Correlation Analysis of HbA2 Levels with Erythrocyte Index in Beta-Thalassemia Patients at RSUD Dr. H. Abdul Moeloek Lampung Province in 2023

Putu Ristyaning Ayu Sangging[1], Fathan Qoriba[1], Hendri Busman[2], Khairunisa Berawi[1], Maulana[1]

[1] Faculty of Medical, Lampung University
[2] Faculty of Mathematics and Natural Sciences, Lampung University
ristya.ayu@gmail.com

Abstract. Thalassemia is a genetic disorder that cause impaired hemoglobin production. Hemoglobin gets destroyed dua to impaired synthesis of hemoglobin chains or globin chains. The purpose of this study was to explore the correlation between hemoglobin A2 (HbA2) levels and erythrocyte index in thalassemia patients at Dr. H. Abdul Moeloek Hospital, Lampung Province in 2023. This study used an analytical observational method with a cross-sectional approach with total sampling technique. The number of samples was 39 beta thalassemia patients who fit the inclusion and exclusion criteria. The research was conducted in September-November 2024 at the Medical Record Installation of Dr. H. Abdul Moeloek Hospital Lampung Province. Data were analyzed univariate and bivariate with Spearman correlation test to determine the relationship between HbA2 and each erythrocyte index. It was found that most subjects had increased hbA2 levels (66.7%) and decreased MCV (97.4%) and MCH (92.3%) levels. There was a significant correlation between HbA2 levels with MCV (p= 0.001; r= -0.525) and HbA2 with MCV (p=0.001; r= -0.508). This study shows that increased HbA2 levels correlated with decreased MCV and MCH values in beta-thalassemia patients, while there is no significant correlation with MCHC.

Keywords: HbA2, Erythrocyte Index, Beta-thalassemia.

1 Introduction

1.1 Background

Thalassemia patients produce abnormal hemoglobin, leading to anemi and other complications. Anemia can be caused by decreased red blood cell production, bleeding, red blood cell forming substance deficiency, genetic diseases, hemolysis, erythropoietin hormone deficiency and other long-term diseases. There are 3 major classes of anemia: hypochrome microcytic anemia, normochrome normocytic anemia and macrocytic anemia (Suryani et al., 2016). Thalassemia is classified as hypochrome microcytic anemia. Thalassemia can be divided into several types, one of them is beta thalassemia, where there is a decrease in the production of beta globin chains.

© The Author(s) 2025
S. Hadi et al. (eds.), *Proceedings of the 5th International Conference on Applied Sciences, Mathematics, and Informatics (ICASMI 2024)*, Advances in Physics Research 13,
https://doi.org/10.2991/978-94-6463-730-4_20

According to the World Health Organization (WHO) (2022), more than 8 million babies are born with genetic disorders each year worldwide and 11.3% of the 2.68 million babies who die are caused by genetic disorders. In Indonesia, thalassemia is one of the most common genetic disease that requires special attention in handling such as routine blood transfusions and medication to manage symptoms and complications that arise (Kemenkes RI, 2018). There were around 5,000 patients in 2011 and an increase in 2017 of 9,121 patients (Kemenkes, 2020) while in Lampung there were 147 thalassemia children who received routine blood transfusions in 2021 (Puput, 2018).

Based on the Indonesian Pediatric Association (IDAI) media service guidelines, a complete hematological examination including decreased Hb, decreased erythrocyte index (MCV, MCH and MCHC, increased RDW), peripheral blood smear preparations (microcytes, hypochromes, anisocytosis, poikilocytosis, young erythrocyte cell/normoblasts, fragmentocytes and target cell) and Hb electrophoresis (HbA2 increased) are used to diagnose thalassemia (Kemenkes RI, 2018). HbA2 is often used as a diagnostic marker for beta thalassemia because HbA2 levels are often elevated as a compensatory response to deficiency in beta globin chain production (Susanto and Susanti, 2019).

Another important parameter in the hematological evaluation of thalassemia patients is the erythrocyte index, such as Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH) and Red Cell Distribution Width (RDW). MCV measures the average volume of red blood cells (Susanto and Susanti, 2019), MCH measures the average amount of hemoglobin in each red blood cell and RDW measures the variation in red blood cell size. Changes in erythrocyte indices in thalassemia patients can indicate the severity of anemia and the efficacy of therapy (Hieronymus and Titah, 2018).

