

## A retrospective survey on follow-up of splenectomy patients due to $\beta$ -thalassemia and Sickle cell Anemia in Karbala, Iraq during 2010-2023

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### Abstract

**Background:** Hemoglobinopathy is considered a common monogenetic genetic disorder worldwide. Splenectomy is considered a therapeutic strategy in patients with hemoglobinopathy. The aim of current study was to provide a survey on the splenectomy and 5 years follow-up in different clinical forms of  $\beta$ -thalassemia (intermedia, Major) and Sickle cell Anemia (SCA) patients who referred to Hereditary Blood Disease Center in the Karbala Teaching Hospital for Children in Karbala, Iraq.

**Materials and Methods:** In this retrospective study we tried to evaluate 126 hemoglobinopathy and thalassemia patients from Karbala City, Iraq. All cases of splenectomy due to hemoglobinopathy and thalassemia during 2010-2023 who referred to the Hereditary Blood Disease Center in the Karbala Teaching Hospital for Children in Karbala, Iraq were included. Patient data was collected at three-time points. The first was after the splenectomy, the second during 1-5 years, and the third step after 5 years. Clinical and laboratory data were retrieved from the patient's file.

**Results:** The mean age of splenectomy of included patients was  $14.1 \pm 7.5$  years. From 126 cases, 103 (81.74%) were  $\beta$ -Thalassemia, 13 (10.32%) were SCA, and 10 (7.94%) were Sickle cell beta-thalassemia. The mean age in SCA was significantly less than two other groups (mean age in  $\beta$ -Thalassemia, SCA and Sickle cell beta thalassemia were  $18.2 \pm 8.7$ ,  $24.2 \pm 12.7$  and  $25.2 \pm 9.5$ , respectively) ( $p=0.008$ ). Platelet and WBC count represents a significant increase during 1-5 years after splenectomy in comparison with 1 year after splenectomy (for Platelet and WBC  $p=0.03$  and  $0.001$ , respectively).

**Conclusion:** splenectomy is considered the last therapeutic option in hemoglobinopathy patients. All Hemoglobinopathy patients represented significant improvement after splenectomy. Because there was no suitable treatment in the past, splenectomy was considered a therapeutic solution. It should be said that periodic follow-up of splenectomy patients in hemoglobinopathy plays an important role in improving the management of these diseases.

**Keywords:**  $\beta$ -thalassemia, Hemoglobinopathy, Sickle cell Anemia

### Introduction

Hemoglobinopathy is considered a common monogenetic genetic disorder all around the world. It's been estimated that there are more than 42 million carriers for hemoglobinopathy. Genetic errors in hemoglobin (Hb) synthesis lead to Hemoglobinopathy. Hemoglobinopathy can be divided into two different diseases including Thalassemia (absence or complications in the synthesis of a specific globin chain e.g.  $\alpha$  or  $\beta$ ) and hemoglobin variants (e.g. HbS or S hemoglobin).

Two of the more common types of hemoglobinopathies are Sickle cell hemoglobin (HbS), known as Sickle cell Anemia (SCA), and  $\beta$ -thalassemia (1, 2). SCA is caused by  $\beta$ -globin A>T (glutamate to valine) at codon 6, which can cause polymerization of Hb in stress. This polymerization leads to Sickle-shaped Red blood cells (RBCs) and stork attack (3). Another important Hemoglobinopathy form is thalassemia. Thalassemia is an inherited disease that leads to ineffective erythropoiesis. The thalassemia is caused by a defective  $\alpha$  or  $\beta$  chain. A defective gene could be presented in the form of

carrier, intermedia, or major thalassemia (4). The prevalence of thalassemia increased from 33.5 to 37 in 100,000 from 2010 to 2015 while the incidence rate decreased in live births in Iraq (5). Another important disease in hemoglobinopathy is the HbS and a defective  $\beta$  chain in heterozygote format known as Sickle cell- $\beta$ -thalassemia. Sickle cell- $\beta$ -thalassemia has a low prevalence compared with thalassemia. SCA patients are mostly faced with spleen disorders due to sequestration while in thalassemia patients the main cause of spleen disorders and splenomegaly is hypersplenism (6).

