+	47	20.3
O-	4	1.7
O+	91	39.2
A-	3	1.3
A+	67	28.9
	Mean	**Quartile (%)**
Age	22	20

The majority of the patients were on TDT 214 (92.6%), 38 (16.5%) admitted to the hospital due infection. 25 (65.8%) had positive culture, 183 (79.2%) were not splenectomise, 22 (88.0%) received antibiotics, 187 (81.0%) were not on prophylaxis. 151 (65.4%)were using defroxaime, 157 (68.0%) were on other chelating drugs, 19 (76.0%) were cured from infection, and only 4 patients (16.0%) had recurrence episode, with mean Hospital stay of 28 days (Table 2).

Most of the patient were infected by *Escherichia coli, Staphylococcus aureus* and *Klebsiella pneumoniae* with percentage of (24.1%,13.8%,13.8%) respectively (Table 3).

The result revealed a significant association between (TDT, NTDT) and the presence of positive culture ($P \leq 0.036$), where the infection was higher among TDT patients. On the other hand, there was no significant association between the presence of positive culture and (splenectomy, prophylaxis, deferoxamine, and other chelating drugs) p-value >0.05 (Table 4).

Table 2. *Medical history.*

Variables	N	%
TDT_NTDT		
NTDT	17	7.4
TDT	214	92.6
Admitted due to infection		
No	193	83.5
Yes	38	16.5
Positive cultures		
No	13	34.2
Yes	25	65.8
Patients undergone splenectomy		
No	183	79.2
Yes	48	20.8
Patients received antibiotics		
No	3	12
Yes	22	88
Patients on prophylaxis		
No	187	81.0
Yes	44	19.0
Patients on defroxaime		
No	80	34.6
Yes	151	65.4
Patients on other chelating agents		
No	74	32.0
Yes	157	68.0
Patients cured from infection		
No	6	24
Yes	19	76
Patients had recurrence episode		
No	21	84
Yes	4	16
Variables	**Mean**	**Quartile (%)**
Hospital stay duration	28	20

Table 3. *Names of bacteria.*

Bacteria names (n=12)	N	%
Escherichia coli	7	24.1
Staphylococcus aureus	4	13.8
Klebsiella pneumoniae	4	13.8
Acinetobacter	2	6.9
Acinetobacter baumannii	2	6.9
Streptococcus pyogenes	2	6.9
Mixed bacteria	2	6.9
Mycobacterium tuberculosis	1	3.4
Enterococcus faecalis	1	3.4
Salmonella	1	3.4
Diphtheroid	1	3.4

Table 4. *The relation between presence of positive and other risk factors.*

Variables		Positive culture		P value
		Yes	No	
TDT_NTDT	NTDT	5	12	0.036
	TDT	20	194	
Splenectomy	Yes	6	42	0.888
	No	19	154	
Prophylaxis	Yes	7	18	0.073
	No	37	169	
Defroxamine	Yes	13	18	0.195
	No	138	68	
Other chelating drugs	Yes	15	142	0.304
	No	10	64	

Discussion

In this retrospective study, we aimed to determine the prevalence and risk factors of severe bacterial infections in NTDT and TDT thalassemia patients at a tertiary hospital in Jeddah, Saudi Arabia. Infections are frequent in thalassemia patients, more than 10% present with severe Infection [15,28-31]. In the present study we reviewed 231 patients (51.5% females, 48.5% males). This study has evaluated that there were Sixty five percent of thalassemic patients had positive blood cultures. In other study by Wang et al, in 2003, recorded 22.5% of TDT had bacterial infection episodes [16].

Regarding our records, the significant organisms infection in TDT were *Escherichia coli* (24.1%) Staphylococcus aureus (13.8%) and *Klebsiella* (13.8%). Similarly, In Belgium, they found gram-negative bacteremia by cause of *Escherichia coli* and *Staphylococcus aureus* in gram-positive were the most causative agents in hemodialysis patients [32]. In Thailand, in cases of severe infection of β thalassemia, half the causative organisms were gram-negative bacilli such as *Escherichia coli* and *Klebsiella pneumoniae* [30]. Both TDT and hemodialysis patients have the same risk of exposure to blood-related infections.

151 of thalassemic patients use deferoxamine as iron chelation therapy, and 13 of them have positive bacterial culture. A study illustrates the effect of deferoxamine treatment on thalassemic patients showed that the infection level raised from 5 to 15 per 100 patients, a patient using deferoxamine are more liable to get infected by *Yersinia* spp [15,33]. Deferoxamine has a special effect when it comes to *Yersinia enterocolitica* infection. It interacts with an immune cell that will lead to reducing the immune system, and *Yersinia enterocolitica* has an outer protein membrane combined with ferrioxamine and release of deferoxamine with free iron [34,35]. There is a possible interaction between the type of iron-chelating therapy and infection based on the literature review.