Research on the correlation between HbA2 levels and erythrocyte index in thalassemia patients is important to improve the accuracy of diagnosis and management of this disease. Understanding the relationship between the two helps clinicians determine appropriate therapy where erythrocyte index is used as a screening test for thalassemia types with MCV values for thalassemia major patients of 50-60 fL and MCH 12-18 pg (Kemenkes, 2018). Variations in HbA2 levels and erythrocyte index in patients with different degrees of severity still require further research to confirm the underlying mechanisms and will contribute to clinical guidelines in Indonesia. Developments in hematology technology provide opportunities for more comprehensive research (Brancaleoni et al., 2016), but in under-resourced remote areas simple and rapid methods are still needed for more practical diagnosis (Kemenkes, 2018).

1.2 Problem Statement

Based on the background that has been described, the problem formulation in this study is whether there is a correlation between HbA2 levels and erythrocyte index in beta thalassemia patients?

1.3 Objectives of the Study

Based on the problem formulation that has been described, the objectives of the study are as follows:

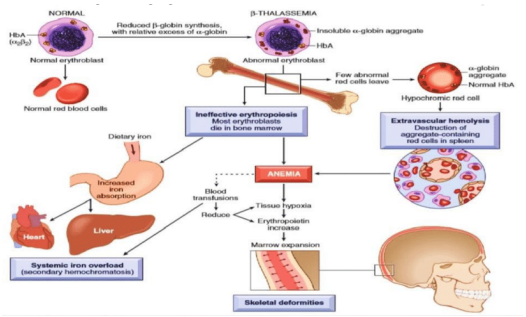
1. Knowing the correlation between HbA2 levels and Erythrocyte Index in beta thalassemia patients.
2. To know the level of hbA2 in beta thalassemia patients.
3. To determine the Erythrocyte Index (MCV, MCH and MCHC) in patients with beta thalassemia patients.

2 Review of Related Literature

Types of hemoglobin found in normal humans: HbA consists of two pairs of alpha and beta globin chains (α2β2), HbA2 consists of two pairs of alpha and delta globin chains (α2δ2) and HbF consists of two pairs of alpha and gamma globin chains (α2γ2). HbA has the highest composition in blood circulation reaching 97% while HbA2 has 2-3% and HbF (Setiati et al., 2014). Beta globin chain synthesis is decreased in beta thalassemia due to mutations. There is an increase in HbF and HbA2 and fewer thalassemia mutations caused by deletions. Excess globin chains occur due to reduced globin synthesis (Rujito, 2019).

Thalassemia major is managed with red blood cell transfusions. The purpose of transfusion is primarily to suppress erythroid expansion, but it also serves to reduce symptoms of anemia and inhibit gastrointestinal absorption of iron. Clinical signs of erythroid enlargement, such as facial changes, bone enlargement, and splenomegaly, along with severe anemia and growth retardation, are indications for transfusion. Most transfusion regimens require a pretransfusion hemoglobin of 9-10 g/dL and a post-transfusion hemoglobin of 13-14 g/dL. As a result, patients who receive transfusions regularly are at risk of iron overload, transfusion reactions and red blood cell antibody formation. As a result, it is very difficult to find the right blood donor for the next transfusion (Karimi et al., 2014).

Normal HbA consists of four globin chains referred to as polypeptides consisting of two alpha chains and two beta chains. These four chains combine to form four heme complexes. The synthesis of beta globin chains is defective in thalassemia beta leading to ineffective hematopoiesis and anemia. Thalassemia beta major is associated with severe anemia that can cause the kidneys to release erythropoietin, a hormone that stimulates the bone marrow to produce more red blood cells. In addition, erythropoiesis can cause hepatosplenomegaly by stimulating extra-modular hematopoiesis tissue in the liver and spleen. Increased iron absorption from the gastrointestinal tract is a consequence of anemia that can lead to iron accumulation of 2-5 grams per year (Kumar et al., 2015; At-makusuma and Setyaningsih, 2014).