The splenectomy is sometimes and rarely considered in thalassemia and SCA patients, respectively. In the past, when access to treatment protocols was not possible, splenectomy was considered the standard treatment. The major causes of splenectomy in thalassemia and SCA are hypersplenism (it is defined based on criteria such as pancytopenia, and transfusion needed per year) and sequestration crisis. A spleen mass of more than 1kg is considered hypersplenism and is indicated for splenectomy in patients (7). The splenectomy complications include sepsis (8), infection with encapsulated bacteria, and thromboembolic condition (9). Following hemoglobinopathy and splenectomy patients is important due to the complexity of the clinical condition in case of the combination of hemoglobinopathy or splenectomy with other infectious or non-infectious diseases (9-12).

The current study aimed to provide a survey on the splenectomy and 5 years follow-up in different clinical forms of  $\beta$ -thalassemia (intermedia, Major) and SCA patients who were referred to the Hereditary Blood Disease Center in the Karbala Teaching Hospital for Children in Karbala, Iraq.

## Materials and Methods

### Patient's, inclusion and exclusion criteria, and follow-up

This retrospective study tried to evaluate 126 splenectomy patients due to hemoglobinopathy in Karbala city of Iraq. All study protocols confirmed by the medical college of Kerbala University approved the study (ethical code No. 27 on 14/11/2023). Inclusion criteria were hemoglobinopathy, indication for splenectomy, ethical considerations, and availability of follow-up files. All cases of splenectomy due to hemoglobinopathy and thalassemia during 2010-2023 years who were referred to the Hereditary Blood Disease Center in the Karbala Teaching Hospital for Children in Karbala, Iraq with an available file for at least five years of follow-up were included. Patients included  $\beta$ -thalassemia (intermedia, Major), SCA, and Sickle cell- $\beta$ -thalassemia patients. It needs to be mentioned all other medical protocols for these patients were considered and the splenectomy was not performed as a main or first-line clinical solution. Only a few numbers of hemoglobinopathy patients who were referred to the mentioned center which clinically indicated splenectomy underwent splenectomy and were included in this study. All patients with follow-up of less than 5 years or incomplete data of follow-up were excluded. Patients with 5 years of follow-up were included in 13 cases of SCA, 103 cases of  $\beta$ -Thalassemia, and 10 cases of sickle cell- $\beta$ -Thalassemia.

### Clinical data collection and splenectomy

Patient data was extracted from the file. Data included the patient's diagnosis, age (mean  $\pm$  SD), cause of splenectomy, and laboratory parameters in three time points including before splenectomy, after splenectomy, one visit during 1-5 years after splenectomy, and 5 years after splenectomy. Laboratory parameters included white blood cell (WBC) and

platelet (Plt) count at each time point. Furthermore, vaccination history and blood transfusion episodes after and before splenectomy were recorded. All clinically indicated auxiliary treatments after splenectomy and prophylaxis antibiotic therapy were performed for all of the included patients.

### **Statistically evaluation**

The descriptive and analytic statistical evaluation was performed in SPSS version 22 (IBM, SPSS). The statistically significant is considered as  $p < 0.05$ . The Kolmogorov–Smirnov test used parametric or non-parametric assessment of numerical data. All non-parametric variables with two categories as an independent variable and numerical values as a dependent variable were evaluated by the Mann-Whitney U test (only used for age between two groups) and nominal variables were evaluated by chi-square test. The Fisher exact test was used in case of limitation for the chi-square test. Based on the nature of selected statistical tests differences were evaluated between each two groups of disease in every step of assessment.

## **Results**

### **Patient's demographical data**

Patients were including 62 (49.2%) and 64 (50.8%) male and female, respectively. The mean age of included patients at the time of splenectomy was  $14.1 \pm 7.5$  years. The data about the age were extracted from the patient's file and it represented the exact age when the splenectomy was performed.

### **Cause of splenectomy and clinical data**

The diagnosis for all patients was obtained based on patients' records and files. From 126 cases, 103 (81.74%) were  $\beta$ -Thalassemia, 13 (10.32%) were SCA, and 10 (7.94%) were Sickle cell beta-thalassemia.

