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RESEARCH ARTICLE
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ASSESSMENT OF SPLENIC FUNCTION AMONG TRANSFUSION DEPENDENT THALASSEMIA PATIENTS

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Abstract:
Transfusion-dependent thalassemia is a chronic disease that affects many individuals and has a significant impact on the healthcare system and society. This study sought to explore the prevalence and factors contributing to hypersplenism in transfusion-dependent thalassemia patients in the Khyber Pakhtunkhwa province of Pakistan. A single-center-based retrospective study was conducted on 50 randomly selected patients over a period of three months From February 2019 to April 2019 and data was analyzed using established statistical techniques. The results showed that all (n=50, 100%) of the participants developed hypersplenism at an average age of 6.86±1.9 years and underwent a splenectomy at an average age of 15.1±4.6 years. The study found that the average number of annual transfusions received by the patients was 19.1±7.7, with no significant change in transfusion frequency after splenectomy.

Key-words: Thalassemia, Hypersplenism, Transfusion-Dependent Thalassemia**,** Splenectomy.

INTRODUCTION:

Transfusion-dependent thalassemia is a chronic disease that affects many individuals and has a significant impact on the healthcare system and society in general.[1] People with this disease require frequent blood transfusions, usually every three weeks, to maintain their health. However, these transfusions can also cause a range of complications, including hypersplenism. This condition can be extremely serious and lead to other medical issues and in severe cases, death.[2] Once developed, hypersplenism expedites ancillary complications, often culminating in serious morbidities or even mortality. Increased frequency of blood transfusions and cytopenia are the key markers for the disease.[3] Despite the impact of transfusion-dependent thalassemia and hypersplenism on patients and society, the exact frequency and causes of hypersplenism in this population have not yet been studied in detail in the Khyber Pakhtunkhwa province of Pakistan. To address this issue, a study was carried out to explore the prevalence and factors contributing to hypersplenism among transfusion-dependent thalassemia patients in KP. The study's objectives were to outline the key problems surrounding hypersplenism, to lay the foundation for future research on this topic in the local

thalassemia population. This study will provide crucial insights into the experiences and challenges faced by transfusion-dependent thalassemia patients in KP and help to inform the development of effective treatments and care strategies for this patient population. The results of this study will also have important implications for healthcare providers, policymakers, and advocacy organizations working to support individuals with transfusion-dependent thalassemia.

OBJECTIVES:

1.Assessment of the Prevalence of Hypersplenism in Transfusion-Dependent Thalassemia Patients.
2.Determining the Timing of Hypersplenism Onset in Transfusion-Dependent Thalassemia.
3.Examining the Connection between Transfusions and the Development of Hypersplenism in Thalassemia Patients.

METHODOLOGY:

The study design was a single-centre-based retrospective study that aimed to explore a specific research question. The study was carried out over a period of of three months From February 2019 to April 2019 and data was collected from the records of 50 randomly selected patients from a hospital in Peshawar with the consent of the Fatimid Foundation. The sampling technique used in this study was convenience sampling, and the data was recorded using a self-structured questionnaire. The study's inclusion criteria were transfusion-dependent thalassemia patients who were registered at the Fatimid Foundation in Peshawar, of either gender and aged 15 years or older, and residents of the Khyber Pakhtunkhwa province of Pakistan. The exclusion criteria were patients registered with multiple transfusion centres. The recorded data were analysed using Excel sheets and SPSS version 23. Arithmetic means were calculated for nominal data, and the Chi-square or Fisher's exact test was used for comparative analysis of qualitative parameters. For quantitative variables, the student’s t-test was employed to compare among dichotomous groups. The design for this study has been thoroughly evaluated and was accepted by the research board and ethical committee of Northwest School of Medicine. The lack of participant’s consent was due to the retrospective design of the research project, and the patients/guardians had already consented to the sharing and publishing of their clinical data. In a nutshell, the study employed a well-structured methodology with a clear aim and defined inclusion and exclusion criteria to ensure the validity and reliability of the results. The analysis of the recorded data was carried out using established statistical techniques to provide insights into the research question.