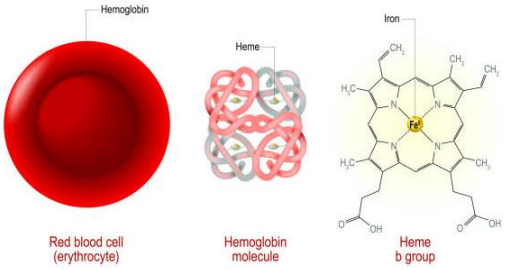


a

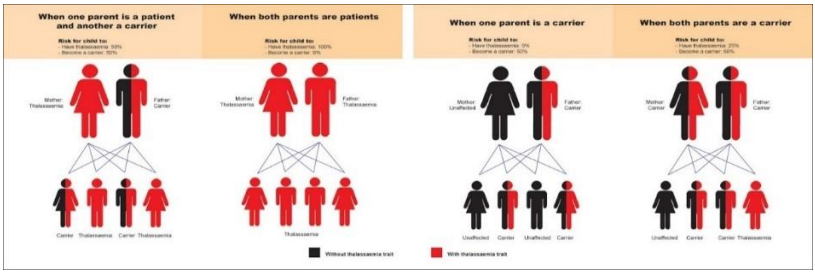
Clinical manifestations of thalassemia major are characterized by a mongoloid face, incomplete body growth, changes in bones such as deformities and spontaneous fractures and enlarged liver and spleen are early symptoms of thalassemia major which usually has severe anemia and appears at the age of 6 to 24 months (Lantip, 2019).

The structure of Hb consists of two main structures: heme and globin and an additional structure consisting of four polypeptide chains made up of amino acids bound into chains in a specific order. Each heme molecule consists of four heme structures with iron at the center and two pairs of globin chains. In erythropoiesis, the polychromatic normoblast stage initiates hemoglobin synthesis (Kiswari, 2014).

Structure of hemoglobin



a



a

In support of diagnosis, one of the parameters of routine blood tests is the erythrocyte index test. The calculation of the erythrocyte index is based on data about the erythrocyte cell count, hemoglobin level and hematocrit value. It provides information on the average volume of erythrocytes, hemoglobin content per erythrocyte and average hemoglobin concentration. This examination process is used to identify anemia based on its morphology and type of anemia (Nugraha and Badrawi, 2018). The erythrocyte index is used to determine the type of anemia and evaluate the morphology of anemia. The calculation values used are (Aini, 2021): MCV, MCH and MCHC.

2.1 Correlation of HbA2 Level with Erythrocyte Induction in Thalassemia Patients

A complete hematology laboratory examination based on the medical service guidelines of the Indonesian Pediatric Association (IDAI) showed that Hb decreased, erythrocyte index (MCV, MCH, and MCHC decreased, RDW increased), peripheral blood smear preparations (microcytes, hypochromes, anisocytosis, poikilocytosis, young erythrocyte cells/normoblasts, fragmentocytes, and target cells), and Hb electrophoresis (increased HbA2) (Susanto and Susanti, 2019).

The erythrocyte index in thalassemia patients often shows a microcytic hypochromic pattern. MCV levels are usually low indicating smaller than normal red blood cell size. MCH levels are also usually low indicating a lower amount of hemoglobin per red blood cell. Low MCHC levels also indicate a lower amount of hemoglobin per red blood cell. This pattern is characteristic of thalassemia and helps in the diagnosis and surveillance of the disease (Susanto and Susanti, 2019).

Measurement of HbA2 levels is one of the important diagnostic tests for beta thalassemia. Elevated HbA2 levels can help in identifying individuals who may have beta thalassemia even before obvious clinical symptoms appear. Phenotypically, thalassemia carriers manifest in a mild form of the disease characterized by slightly increased erythrocyte count, decreased MCV, decreased MCH and characteristic elevated HbA2 levels, which form the basis of the diagnosis. Elevated HbA2 in thalassemia carriers may be the result of transcriptional and sometimes post-translational effects (Al-Amodi et al., 2018).

Most laboratories determine HbA2 levels using quantitative methods such as capillary electrophoresis and high-pressure liquid chromatography (HPLC). In the past, HbA2 level of 4% was considered a sign of thalassemia trait. Thalassemia carriers with a “borderline level of HbA2”, that is a HbA2 level that is between the upper limit of normal and the lower limit typical of thalassemia carriers. Marini's (2023) research on HbA2 found that the lowest HbA2 value in iron deficiency anemia was 1.8% and the highest HbA2 value was 3.1%. The data showed that 20 out of 20 patients with iron deficiency anemia had normal HbA2 levels. In thalassemia, the lowest HbA2 value was 3.3% and the highest HbA2 value was 9.3% (Colaco and Nadkarni, 2021).