The cause for splenectomy in SCA patients was sequestration and in  $\beta$ -thalassemia was hypersplenism. The splenectomy was

performed by laparoscopy 25 (20%) and 100 (80%) by open surgery (the type of operation for one patient was not available). Furthermore, more information is provided in *Table I*. There was a statistically significant difference between the ages of included patients with disease groups during the age evaluation the mean age of SCA and SCA- $\beta$ -Thalassemia were merged and evaluated with  $\beta$ -Thalassemia patients' mean age. This merging was due to low frequency and high similarity between SCA alone and SCA- $\beta$ -Thalassemia groups. The mean age at the splenectomy time in both SCA and SCA- $\beta$ -Thalassemia groups was significantly less than  $\beta$ -Thalassemia ( $p = 0.008$ ). Furthermore, the blood transfusion pattern represents a statistically significant difference between before splenectomy and disease groups ( $p = 0.001$ ), After splenectomy and disease groups ( $p = 0.001$ ), and between after and before splenectomy in all groups ( $p = 0.02$ ). as it was clear,  $\beta$ -Thalassemia patients require more transfusion episodes regardless of splenectomy.

### **Follow-up of patients**

Patient data was collected in three time points except the age which was collected only at the time of splenectomy. The first was just after the splenectomy, the second during 1-5 years, and the third step after 5 years. During all of these three steps, platelet and WBC counts were evaluated. The Blood transfusion episodes after and before splenectomy, vaccination, and infection history were evaluated (*Table I* and *Table II*). There was a statistically significant difference between different groups of disease and 1-5 years platelet count ( $p = 0.048$ ). Also, differences between different groups of disease and after 5 years of follow-up for WBC count ( $p = 0.005$ ). A statistically significant difference between WBC count and Platelet count in  $\beta$ -thalassemia patients was seen between different follow-up time

points. Platelet and WBC count represents a significant improvement in comparing 1 year after splenectomy with 1-5 years after

splenectomy (for Platelet and WBC  $p=0.03$  and  $0.001$ , respectively) (Figure I and II).

Table I: A survey of patients with splenectomy and five-year follow-up episodes

| Variables  | SCA                | Sickle cell $\beta$ -thalassemia | $\beta$ -thalassemia | P-value        |              |                    |
|--|--------------------|----------------------------------|----------------------|----------------|--------------|--------------------|
| <b>Age at the splenectomy time (mean <math>\pm</math> SD)</b>  | 12.4 $\pm$ 6.9     | 18.8 $\pm$ 12.5                  | 13.5 $\pm$ 6.8       | <b>0.008**</b> |              |                    |
| <b>Gender</b>  | Male               | 6 (53.8%)                        | 6 (60%)              | 49 (47.6%)     | 0.7          |                    |
|  | Female             | 7 (46.2%)                        | 4 (40%)              | 54 (52.4%)     |              |                    |
| <b>Splenectomy cause</b>   | Sequestration      | 13 (100%)                        | 3 (30%)              | 0              | <b>0.001</b> |                    |
|  | hypersplenism      | 0                                | 7 (70%)              | 103 (100%)     |              |                    |
| <b>Blood transfusion</b>   | Before splenectomy | 0                                | 7 (63.6%)            | 4 (66.7)       | 5 (6.8%)     | <b>&lt;0.05***</b> |
|  |                    | 1-2 in months                    | 2 (18.2%)            | 2 (33.3%) *    | 15 (20.3%)   |                    |
|  |                    | 2-3 in months                    | 1 (9.1%)             | -              | 46 (62.2%)   |                    |
|  |                    | > 3 per month                    | 1 (9.1%)             | -              | 8 (10.8%)    |                    |
|  | After splenectomy  | 0                                | 2 (15.4%)            | 1 (10%) *      | 5 (7.8%) *   |                    |
|  |                    | 1-2 in months                    | 11 (84.6%)           | 3 (30%)        | 52 (81.3%)   |                    |
|  |                    | 2-3 in months                    | -                    | -              | 6 (9.4%)     |                    |
|  |                    | > 3 per month                    | -                    | -              | 1 (1.6%)     |                    |
| <b>Surgery</b>   | Laparoscopy        | 3 (23.1%)                        | 3 (30%)              | 19 (18.6%)     | 0.6          |                    |
|  | Open Surgery       | 10 (76.9%)                       | 7 (70%)              | 83 (81.4%)     |              |                    |
| <b>Vaccination Status before splenectomy</b>   | Yes                | 12 (92.3%)                       | 10 (100%)            | 90 (87.4%)     | 0.4          |                    |
|  | No                 | 1 (7.7%)                         | -                    | 13 (12.6%)     |              |                    |
| <b>Infection episode after splenectomy</b>   | Yes                | 1 (7.7%)                         | 2 (20%)              | 9 (8.7%)       | 0.4          |                    |
|  | No                 | 12 (92.3%)                       | 8 (80%)              | 94 (91.3%)     |              |                    |
| <p>All statistical evaluation in this table was performed by chi-square and Fisher exact test (in case of empty cells) and Mann-Whitney U test for numerical values such as age<br/> * Valid percent is provided due to limited data from some of the included patients.<br/> ** Sickle cell <math>\beta</math>-thalassemia and SCA were considered as one group and <math>\beta</math>-thalassemia as another group, the age was evaluated by the Mann-Whitney U test.<br/> *** Blood transfusion was a statistically significant difference between before splenectomy and disease groups (0.001), between after splenectomy and disease groups (0.001), and between after and before splenectomy (0.02)</p> |                    |                                  |                      |                |              |                    |