Microbial agents collaborate with thalassemic hosts when the serum iron levels elevated [33]. Flowing iron overload patients start presented with symptoms (thyroid, hepatic, cardiac and growth disorders) after initiation of chelator therapy, improvement in ferritin level and symptoms was observed, but on the reverse side, the rate of infections raised [15].

This study showed that 68% of thalassemia patients are on iron-chelating therapy other than deferoxamine. However, iron chelating therapy other than deferoxamine did not show a statistically significant association with a bacterial infection. Supporting this, previous studies have found iron-chelating therapy not to enhance the growth of pathogenic organisms in patients with thalassemia [36,37]. Three predisposing factors will elevate the infection rate in thalassemia, the chronicity of the disease, splenectomy, and using deferoxamine as iron chelator therapy [5].

The spleen provides our bodies by important function; it filters our blood as part of the immune system. In this study, we found the relation between the positive culture and splenectomy not significant, which is unexpected. It appears to be different from another study, which indicates that 80% of the patients *had S. pneumoniae* infection after they underwent to splenectomy by two years and that was before the introduction of the anti-pneumococcal vaccine, and they indicate that the patients who underwent to splenectomy due to beta-thalassemia have the higher rate of infection than those who had splenectomy for another reason [38]. It shows this result because they divided those children's who had splenectomy into three groups according to the cause of the splenectomy as if the reason was severe primary disease this by itself will compromise the immunity of the child but if it were due to accidental injury or mild benign condition the risk would below. And there is another study showed that splenectomy increases the susceptibility to the infections especially in younger patients [39]. Other study conducted in Saudi Arabia and they showed that splenectomy could be performed in thalassemic patients over five years of age safely the reason behind this in their research it could be due to the given prophylaxis after the splenectomy on discharge as oral penicillin, 500 mg twice daily throughout the follow-up period. And they also indicate that post-splenectomy septicemia is still considered a significant risk in patients under five years of age [40]. In our study, the patients with Who are not splenectomize they had positive culture more than those who underwent to splenectomy it could be due to the big difference between the numbers of the patients who underwent to splenectomy from those who have not, with that we collected in our sample at a tertiary hospital in Jeddah, Saudi Arabia. Or it could be due to the increased exposure to the blood transfusion in the patient who doesn't undergo to splenectomy which considers as a risk factor for iron overload, and that will predispose them to the infection.

In 19% of patients receive prophylaxis for infection prevention, this study has documented a non-significant correlation between positive cultured blood specimens and prophylaxis use; only seven patients used prophylaxes and reported positive cultures, while such relation was unavailable in other papers. Post-splenectomy sepsis considered to be higher among thalassemia major patients [26]. As the spleen is necessary for the body defense against infection. In the case of spleen absence patients should be protected against the most fearsome organisms (*Streptococcus pneumoniae, Haemophilus influenza type B, Neisseria meningitides*) [41]. However, immunizations do not fully prevent the infection [42]. But penicillin prophylaxis has been attributed to reducing the incidence of pneumococcal bacteremia by 84%. Both incidence and mortality of post-splenectomy sepsis decreased, by 47% and 88% respectively, with the use of antibiotic prophylaxis [43]. For this reason, it is essential for patients who underwent splenectomy to receive penicillin prophylaxis and vaccinations to reduce the risk of developing sepsis. Furthermore, the mean duration of hospital stay admitted due to infection is 28 days. In the present study, 25 patients with a positive culture for infection, only four patients had a recurrence of the disease.

A limitation of this study is that the relation between iron overload and bacterial infection was not included due to poor documentation of serum ferritin levels. As it is a common disease in our country, we recommend creating a database for thalassemia patients for easier access to information and more accurate results. Researches on a more significant population and different centers need to be done.

Conclusion

In conclusion, patients who undergone splenectomies are not susceptible to bacterial infections. Deferoxamine or iron-chelating drugs does not increase the risk of bacterial infection in patients with thalassemia. Finally, a prophylactic antibiotic is not useful in decreasing the bacterial infection in thalassemia. Evaluation for iron excess should be performed regularly in patients with NTDT and TDT. Early recognition of bacterial infection in patients with TDT and NTDT may reduce morbidity and mortality. Further studies should add variables such as serum ferritin level, hemoglobin level, thalassemia face to consider risk factors.

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