3 Research method

This study was conducted using a descriptive correlational method that aims to determine the relationship between HbA2 levels and erythrocyte index in thalassemia patients. This study uses a cross-sectional approach which means that researchers see the dynamics of the correlation between the independent variable and the dependent variable through observation or data collection at once. The data used is secondary data, namely medical records where researchers try to determine the relationship between the independent variable and the dependent variable.

This study was conducted in the medical record room of Dr. H. Abdul Moeloek Hospital in September-December 2024. The population in this study were all beta thalassemia patients at Dr. H. Abdul Moeloek Hospital in 2023 which amounted to 39 patients with research samples taken using total sampling technique that met the inclusion and exclusion samples. The inclusion criteria of this study were HbA2 and erythrocyte index data in medical records and beta-thalassemia patients aged 0-18 years (cut off age based on IDAI) while the exclusion criteria were incomplete or illegible medical records.

4 Research Finding and Discussion

4.1 Univariate analysis

In the univariate analysis that has been done, there are 39 beta thalassemia patients at Dr. H. Abdul Moeloek Hospital in 2023. The distribution of subject characteristics is divided by age, gender and frequency of transfusion. In the age category, most subjects were aged 11-15 years as many as 17 subjects (43.6%), followed by the age range 16-18 years with 9 subjects (23.1%), age 6-10 years with 8 subjects (20.5%) and age 0-5 years with 5 subjects (12.8%). Based on gender, there were more females with a total of 20 subjects (51.3%) while for transfusion frequency, 17 subjects (43.6%) underwent transfusion once every 2 weeks, 16 subjects (41%) underwent transfusion once every 3 weeks and 6 subjects (15.4%) underwent transfusion once every 4 weeks.

Table 1. Patient Characteristics.

	Research Subject	Frequency	Percentage
Age	0-5 years	5	12.8%
	6-10 years	8	20.5%
	11-15 years	17	43.6%
	16-18 years	9	23.1%
	Amount	**39**	**100%**
Gender	Males	19	48.7%
	Female	20	51.3%
	Amount	**39**	**100%**

Transfusion Frequency	Once every 2 weeks	17	43.6%
	Once every 3 weeks	16	41%
	Once every 4 weeks	6	15.4%
	Amount	**39**	**100%**

The results showed that laboratory characteristics related to HbA2, MCV, MCH and MCHC levels varied. A total of 26 subjects (66.7%) showed increased HbA2 levels while 11 subjects (28.2%) were in the normal category and 2 subjects (5.1%) had slightly increased HbA2 levels. In the MCV parameter, the majority of subjects, namely 38 people (97.4%) experienced a decrease while only 1 subject (2.6%) had a normal MCV value. There were no subjects with increased MCV values. In the MCH parameter, 36 subjects (92.3%) experienced a decrease while, in the MCHC parameter, 15 subjects (38.5%) experienced a decrease while 24 subjects (61.5%) had values in the normal range and none had an increase (37%). Overall this data shows that most subjects have increased HbA2 levels, decreased MCV and MCH values, and MCHC values which are mostly within the normal range.

Table 2. Univariate Analysis.

No	Group	Amount	Percentage
1.	HbA2		
	Normal (<3.5%)	11	28.2%
	Slightly increased (3.6%-4%)	2	5.1%
	Increased (>4%)	26	66.7%
	Amount	**39**	**100%**
2.	MCV		
	Decrease (<83 fl)	38	97.4%
	Normal (93-98 fl)	1	2.6%
	Increased (>98 fl)	-	-
	Amount	**39**	**100%**
3.	MCH		
	Decrease (<27 pg)	36	92.3%
	Normal (27-31 pg)	2	5.1%
	Increased (>31pg)	1	2.6%
	Amount	**39**	**100%**
4.	MCHC		
	Decrease (<32%)	15	38.5%
	Normal (32-37%)	24	61.5%
	Increased (>37%)	-	-
	Amount	**39**	**100%**

4.2 Bivariate analysis

In bivariate analysis, Spearman correlation test was used to show the relationship between HbA2 levels and several erythrocyte indices, namely MCV, MCH, and MCHC. In the correlation analysis between HbA2 and MCV, a p-value of 0.001 was obtained with a correlation coefficient (r) of -0.525. This result shows that there is a negative correlation between HbA2 and MCV levels ($p<0.05$). This indicates that an increase in HbA2 levels is associated with a decrease in MCH values. Meanwhile, the correlation analysis between HbA2 and MCHC obtained a p-value of 0.391 and a correlation coefficient of -0.141. This value indicates that there is no significant co-relation between HbA2 and MCHC levels ($p>0.05$). Overall, the results of this analysis showed that there was a negative correlation between HbA2 levels and MCV and HbA2 levels and MCH while the correlation between HbA2 and MCHC was not significant.