Table II: WBC and platelet count during follow-up periods of included patients

| Variables   |                             | SCA     | Sickle cell $\beta$ -thalassemia | $\beta$ -thalassemia | P-value*** |              |
|---|-----------------------------|---------|----------------------------------|----------------------|------------|--------------|
| <b>Platelet count*</b>  | Before splenectomy          | 150-450 | 11 (84.6%)                       | 9 (90%)              | 82 (91.1%) | 0.7          |
|   |                             | <150    | 2 (15.4%)                        | 1 (10%)              | 4 (4.4%)   |              |
|   |                             | <100    | -                                | -                    | 2 (2.2%)   |              |
|   |                             | <50     | -                                | -                    | 2 (2.2%)   |              |
|   | 1 year after splenectomy    | 150-450 | 6 (46.2%)                        | 8 (80%)              | 41 (48.8%) | 0.05         |
|   |                             | <100    | -                                | -                    | 16 (19%)   |              |
|   |                             | >450    | 5 (38.5%)                        | 1 (10%)              | 25 (29.8%) |              |
|   |                             | >1000   | 2 (15.4%)                        | 1 (10%)              | 2 (2.4%)   |              |
|   | 1-5 years after splenectomy | 150-450 | 8 (61.5%)                        | 5 (50%)              | 35 (39.8%) | <b>0.048</b> |
|   |                             | <100    | -                                | -                    | 12 (13.6%) |              |
|   |                             | >450    | 4 (30.8%)                        | 5 (50%)              | 41 (46.6%) |              |
|   |                             | >1000   | 1 (7.7%)                         | -                    | -          |              |
|   | 5 years after splenectomy   | 150-450 | 5 (41.7%)                        | 8 (80%)              | 29 (36.3%) | 0.1          |
|   |                             | <50     | 3 (25%)                          | 2 (20%)              | 32 (40%)   |              |
|   |                             | >450    | 3 (25%)                          | -                    | 9 (11.3%)  |              |
|   |                             | >1000   | 1 (8.3%)                         | -                    | 10 (12.5%) |              |
| P-value****   |                             | 0.3     | 0.1                              | <b>0.001</b>         |            |              |
| <b>WBC count**</b>  | Before splenectomy          | 4-11    | 13 (100%)                        | 10 (100%)            | 103 (100%) | -            |
|   | 1 year after splenectomy    | 4-11    | 4 (30.8%)                        | 6 (60%)              | 38 (47.5%) | 0.6          |
|   |                             | >11     | 7 (53.8%)                        | 3 (30%)              | 35 (43.8%) |              |
|   |                             | >20     | 2 (15.4%)                        | 1 (10%)              | 7 (8.8%)   |              |
|   | 1-5 years after splenectomy | 4-11    | 10 (76.9%)                       | 5 (50%)              | 42 (45.7%) | 0.08         |
|   |                             | >11     | 2 (15.4)                         | 4 (40%)              | 19 (20.7%) |              |
|   |                             | >20     | 1 (7.7%)                         | 1 (10%)              | 31 (33.7%) |              |
|   | 5 years after splenectomy   | 4-11    | 11 (84.6%)                       | 9 (90%)              | 40 (43%)   | <b>0.005</b> |
|   |                             | >11     | 1 (7.7%)                         | 1 (10%)              | 19 (20.4%) |              |
|   |                             | >20     | 1 (7.7%)                         | -                    | 34 (36.6%) |              |
| P-value****   |                             | 0.08    | 0.4                              | <b>0.03</b>          |            |              |
| <p>All statistical evaluation in this table was performed by chi-square and Fisher exact test (in case of empty cells)<br/>                     * The value is <math>10^3</math> per <math>\mu\text{L}</math>, plt assessed in five different groups in each time point based on the count including 150-450, &lt;150, &lt;100, &lt;50, and &gt;450 but empty cells were removed from the table.<br/>                     ** The value is <math>10^3</math> per <math>\mu\text{L}</math>, WBC was assessed in four different groups at each time point based on the count including 4-11, &lt;4, &gt;11 and &gt;20 but empty cells were removed from the table.<br/>                     ***P-value for assessment of platelet and WBC count between different groups of disease (e.g. SCA, Thalassemia)<br/>                     ****P-value for platelet or WBC count in one group of diseases between different time points.</p> |                             |         |                                  |                      |            |              |