RESULTS:

Fifty participants were enrolled in this research project, which included 18 male and 32 female patients, with a mean age of 19.68±2.55 years which ranged from 15 to 27 years. Each participants developed hypersplenism at an average age of 6.86±1.9 years. Out of the 50 patients, 15 underwent a splenectomy at an average age of 15.1±4.6 years. The study found that the average number of annual transfusions received by the patients was 19.1±7.7. Among the splenectomised patients, the annual pre- and post-splenectomy transfusion frequencies were 20 and 18 respectively. **[Table 1]** Although the pre-splenectomy transfusion Hb (6.8 g/dl) and post-splenectomy transfusion Hb (7.1 g/dl) remained statistically unchanged, the platelets and leukocytes showed a marked variation. The pre-splenectomy platelets and leukocytes were 210.4 per microliter and 7.3 per microliter, respectively, while the post-splenectomy platelets and leukocytes were 480.7 per microliter and 14.6 per microliter, respectively. **[Table 2]**

Table1: *Mean Annual Pre- and Post-Splenectomy Transfusion Frequencies.*

Variable	**Transfusions Frequency**
Mean Annual Transfusions for All Patients	19.1±7.7
Mean Annual Pre-Splenectomy Transfusions for Splenectomised Patients	20
Mean Annual Post-Splenectomy Transfusions for Splenectomised Patients	18

Table2: *Hb, Platelets and Leukocytes Counts.*

Variable	Pre-splenectomy	Post-splenectomy
Hb	6.8 g/dl	7.1 g/dl
Platelets	210.4 per microliter	480.7 per microliter
Leukocytes	7.3 per microliter	14.6 per microliter

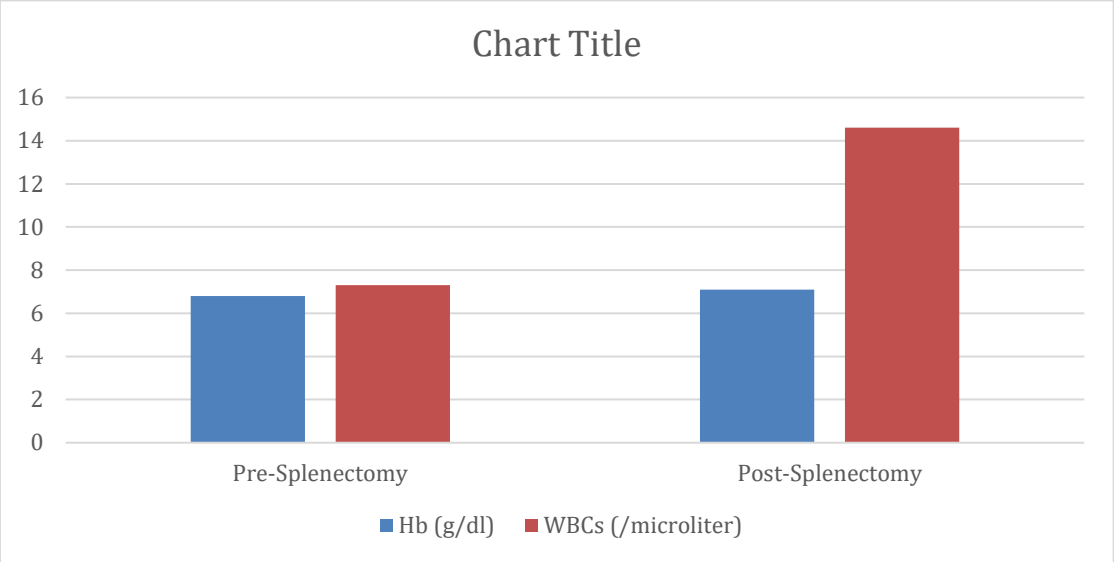

Fig 1 – Comparison of Hb and WBC levels in pre and post splenectomy thalassemia patients

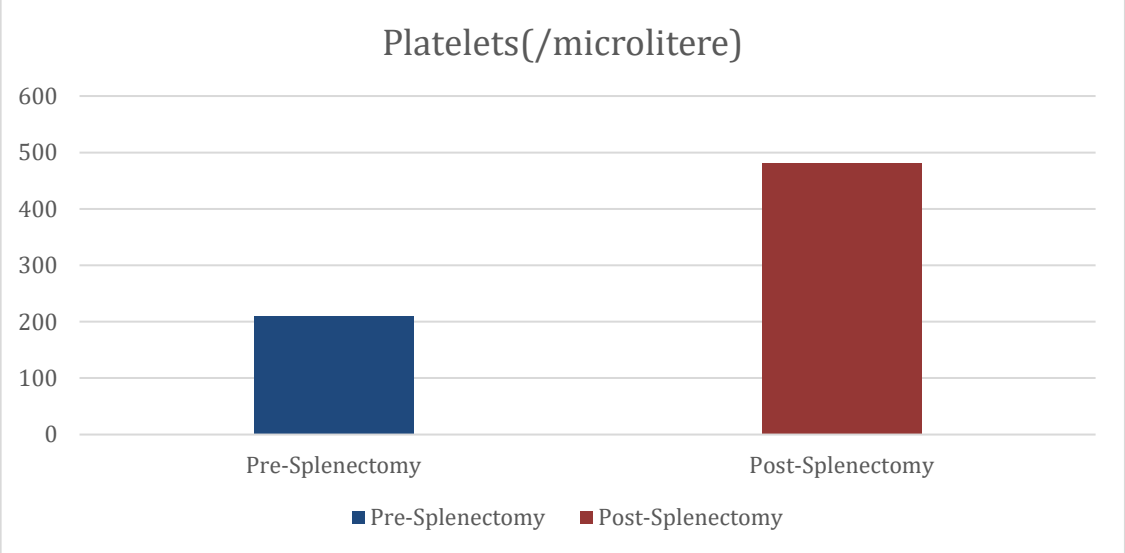

Fig 2 – Comparison of patelet levels in pre and post splenectomy thalassemia patients

DISCUSSION

Patients with beta thalassemia who have hypersplenism may develop anemia due to low numbers of platelets, which can cause prolonged bleeding, and low levels of white blood cells, which increase their chance of infection. Additional issues may arise if left untreated. There are a few ways that thalassemia can affect the spleen: When the spleen breaks down a red blood cell in a thalassemia patient, the iron frequently remains inside the spleen rather than being recycled. Because they are small and irregularly shaped, thalassemic RBCs frequently get caught in spleen. The spleen may enlarge due to one of these conditions. When hemoglobin levels in a person with thalassemia intermedia fall too low, the body may try to make more and more red blood cells. In the event that a patient is not receiving enough transfusions, this is also the case in thalassemia major. In thalassemia, the body needs more of these cells than the bone marrow can make, therefore other

organs, like the spleen, may begin to manufacture them. Normally, these cells are produced in the bone marrow. The spleen may enlarge as a result of this. Additionally, it might result in hypersplenism, a disorder where the spleen becomes overactive.[4]
The objectives of this study included assessment of the prevalence and timing of onset of hypersplenism in transfusion dependent thalassemia Patients and examining the relation between transfusions and the development of hypersplenism. All of the participants enrolled in the study developed hypersplenism at an average age of 6.86±1.9 years and 15 underwent a splenectomy at an average age of 15.1±4.6 years. This area still remains unexplored as to what age does the spleen enlarge and after hypersplenism how long does it take for the indication of the splenectomy. The average number of transfusions were observed for patients with the splenectomy and the ones with the intact spleen. The study found that the average number of annual transfusions received by the patients was 19.1±7.7. Among the splenectomised patients, the annual pre- and post-splenectomy transfusion frequencies were 20 and 18 respectively. Although the pre-splenectomy transfusion Hb (6.8 g/dl) and post-splenectomy transfusion Hb (7.1 g/dl) remained statistically unchanged, the platelets and leukocytes showed a marked variation. The pre-splenectomy platelets and leukocytes were 210.4 per microliter and 7.3 per microliter, respectively, while the post-splenectomy platelets and leukocytes were 480.7 per microliter and 14.6 per microliter, respectively. In a similar study, against groups that didn't get splenectomy, had blood transfusions more frequently, eight out of 58 post-splenectomy participants received blood transfusions less than four times annually (p=0.014). There was no discernible difference in the average hemoglobin concentration in both the post-splenectomy (7.50 (SD 0.87) g/dL) and non-splenectomy (7.22 (SD 0.87) g/dL) groups (p=0.088). In comparison, groups that did not received splenectomy, they had a median of 12 (6 to 36), and post-splenectomy groups had a median blood transfusion frequency of 8 (0 to 24) times during a year (p=0.005). Compared to non-splenectomy subjects, post-splenectomy groups received more cleaned PRC. Additionally, there was a considerable increase in ferritin and transferrin saturation in the post-splenectomy group compared to the non-splenectomy group, indicating a severe iron overload. The widely used iron chelation therapy in both populations is deferiprone as well.[5]

As the spleen begins to function more quickly in hypersplenism, it begins to destroy more and more red blood cells, which lowers haemoglobin levels. This could lead to a patient with thalassemia major needing blood more frequently or a patient with thalassemia intermedia starting transfusion therapy. As a result of more frequent transfusions, the body is exposed to more iron, which needs to be eliminated by chelation therapy. Since hypersplenism typically cannot be reversed, it is crucial to stop it from occurring. To do this, make sure that the patient is receiving blood transfusions at the proper rate. Once the patient has received enough blood to stop needing the enhanced production, the size of the spleen can be decreased. Splenectomy surgery may occasionally be required to treat hypersplenism.[6] Nonetheless, the measurement of pros and cons for the splenectomy has to considered very carefully. Morris and Bullock presented the first experimental evidence of the spleen's protective function against infections in the early 1900s.[6] They discovered that rats undergoing splenectomies had post-surgical mortality rates that were noticeably greater than those of rats who underwent mock procedures. The reason for this increased mortality was determined to be sepsis caused by the bacillus which is responsible for rat plague. Two quick studies were the catalyst for the discovery of the critical role of the spleen in immune defence several years later. In a cohort of kids who had had splenectomy, a number of examples of overwhelming post-splenectomy infections (OPSI) caused by encapsulated bacteria were described by King and Schumacker[6]. The term "hyposplenism" was created by Dameshek[6] to describe a celiac disease patient in whom Howell-Jolly bodies were found on a peripheral blood smear and the post-mortem examination confirmed an atrophic spleen. Today, hyposplenism is recognised as an acquired ailment that may be linked to a number of disorders and can result in a shrinkage of the spleen.[7,8] Asplenia, or the lack of the spleen, is a condition that is more usually the outcome of surgery than congenital disease. Although fundamental research has shed light on the spleen's function in the immune response[9,10] and literature have confirmed the link between impaired splenic function and increased mortality

and morbidity from infectious complications[11] basic studies have also provided extensive details regarding the spleen's role in the immune system's response.
Importantly, some patients may experience negative effects from splenectomies. The most well-known and detrimental side effects in splenectomized individuals include a higher probability for contracting infections and pulmonary hypertension.[12,13] According to certain studies, pulmonary hypertension can occur in as many as 59–75% of people.[14] In a prior research, splenectomies were discovered to be a substantial risk factor for the development of pulmonary hypertension. After a splenectomy, incidents of thromboembolic events have also been documented.[15] However, there is a dearth of information on the prevalence of these incidents of thrombosis and how splenectomies are connected to them. Patients who had undergone splenectomies and had immune system impairment and a hypercoagulable state were more likely to suspect problems.[16] In a study the medical records of 20 control participants with intact spleens and 50 patients with transfusion-dependent thalassemia (TDT) who had undergone splenectomy were retrospectively reviewed. Ten years old was the mean age for splenectomies. After having a splenectomy, twenty-seven (54%) patients switched to NTDT from TDT, demonstrating the effectiveness of the procedure. Total 23 TDT patients were labelled as "splenectomy non-responders" because they continued to require transfusions. The variables that strongly predicted a greater splenectomy response. [17]

The main objective of a splenectomy in TDT patients is to reduce the need for RBC transfusions. According to studies, patients who undergo splenectomy experience a reduction in their need for transfusions, and numerous thalassemia patients switch from TDT to NTDT. Our study eventhough did not show any statistically significant change in the pre-splenectomy transfusion Hb (6.8 g/dl) and post-splenectomy transfusion Hb (7.1 g/dl), however, the platelets and leukocytes showed a marked variation. The findings of a study however suggested that splenectomy could lessen the need for transfusions.[18] Hb-H illness and patients of age >10 years at the time of spleen removal were factors that were linked to a higher level of effectiveness. The findings suggest that a less serious form of thalassemia responds better to splenectomies.[18]

Studies have shown that Hb levels and the platelet count increased following the removal of an enlarged spleen that could lead to cytopenia.[19] According to a retrospective investigation of post-splenectomized thalassemia intermedia patients, their platelet counts were higher than those of the non-splenectomized group, which is in line with our findings.[20] Similar to this, Ya-Li Zhou et al. found greater Hemoglobin levels, WBC counts, and platelet number in splenectomized patients with Hb H/CS illness. Increased Hb levels would be a benefit of splenectomy in alpha thalassemia patients, which agreed with the outcomes of our investigation.[21]

The study we conducted has a number of limitations. Our data lacked information on the causes of splenectomy, additional biochemical indicators for the risk of pulmonary hypertension, thrombosis and the frequency of infections being an important post-splenectomy complication.

CONCLUSION:

The latest research delves into the prevalence of hypersplenism in the transfusion-dependent thalassemia patient population and uncovers a common occurrence. Despite the common assumption that splenectomy could alleviate transfusion needs, the study results paint a different picture, as the procedure appears to have little impact on improving the frequency of blood transfusions in these patients.

RECOMMENDATIONS:

According to the findings of the current study, it is recommended that individuals with transfusion-dependent thalassemia be closely monitored for the onset of hypersplenism. To prevent the development of hypersplenism, maintaining a pre-transfusion HB level of at least 9 g/dL is advised.

In cases where hypersplenism does develop, early splenectomy should be considered to prevent the onset of additional complications.

REFERENCES

1. Esmaeilzadeh F, Azarkeivan A, Emamgholipour S, Akbari Sari A, Yaseri M, Ahmadi B, et al. Economic Burden of Thalassemia Major in Iran, 2015. J Res Health Sci 2016;16(3):111-5.
2. Borgna-Pignatti C, Gamberini MR. Complications of thalassemia major and their treatment. Expert Rev Hematol 2011;4(3):353-66.
3. Lv Y, Lau WY, Li Y, Deng J, Han X, Gong X, et al. Hypersplenism: History and current status. Exp Ther Med 2016;12(4):2377-82.
4. Piga A, Serra M, Longo F, Forni G, Quarta G, Cappellini MD, Galanello R. Changing patterns of splenectomy in transfusion-dependent thalassemia patients. American journal of hematology. 2011 Sep;86(9):808-10.
4. Sari TT, Gatot D, Akib AA, Bardosono S, Hadinegoro SR, Harahap AR, Idjradinata PS. Immune response of thalassemia major patients in Indonesia with and without splenectomy. Acta Medica Indonesiana. 2016 May 16;46(3).
5. Merchant RH, Shah AR, Ahmad J, Karnik A, Rai N. Post splenectomy outcome in β-thalassemia. The Indian Journal of Pediatrics. 2015 Dec;82:1097-100.
6. Di Sabatino A, Carsetti R, Corazza GR. Post-splenectomy and hyposplenic states. The Lancet. 2011 Jul 2;378(9785):86-97.
7. William BM, Thawani N, Sae-Tia S, Corazza GR. Hyposplenism: a comprehensive review. Part II: clinical manifestations, diagnosis, and management. Hematology. 2007 Apr 1;12(2):89-98.
8. Mebius RE, Kraal G. Structure and function of the spleen. Nature reviews immunology. 2005 Aug 1;5(8):606-16.
9. Kruetzmann S, Rosado MM, Weber H, Germing U, Tournilhac O, Peter HH, Berner R, Peters A, Boehm T, Plebani A, Quinti I. Human immunoglobulin M memory B cells controlling Streptococcus pneumoniae infections are generated in the spleen. The Journal of experimental medicine. 2003 Apr 7;197(7):939-45.
10. William BM, Thawani N, Sae-Tia S, Corazza GR. Hyposplenism: a comprehensive review. Part II: clinical manifestations, diagnosis, and management. Hematology. 2007 Apr 1;12(2):89-98.
11. Taher AT, Musallam KM, Karimi M, El-Beshlawy A, Belhoul K, Daar S, Saned M, Cesaretti C, Cappellini MD. Splenectomy and thrombosis: the case of thalassemia intermedia. Journal of Thrombosis and Haemostasis. 2010 Oct 1;8(10):2152-8.
12. Cappellini MD, Cohen A, Porter J, Taher A, Viprakasit V, editors. Guidelines for the management of transfusion dependent thalassaemia (TDT). Nicosia, Cyprus: Thalassaemia International Federation; 2014.
13. Phrommintikul A, Sukonthasarn A, Kanjanavanit R, Nawarawong W. Splenectomy: a strong risk factor for pulmonary hypertension in patients with thalassaemia. Heart. 2006 Oct 1;92(10):1467-72.
14. Cappellini MD, Robbiolo L, Bottasso BM, Coppola R, Fiorelli G, Mannucci AP. Venous thromboembolism and hypercoagulability in splenectomized patients with thalassaemia intermedia. British journal of haematology. 2000 Nov;111(2):467-73.
15. Bazi A, Shahramian I, Yaghoobi H, Naderi M, Azizi H. The role of immune system in thalassemia major: a narrative review. Journal of Pediatrics Review. 2018 Jul 10;6(2):29-36.
16. Osataphan N, Dumnil S, Tantiworawit A, Punnachet T, Hantrakun N, Piriyakhuntorn P, Rattanathammethee T, Hantrakool S, Chai-Adisaksopha C, Rattarittamrong E, Norasetthada L. The long-term efficacy in blood transfusions, hematologic parameter changes, and complications after splenectomy in patients with transfusion-dependent thalassemia. Transfusion and Apheresis Science. 2022 Dec 9:103620.
17. Rachmilewitz EA, Giardina PJ. How I treat thalassemia. Blood, The Journal of the American Society of Hematology. 2011 Sep 29;118(13):3479-88.

18. Sharma A, Mathew ME, Puri L. Splenectomy for people with thalassaemia major or intermedia. Cochrane Database of Systematic Reviews. 2019(9).
19. Taher AT, Musallam KM, Nasreddine W, Hourani R, Inati A, Beydoun A. Asymptomatic brain magnetic resonance imaging abnormalities in splenectomized adults with thalassemia intermedia. Journal of Thrombosis and Haemostasis. 2009 Jan 1;8(1):54-9.
20. Zhou YL, Zhang XH, Liu TN, Wang L, Yin XL. Splenectomy improves anaemia but does not reduce iron burden in patients with haemoglobin H Constant Spring disease. Blood Transfusion. 2014 Oct;12(4):471.
21. Sirachainan N. Thalassemia and the hypercoagulable state. Thrombosis research. 2013 Dec 1;132(6):637-41.