Table 3. Bivariate Analysis HbA2 and MCV.

No	Group	P-Value	*R*
1.	HbA2	0.001	-0.525
2.	MCV		

Table 4. Bivariate Analysis HbA2 and MCV.

No	Group	P-Value	*R*
1.	HbA2	0.001	-0.508
2.	MCH		

Table 5. Bivariate Analysis HbA2 and MCV.

No	Group	P-Value	*R*
1.	HbA2	0.391	-0.141
2.	MCHC		

4.3 Discussion

This study analyzed the characteristics of subjects and the relationship between HbA2 levels and erythrocyte index in thalassemia patients. Of the 39 subjects studied, the majority were aged 11-15 years (43.6%) with an almost equal distribution of gender between males (48.7%) and females (51.3%). The most common transfusion frequency was once every 2 weeks (43.6%). The high prevalence of thalassemia in 11-15 year old can be attributed to several factors such as early detection because symptoms of hemoglobin imbalance appear when the body needs more oxygen during growth. The results of this study are in line with the research of Anggororini et al (2010) at Hasan Sadikin Bandung General Hospital where out of 30 samples, the highest age was found to be 10-14 years old as many as 24 people (81%) (Fatmasyithah and Rahayu, 2014).

Based on gender, the majority of respondents in this study were female. This is different from research conducted by Thavorncharoensap et al. (2010) in Thailand, Ayoub et al. (2013) in Saudi Arabia, and Swandi (2018) in Medan which showed that there were more male patients than female. In accordance with Mendel's law, the thalassemia

gene is inherited autosomal recessively, which means it is independent of gender. Therefore, children of trait carriers have a 25% chance of being born normal, 50% becoming sufferers and 25% having a carrier trait (Irdawati et al., 2021). In this study, the majority of respondents received blood transfusions once every 2 weeks. This finding is in accordance with the theory of Rujito (2019) which states that the frequency of transfusions in thalassemia major ranges from 2-4 weeks, depending on the severity of the disease. Children with thalassemia major need more attention during therapy.

Blood transfusion in thalassemia patients aims to replace damaged red blood cells and maintain hemoglobin (Hb) levels in the body. Thalassemia major requires lifelong blood transfusion, in contrast to thalassemia minor which is only a carrier. Blood transfusion is performed on thalassemia major patients when the Hb level is <7 g/dL. The importance of blood transfusion is crucial to maintain the survival of thalassemia patients. Hemoglobin levels can be affected by age, gender and transfuse frequency. Age and gender are the determining factors of hemoglobin levels with hemoglobin values tending to increase during puberty (Mariani et al., 2014).

Laboratory examination results showed that most subjects (66.7%) had elevated HbA2 levels, while the majority of MCV and MCH values decreased, in 97.4% and 92.3% of subjects, respectively. Most of the MCHC values were within the normal range (61.5%). The Spearman correlation test between HbA2 levels and erythrocyte index showed a significant negative correlation between HbA2 and MCV ($p= 0.001$, $r= -0.525$) and HbA2 and MCH ($p= 0.001$, $r= -0.508$). However, no significant correlation was found between HbA2 and MCHC ($p= 0.391$, $r= -0.141$) indicating that increased HbA2 levels were associated with decreased MCV and MCH values but were not associated with changes in MCHC values.

Overall, the results of this study showed that elevated HbA2 levels in thalassemia patients were associated with decreased MCV and MCH values but had no significant association with MCHC. These findings provide important insights in understanding the hematological profile of thalassemia patients which may help in the diagnosis and management of the condition. This study also revealed a significant correlation between HbA2 levels with MCV and MCH which supports the hypothesis that elevated HbA2 levels are associated with lower MCV and MCH values in thalassemia patients. This is consistent with the findings of previous studies showing that MCV and MCH levels in thalassemia patients are lower compared to the general population, which is caused by gene mutations (Muktiarti et al., 2016).