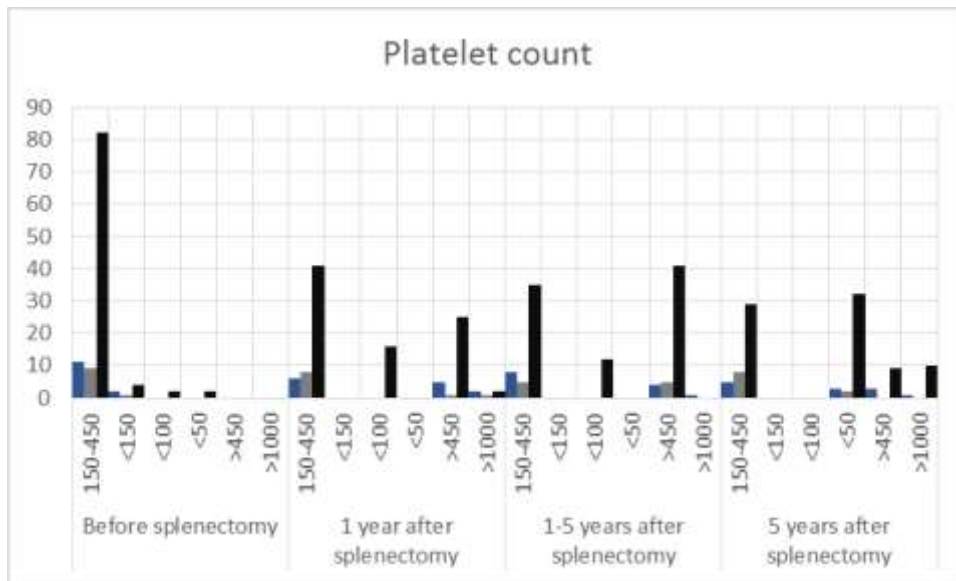


Figure 1. A significant improvement in 1-5 years after splenectomy for platelet count in SCA (Blue), Sickle cell  $\beta$ -thalassemia (Gray), and  $\beta$ -thalassemia (black)

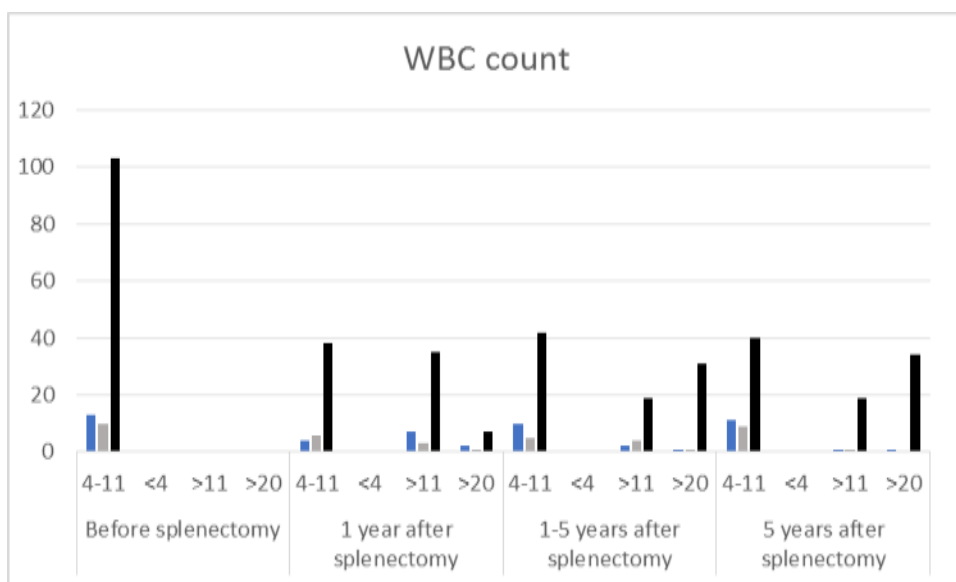


Figure 2. A significant improvement in 5 years after splenectomy for WBC count in SCA (Blue), Sickle cell  $\beta$ -thalassemia (Gray) and  $\beta$ -thalassemia (black)

## Discussion

The spleen is a lymphatic organ with hematopoietic function during uterus life and immune function during adult life. Splenectomy is considered as part of therapeutic approaches in hematological diseases. The main hematological diseases associated with splenectomy are hemolytic

anemia, platelet disorders, and Lymphoproliferative disorders. One of the main indications for splenectomy in hematological conditions is hemoglobinopathy (13). As mentioned earlier, the current study aimed to provide a survey on the splenectomy and 5 years follow-up in different clinical forms of  $\beta$ -

thalassemia (intermedia, Major) and SCA patients who were referred to Hereditary Blood Disease Center in the Karbala Teaching Hospital for Children in Karbala, Iraq.

The mean age of included patients was  $24.4 \pm 9.9$  62 (49.2%), and 64 (50.8%) were male and female, respectively. From 126 cases, 103 (81.7%) were  $\beta$ -Thalassemia, 13 (10.3%) were SCA and 10 (7.9%) Sickle cell beta-thalassemia. Demographical data from the current study seems to be in confirming for previous studies in Iraq (14, 15). Al-Allawi et al. report  $\beta$ -Thalassemia as a major hemoglobinopathy disorder in Iraq and low frequency of SCA (16).

In the current study, during all three time points platelet and WBC count were evaluated. There was a statistically significant difference between different groups of disease and 1-5 years platelet and WBC count. Weng and colleagues indicated that a higher level of WBC in splenectomy patients could be found in short term. This WBC count in splenectomy patients due to trauma could be a predictive marker for infection (17). Elevated WBC in the long term after splenectomy due to injuries is described by Wernick et al. (18). The long-term follow-up of SCA patients by Pinto revealed that the splenectomy did not affect increasing fatal outcomes and is recommended (19).

Reducing the need for blood transfusion in thalassemia patients after splenectomy in the Iraqi population was also reported by Azeez (20). In our study, 12 (92.3%) from SCA, 10 (100%) of Sickle cell  $\beta$ -thalassemia, and 90 (87.4%) of  $\beta$ -thalassemia patients were vaccinated before splenectomy. This finding confirms other available documents due to its importance for prevention after splenectomy infection episodes. Also, The dramatic effect of vaccination before splenectomy for presentation of infections in thalassemia patients was established

earlier (21). Regardless of blood transfusion episodes, the platelet count increase after splenectomy was demonstrated by Merchant et al. (22). The results of the current study are on the same page with this finding.

By considering all, the current study seems to confirm previous studies in this field about Iraqi hemoglobinopathy patients. Furthermore, some differences might be due to geographical differences or evaluated patient populations. The fact is, that this group of patients needs more research and focus for improving quality of life and treatment.

This study faced some limitations; the major one is the limited number of included patients. Also, more time for follow such as thrombosis could help provide a more comprehensive view of splenectomy in hemoglobinopathy patients. Another limitation of the study could be due to the statistical evaluation. During the statistical evaluation, a gap about the effect of age as an influencing factor in the outcome of the evaluation was not removed. It might affect the outcome in some cases. In this regard, it should be noted that it's a preliminary study performed in the way of providing some information about splenectomy in hemoglobinopathies patients in Iraq and further more complete studies are required for a clear conclusion.

## **Conclusion**

Thalassemia is the major form of Hemoglobinopathy in evaluated patients with splenectomy in Iraq. Splenectomy is considered the last therapeutic option in hemoglobinopathy patients. All Hemoglobinopathy patients represented significant improvement after splenectomy. Because there was no suitable treatment in the past, splenectomy was considered a therapeutic solution. It should be said that periodic follow-up of splenectomy patients in hemoglobinopathy

plays an important role in improving the management of these diseases.

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### Authors' contribution

All authors confirmed and edited the final version of the manuscript. IMMA, Concept, design, and manuscript preparation, AAH, manuscript preparation and data collection, IMSA, manuscript preparation and data collection.

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There is no funding source for this study.

### Conflict of interest

There is no conflict of interest.

### Ethical considerations

All study protocols confirmed by the medical college of Kerbala University approved the study (ethical code No. 27 on 14/11/2023).

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