Erythrocyte index is a parameter used to evaluate the size, volume and concentration of hemoglobin in red blood cells with MCV, MCH and MCHC as the main parameters. MCV level indicates the average volume of red blood cells, MCH indicates the average amount of hemoglobin per red blood cell and MCHC indicates the average concentration of hemoglobin in red blood cells. In thalassemia patients, the erythrocyte index often shows a microcytic hypochromic pattern with low MCV levels indicating smaller red blood cell volume and low MCH levels indicating less hemoglobin in the red blood cells. This pattern is very helpful in the diagnosis and surveillance of thalassemia (Susanto and Susanti, 2019). Erythrocyte index is also used for screening thalassemia types with MCV values in major thalassemia ranging from 50-60 fL and MCH values between 12-18 pg. Diagnosis of beta minor thalassemia is characterized by microcytic

erythrocytes, MCV less than 80 fL, MCH less than 27 pg and hemoglobin levels at normal levels (HbA2 less than 3.5%). Beta gene mutations that occur during beta globin chain synthesis cause a decrease in erythrocyte index levels in thalassemia beta major with the thalassemia beta major group having lower levels than the thalassemia beta minor group due to a greater number of gene mutations (Wati and Astuti, 2020).

HbA2 is a minor component of hemoglobin which is usually only about 2-3% of total hemoglobin in healthy individuals, but in patients with β-thalassemia HbA2 levels increase as compensation for the reduced production of beta globin chains. Elevated HbA2 levels can be a diagnostic marker for β-thalassemia minor where HbA2 levels in thalassemia patients tend to be higher than in normal individuals. Research suggests that elevated HbA2 is related to beta globin gene mutation which reduces beta chain synthesis and increases compensation of other globin chains including HbA2. High HbA2 levels along with low MCV and MCH values can be used as early indicators to diagnose thalassemia especially in individuals with mild anemia symptoms. These results also provide insights for the development of thalassemia screening in high-risk populations helping to detect minor thalassemia cases that may be missed. This study underscores the importance of HbA2, MCV, and MCH levels in early diagnosis and monitoring of thalassemia and shows the potential of diagnostic biomarkers that can support more effective treatment for thalassemia patients (Hidayat et al., 2023; Rujito, 2019).

5 Conclusion and Suggestion

5.1 Conclusion

Based on the results of research that has been conducted at Dr. H. Abdul Moeloek Hospital Lampung Province in 2023 regarding the correlation of HbA2 levels with erythrocyte index in beta thalassemia patients can be concluded:

1. There is a negative correlation between HbA2 levels with MCV and MCH, while there is no correlation between HbA2 levels with MCHC in beta thalassemia patients at RSUD Dr. H. Abdul Moeloek in 2023.
2. The majority of patients in this study had elevated HbA2 levels.
3. The majority of patients in this study had a decrease in erythrocyte index.

5.2 Suggestion

Suggestions for future research are as follows:

1. Future researchers can examine medical records from several hospitals in Bandar Lampung to obtain a sample size that can represent the population.
2. Future researchers can involve the thalassemia community to obtain data directly (primary data).
3. Future researchers can collect primary data through direct blood laboratory tests on thalassemia patients.

References

1. Aini: Indeks Eritrosit. Dalam Bahan Ajar: Hematologi 1, pp. 5–7. CV. AA. Rizky, Banten (2021)
2. Al-Amodi, E., Ghanem, S., Aldakeel: Hemoglobin A2 (HbA2) as a Measure of Unreliability in Diagnosing β-thalassemia Trait (β-TT). Current Medical Research and Opinion **34**(5), 945–951 (2018)
3. Anggororini, D., Fadlyana, E., Idjradinata, P.: Korelasi Kadar Ferritin Serum dengan Kematangan Seksual pada Anak Penyandang Thalassemia Mayor. Majalah Kedokteran Indonesia **60**(10), 462–467 (2010)
4. Ayoub, M.D., Radi, S.A., Azab, A.M., Abulaban, A.A., Balkhoyor, A.H., Bedair, S.W., et al.: Quality of Life among Children with Beta-thalassemia Major Treated in Western Saudi Arabia. Saudi Medical Journal **34**(12), 1281–1286 (2013)
5. Brancaleoni, V., Pierro, D.E., Motta, L., Cappellini, M.D.: Laboratory Diagnosis of Thalassemia. Journal of Laboratory Hematology **38**(1), 32–40 (2016)
6. Colaco, S., Nadkarni, A.: Borderline HbA2 Levels: Dilemma in Diagnosis of Beta-thalassemia Carriers. Mutation Research-Reviews in Mutation Research **788**(6), 1083–1087 (2021)
7. Fatmasyithah, V., Rahayu, M.S.: Gambaran Penderita Thalassemia di Ruang Rawat Anak Rumah Sakit Umum Cut Meutia Aceh Utara. JESBIO **3**(5) (2014)
8. Hieronymus, R.P., Titah, D.R.: Gambaran Indeks Eritrosit pada Anak Jalanan di Kota Yogyakarta. Journal of Health **6**(1), 12–15 (2018)
9. Hidayat, H., Fitriani, D., Nur, M., Randi, Aldiansyah, A.: Korelasi Antara Kadar HbA2 dengan Nilai Indeks Mentzer pada Pasien Thalassemia di RSUD DR. H. Abdul Moeloek Provinsi Lampung Tahun 2022. Jurnal Kesehatan Terpadu **2**(3), 154–163 (2023)
10. Irdawati, Syaiful, A.A., Haryani, A.: Hubungan Usia Anak Penderita Thalassemia dengan Frekuensi Transfusi. Jurnal Berita Ilmu Keperawatan **14**(2), 73–79 (2021)
11. Karimi, M., Cohan, N., De Sanctis, V., Mallat, N.S., Taher, A.: Guidelines for Diagnosis and Management of Beta-thalassemia Intermedia. Pediatric Hematology and Oncology **31**(7), 583–596 (2014)
12. Kemenkes RI, http://www.p2ptm.kemkes.go.id/informasi-p2ptm/thalassemia, last accessed 2024/08/25
13. Kementerian Kesehatan Republik Indonesia: Infodatin: Kelainan Bawaan. Pusat Data dan Informasi Kementerian Kesehatan Republik Indonesia (2018)
14. Kumar, V., Abbas, A.K., Aster, J.C.: Red Blood Cell and Bleeding Disorders. 9th edn, pp. 635–638. Elsevier Saunders, Philadelphia (2015)
15. Lantip: Thalassemia: Genetik Dasar dan Pengelolaan Terkini. Universitas Jenderal Soedirman (2019)
16. Muktiarti, D., Wahidiyat, P.A., Nainggolan, I.M., Setianingsih, I.: Thalassemia Alfa Mayor dengan Mutasi Non-Delesi Heterozigot Ganda. Sari Pediatri **8**(3), 244–250 (2016)
17. Nugraha, G., Badrawi, I.: Pedoman Teknik Pemeriksaan Laboratorium Klinik **57**, 1–173 (2021)
18. Puput: Darurat Penyebaran Thalassemia di Jakarta (2018)
19. Rujito, L.: Thalassemia: Genetik Dasar dan Pengelolaan Terkini. Angewandte Chemie International Edition **6**(11), 951–952 (2019)
20. Setiati, S., Alwi, I., Sudoyo, A.W., K, M.S., Setiyonadi, B., Syam, A.F.: Buku Ajar Ilmu Penyakit Dalam. 6th edn (2014)
21. Suryani, E., Wiharto, Wahyudiani: Identifikasi Anemia Thalassemia Beta Mayor Berdasarkan Morfologi Sel Darah Merah. Scientific Journal of Informatics **2**(1), 15–28 (2018)

22. Susanto, H., Susanti, D.: Korelasi Kadar HbA2 dengan Indeks Mentzer pada Pasien Thalassemia di RS Hermina Depok. Anakes: Jurnal Ilmiah Analis Kesehatan **5**(1), 53–64 (2019)
23. Swandi, M.: Karakteristik Penderita Thalassemia yang Dirawat Inap di RSUP H. Adam Malik Medan Tahun 2014–2017 (2018)
24. Thavorncharoensap, M., Torcharus, K., Nuchprayoon, I., Riewpaiboon, A., Indaratna, K., Ubol, B.O.: Factors Affecting Health-related Quality of Life in Thai Children with Thalassemia. BMC Blood Disorders **10**(1) (2010)
25. Wati, M., Astuti, T.D.: Systematic Review: Analisis Indeks Eritrosit pada Kasus Thalassemia. Skripsi (2020)
26. World Health Organization (WHO): Data and Statistics Prevalence of Thalassemia Worldwide (2022)

Open Access This chapter is licensed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0/), which permits any noncommercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license and indicate if changes were made.

The images or other third party material in this chapter are included in the chapter's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the chapter's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder.