BJMS
Borneo Journal of Medical Sciences

ORIGINAL ARTICLE

Prevalence and Characteristics of Undiagnosed Hemoglobinopathies Among Adolescents in a High Beta-Thalassemia Prevalence Area: A Cross-Sectional Study

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Received: 13 November 2024

Accepted: 19 February 2025

Published : 2 September 2025

DOI: https://doi.org/10.51200/bjms.v19i3.5598

Keywords: *Hemoglobinopathies, Thalassemia, Prevalence, Disease attributes, Adolescent*

ABSTRACT

Research on hemoglobinopathies mainly targets school-aged and adult groups, underscoring a lack of studies on adolescents nearing reproductive age. The primary objective was to determine the prevalence of hemoglobinopathies among adolescents who had not been previously screened. Additional objectives were to explore possible associations between undiagnosed hemoglobinopathies, socio-demographic factors, and specific characteristics of these disorders. This cross-sectional observational study included 149 adolescents aged 10 to 24. All participants underwent physical examinations and hematological analyses. The collected data were analyzed using established statistical methods. Among the 149 adolescents studied, 8.7% (13 individuals) had hemoglobinopathies, with the majority being Kadazandusun (92.3%). Specific findings included two cases of hemoglobin E trait and eleven of beta-thalassemia trait. Those with hemoglobinopathies were typically 1.5 years younger than those without. Statistically, they had a higher prevalence of microcytes (61.5% vs. 27.2%, p=0.024) and hypochromic red cells (61.5% vs. 27.9%, p=0.028), increased red cell counts (mean difference of 0.92, p<0.01), decreased hemoglobin levels (mean difference of -1.3, p=0.016), and elevated platelet counts (mean difference of 54.28, p=0.01). Hemoglobin electrophoresis showed higher hemoglobin A2 (mean difference of 9.47%, p=0.004) and fetal hemoglobin levels

(mean difference of 1.16%, p=0.009). Even in a highly prevalent area with thalassemia, where the true prevalence of undiagnosed hemoglobinopathies in adolescent age groups was unknown, the actual prevalence was high at 8.7% thus proving the need to increase more screening in this group of apparently healthy adolescents to prevent potential development of new cases of beta-thalassemia major.

INTRODUCTION

Background

Hemoglobinopathies encompass a group of genetic disorders characterized by abnormalities in hemoglobin structure or production. These disorders are divided into qualitative defects, like sickle cell anemia, which involves issues with hemoglobin structure; and quantitative defects, like thalassemia, which pertains to hemoglobin production (Shrestha & karki, 2013).

Thalassemia is one of the most common autosomal recessive disorders and is highly prevalent in countries within the tropical belt, including Malaysia (Cao & Kan, 2013 & Weatherall, 2018). Malaysia, a diverse multi-ethnic country, comprises Malays and other indigenous groups making up 67.4% of the population, Chinese at 24.6%, Indians at 7.3%, and others at 0.7%. In this ethnically varied landscape (Alwi & Syed-Hassan, 2022), thalassemia, including both alpha- and beta-thalassemia, emerges as one of the most prevalent genetic diseases in the nation.

As of 28 November 2018, 8,681 patients with thalassemia had been registered in the Malaysian Thalassemia Registry (MTR). Out of these, 7,984 (91.97%) were alive, with 130 (1.63%) reported as cured by stem cell transplantation. Another 614 patients (7.7%) were lost to follow-up, while the remaining 697 patients (8.03%) had passed away (Ibrahim et al., 2020). Sabah, a state in East Malaysia located on Borneo Island, has a diverse population around of 3.2 million people, encompassing 33 ethnic groups. According to the latest national census, the main indigenous ethnic groups include Kadazandusuns, Bajau, Malays, and Muruts" (Tangit, 2017). A study on Indigenous people revealed that 30% (193/645) of the sample tested positive for the following: beta-thalassemia trait (78%; 151/193), HbE trait (10%; 20/193), Homozygous HbE (2%; 4/193) and other hemoglobinopathies (7%; 13/193). The remaining 3% (5/193) of the abnormal results were inconclusive, necessitating further molecular analysis (Pauzy et al., 2018).

Study Rationale

The National Thalassemia Prevention and Control Program in Malaysia was established in 2004 to reduce the prevalence of thalassemia and improve the management of affected individuals in the country. This program focuses on the early detection of thalassemia carriers and other hemoglobinopathies, targeting couples before marriage and pregnant women. In 2016, a school-based screening initiative was implemented under this program, targeting Form 4 students (typically aged 16) to identify carriers early (Ministry of Health Malaysia, 2020).

While many studies focus on school-based and adult populations, further attention on adolescents is still required as this age group represents an important group that will soon enter the reproductive phase of life, thus detection needs to be more thorough and widespread screening should be conducted. Additionally, there is evidence that pockets of adolescents missed the National Thalassemia Prevention and Control Program in a study showing that the lack of knowledge and misconceptions about the disease including fear of social stigma or discrimination (Wong et al.,2011) were among the factors leading to refusal to the program. A study in 2020 also showed that parents refused screening for their children, believing that their children are not at risk of thalassemia as there were no thalassemia major or carrier in their family (Che Mat et al.,2020).

By focusing on adolescents, adolescents' awareness and understanding of their carrier status can influence community health behaviors, fostering a generation that is more knowledgeable and proactive. Accurate data backed by widespread screening in this age range will serve as the cornerstone for successful public health initiatives, allowing stakeholders and governments to more strategically allocate resources. Future generations' healthcare costs related to treating thalassemia and other hemoglobinopathies may be decreased in the long run by early intervention through adolescent screening.

The primary objective of this study was to determine the true prevalence of hemoglobinopathy in apparently healthy, undiagnosed adolescents in a high-prevalence area for beta-thalassemia major in Sabah. Additional objectives include examining the association between undiagnosed hemoglobinopathy and sociodemographic factors, clinical findings from physical examination, hematological parameters, serum iron level and hemoglobin electrophoresis.

MATERIALS AND METHODS

This was a cross-sectional observational study conducted in Kota Kinabalu, Sabah focusing on adolescents in the community, defined as aged between 10 to 24 years (Sawyer et al., 2018). The study was conducted by invitation for adolescents who fulfilled the inclusion criteria of the age range stated above, who may or may not have a family history but never underwent any screening for hemoglobinopathy and were willing to participate in the study by providing informed consent.

Participants were selected via simple random sampling and invited to participate in the study. Once recruited and informed consent was obtained, baseline demographics information was taken such as age, gender, ethnicity, family history of blood disorders, and family history of consanguinity. Anthropometric measurements of height and weight were taken, and body mass index (BMI) was calculated. A clinical examination was performed to assess symptoms of headache and frequency of headache if present, signs of anemia, jaundice, oedema, and measurement of vital signs of systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate were taken. Disease-specific questionnaires are reliable and validated to estimate disease burden and these questionnaires were adopted (Thein et al., 2009). The questionnaire was translated into Malay by the researchers who are proficient in both English and Malay using the forward-backward translation method. Pilot testing was done on 30 participants from the target study population and reliability metrics were assessed, with Cronbach's alpha value of 0.85, indicating strong internal consistency.

In addition, 4 ml of venous blood was collected in ethylene diamine tetraacetate (EDTA) vials, and hematological analysis of hemoglobin level, red cells count, total and differential white cells count, platelets counts was performed with automated cell counter (ABBOT CELL-DYN Ruby Hematology Analyzer) for complete blood counts. The microscopic examination and full blood count results were co-interpreted together with the automated cell counter results by the principal investigator. Serum iron level and reticulocyte counts were measured. The blood was also sent for hemoglobin electrophoresis, which was performed using BIORAD D10 High Performance Liquid Chromatography (HPLC) system. Due to budget limitations, additional tests like DNA analysis and the Isoelectric Focusing (IEF) method to confirm the Hb E and other hemoglobin variants could not be performed.

Sample size was calculated at 130 participants, with a confidence is 95%, expected prevalence was 0.175 and precision

was 0.05 (Naing et al., 2006) as the minimum number of participants. Accounting for a 10% dropout the number was raised to 143 so that if dropout or missing data occurred, the minimum required number for the sample size would still be achieved.

Relevant data were collected which included demographic data, hematological parameters and peripheral blood smear finding were correlated with interpretation of HPLC. Data collected were then transferred to IBM SPSS version 27 for data analysis. Categorical variables were presented as proportions while numerical variables were described as either mean or median depending on the normality of the data distribution. Pearson chi-square or Fisher Exact test was used to compare categorical data variables between normal hemoglobin patients and those with hemoglobinopathies, while independent t-test was used for normally distributed data variables or Mann-Whitney U test was performed if the data were not normally distributed.

RESULTS

A total of 149 adolescents were recruited in this study with 96 out of 149 (64.4%) being females.

Table 1: Baseline demographics and related family information between the two groups of normal hemoglobin and those with hemoglobinopathies.

Description	Normal Hemoglobin (n = 136)		Hemoglobinopathies (n = 13)		p-value
	Mean	(S.D)	Mean	(S.D)	
Age (years old)	21.5	(2.15)	20.0	(3.21)	0.02#
	n	(%)	n	(%)	
Female Gender	87	(90.6)	9	(9.4)	0.94
Ethnicity					0.013
Dusun/Kadazan	71	(52.2)	12	(92.3)	
Others	65	(47.8)	1	(7.7)	
Parental Consanguinity					1.00
Yes	9	(90.0)	1	(10.0)	
No	127	(91.4)	12	(8.6)	
Family history of blood-related diseases					0.16
Yes	17	(81.0)	4	(19.0)	
No	119	(93.0)	9	(7.0)	
Family history of Anemia					0.39
Yes	23	(85.2)	4	(14.8)	
No	13	(92.6)	9	(7.4)	

Note: All comparative analysis were performed using Pearson Chi-Square statistical test except for # was done using independent t-test.

126 individuals (84.5%) were aged between 20 and 24 years and 46.9% of the participants held a diploma degree. All participants never had any screening for hemoglobinopathy previously and upon hemoglobin electrophoresis performed for all participants, the prevalence of hemoglobinopathies was found to be 8.7% (13 out of 149) among adolescents recruited for this study. Two out of 13 were diagnosed with hemoglobin E trait while the other 11 were diagnosed as having beta-thalassemia trait.

Baseline demographic and related family history information on hemoglobinopathy are presented in Table 1, together with comparative analysis using appropriate statistical tools. Between the two groups, those with hemoglobinopathies were younger by 1.5 years than adolescents with normal hemoglobin and 12 out of 13 of those with hemoglobinopathies were of Dusun ethnicity (92.3%, p-value 0.013).

Anthropometry and clinical characterization differences between both groups depicted in Table 2 such as weight, height and BMI were taken and calculated. Clinical examination was performed to look for presence of anemia, jaundice, and organ enlargement, as well as physiological vital signs such as systolic blood pressure, diastolic blood pressure and heart rate. There were no statistically significant differences observed when comparing both groups in terms of anthropometry, clinical examination, and vital signs measurement.

Table 2: Comparative analysis between adolescents with normal hemoglobin and those hemoglobinopathies in term of anthropometric measurements, important clinical findings, and vital signs measurements.

Description	Normal Hemoglobin (n = 136)		Hemoglobinopathies (n = 13)		p-value
Anthropometric Measurements	Mean	(S.D)	Mean	(S.D)	
Height (meters)	1.60	(0.09)	1.57	(0.72)	0.22
Weight (kg)	58.4	(14.4)	55.3	(7.27)	0.20
BMI	22.5	(4.4)	22.4	(3.26)	0.91
Clinical Examination	n	(%)	n	(%)	
Presence of Anemia	27	(87.1)	4	(12.9)	0.57
Presence of Jaundice	0	(0)	0	(0)	
Presence of Oedema	0	(0)	0	(0)	
Presence of Headache	7	(87.5)	1	(12.5)	1.00
Vital Signs Measurement	Mean	(S.D)	Mean	(S.D)	
Systolic Blood Pressure (mm Hg)	113.68	(9.86)	111.54	(5.54)	0.44
Diastolic Blood Pressure (mm Hg)	75.04	(5.62)	73.08	(4.80)	0.23
Mean Arterial Pressure (mm Hg)	87.92	(6.32)	85.90	(4.74)	0.26
Heart Rate (beats/min)	85.16	(11.5)	84.31	(6.42)	0.68

Note: All comparative analysis were performed using independent t-test except for * which was done using Pearson Chi-Square.

For biochemical characterization and differences, all participants had their blood investigations taken for peripheral blood film examination and hematological analysis including hemoglobin level, red cell counts, white blood cell counts, platelets counts, reticulocyte counts, serum iron and

Table 3: Univariate comparative analysis showing differences in terms of peripheral blood film morphology, hematological analysis, and hemoglobin electrophoresis between the two groups having normal hemoglobin and those with hemoglobinopathies.

Description	**Normal (n = 136)**		**Abnormal (n = 13)**		**p-value**
Peripheral Blood Film	n (%)		n (%)		
Microcytic Red Cells					0.022*
Yes	37 (27.2)		8 (61.5)		
No	99 (72.8)		5 (38.5)		
Hypochromic Red Cells					0.023*
Yes	38 (27.9)		8 (61.5)		
No	98 (72.1)		5 (38.5)		
Anisopoikilocytosis					0.06*
Yes	99 (72.8)		7 (46.2)		
No	37 (27.2)		6 (53.8)		
Hematological Analysis	***Mean (S.D)***	***Mean (S.D)***	***Mean diff (95% CI)***	***t-statistic (df)***	
Hemoglobin (g/dL)	13.56 (1.83)	12.26 (1.83)	1.30 (0.24, 2.35)	2.437 (147)	0.016
Red Cell Counts (10^9/L)	4.98 (0.57)	5.91 (0.70)	-0.92 (-1.27, -0.59)	-0.548 (147)	<0.001
Serum Iron Level (µmol/L)	13.24 (6.93)	11.84 (5.58)	1.4 (-2.51, 5.31)	0.705 (147)	0.482
White Cell Counts (10^9/L)	7.89 (1.93)	8.82 (1.80)	-0.93 (-2.03, 0.18)	-1.662 (147)	0.099
Platelets Counts (10^9/L)	299.72 (69.3)	354.00 (80.8)	-54.28 (-94.6, -13.9)	-2.658 (147)	0.009
Reticulocyte Counts (10^9/L)	1.57 (0.43)	1.75 (0.38)	-0.18 (-0.42, 0.06)	-1.491 (147)	0.138
Hemoglobin Electrophoresis					
Hemoglobin A2	3.046 (0.38)	12.52 (9.65)	-9.47 (-11.1, -7.87)	-3.536 (12)	0.004
Fetal Hemoglobin	0.719 (0.18)	1.88 (1.32)	-1.16 (-1.39, -0.91)	-3.139 (12)	0.009

Note: All comparative analysis were performed using independent t-test except for * which was done using Fisher's Exact Test.

hemoglobin electrophoresis to measure the types of hemoglobin and identify abnormal types of hemoglobin including fetal hemoglobin level and hemoglobin A2 level as depicted in Table 3.

Adolescents diagnosed with hemoglobinopathies showed higher microcytes (61.5% v 27.2%, df(1), F(5.1), p-value 0.024) and hypochromic red cells (61.5% v 27.9%, df(1), F(4.8), p-value 0.028) when compared to those with normal hemoglobin. However, there was no statistically significant difference in terms of anisopoikilocytosis appearance between the two groups.

Adolescents with hemoglobinopathies also showed lower hemoglobin level (mean difference 1.30 g/dL, df(147), t(2.437), p-value 0.016), higher red cell counts (mean difference 0.9 x109/L, df(147), t(-0.548), p-value <0.001) and higher platelets counts (mean difference 54.28 x109/L, df(147), t(-2.658), p-value <0.001). Results from hemoglobin electrophoresis showed that those with Hemoglobinopathies had significantly higher hemoglobin A2 proportion (mean difference 9.47%, df(12), t(-3.536), p-value 0.004) and significantly higher fetal hemoglobin proportion (mean difference 1.16%, df(12), t(-3.139), p-value 0.009).

DISCUSSION

In this study, hemoglobinopathies were identified in 8.7% (13 out of 149) of adolescents aged 10 to 24 in Kota Kinabalu, Sabah, showing a higher prevalence in an area with a high prevalence of beta-thalassemia. The prevalence of thalassemia trait among students from Sabah and Sarawak at UiTM Selangor was found to be 7.5% (3 out of 40 volunteers) (Ali et al., 2023). This also indicates a high prevalence of thalassemia trait in this study population.

A cross-sectional observational study in Indonesia assessed knowledge, attitude, and practice using an online questionnaire targeted at youth aged 15–24. Of 906 responses, 878 respondents had poor knowledge (62.1%), a positive attitude (83.3%), and poor practice (54.4%) regarding thalassemia (Wahidiyat et al., 2021). To accurately determine the prevalence of hemoglobinopathies among adolescents, comprehensive studies employing both qualitative and quantitative approaches with larger sample sizes are necessary.

A cross-sectional observational study among anemic patients at Kathmandu Pathlab revealed a hemoglobinopathy prevalence of 47.3% (77 out of 163), with a mean age of 20.45 ± 11.98 years and a slight female predominance (KC & Gyawali, 2017). Although the age range of participants was similar to our study, their population was anemic patients, resulting in a higher prevalence than our findings.

The World Health Organization has advocated for improved education and screening programs, especially in regions with high occurrences of hemoglobinopathies, to facilitate rapid interventions and prevent severe complications (World Health Organization, 2008).

In our study, hemoglobinopathies were more frequently detected in younger adolescents, with those diagnosed being on average 1.5 years younger than those without hemoglobinopathies. This suggests that younger individuals with hemoglobinopathies tend to show symptoms at an earlier age, making routine screenings essential for early identification. This highlights the need for healthcare systems to incorporate genetic testing and comprehensive educational programs to improve early detection and overall healthcare outcomes for affected adolescents. Proactive measures can greatly reduce the impact of these genetic disorders (Cao & Galanello, 2010).

In our study, 12 out of 13 individuals with hemoglobinopathies were of Kadazandusun ethnicity (92.3%, p-value 0.013). One research

indicated that among indigenous groups screened, Kadazandusuns had the highest prevalence of hemoglobinopathies at 35% (87/250), followed by Muruts at 33% (15/45), Malays at 29% (19/65), other races at 26% (46/180), and Bajau at 23% (19/84). This study involved collecting peripheral blood samples from various health clinics and hospitals across Sabah, with participants aged 1 to 73 years from all ethnicities undergoing the same screening procedures (Pauzy et al., 2018). These findings support our finding that a higher number of hemoglobinopathies were detected among Indigenous ethnic communities.

A high prevalence of hemoglobinopathies was reported that 46% of the indigenous population was affected, it was a higher rate than that found in the non-indigenous community (KC & Gyawali, 2017). Approximately 1.5% of the global population are carriers of β-thalassemia. While the global carrier frequencies are generally known, detailed micromapping has seldom been performed. When such mapping has been done, significant variations in carrier rates have been observed within small geographical areas (Colah et al., 2010). The global epidemiology of hemoglobinopathies highlighting the influence of ethnic and genetic backgrounds on the prevalence and clinical presentation of these disorders (Fucharoen & Weatherall, 2012).

In our cohort, 2 out of 13 individuals were identified with hemoglobin E trait, while 11 were diagnosed with beta-thalassemia traits. This aligns with findings from similar studies conducted in Asia and globally, highlighting the significant public health challenge these disorders pose. In Southeast Asia, the most common combination of beta-thalassemia with an abnormal hemoglobin or structural variant showing thalassemic traits is Hb E/β-thalassemia, with a carrier frequency of around 50 percent (Galanello & Origa, 2010). According to the Malaysian Thalassemia Registry, 5,712 thalassemia patients were recorded in 2013, with 1,847 diagnosed with Hb E/β-thalassemia and 2,329 with β-thalassemia major (β-TM) (Alwi & Syed-Hassan, 2022).

A high prevalence of thalassemia in the Sabah population was reported with 23% of those screened having beta-thalassemia trait and 3.1% exhibiting hemoglobin E trait (Pauzy et al., 2018). Another study in Malaysia estimated the β-thalassemia carrier rate to be between 3-5% of the population (Ibrahim, 2009). In contrast, our study focused on adolescents, and found that 11 out of 13 cases were beta-thalassemia traits, indicating a significantly higher prevalence of beta-thalassemia traits in our study group.

A community-based cross-sectional study was conducted in Shan State, Myanmar, among high school adolescents found a prevalence of hemoglobin E trait and hemoglobin E disease at 15.5% (45 out of 290 participants), with 19 cases in males (42.2%) and 26 in females (57.8%) (Aung et al., 2021). The sample size and the prevalence of hemoglobin E traits and diseases were notably higher compared to those reported in our study.

Hemoglobinopathy is a major contributor to anemia and remains a significant health challenge among adolescents. Our study highlights the vital need for early detection and effective management of hemoglobinopathies, presenting new opportunities for tackling this pressing health issue.

Diagnosing hemoglobinopathies involves various methods, including evaluating clinical and family histories, conducting complete blood counts (CBC), assessing red cell indices, and measuring levels of hemoglobin A2 (HbA2), fetal hemoglobin (HbF), the sickling test and hemoglobin electrophoresis. For beta-thalassemia heterozygotes, the hemoglobin pattern typically shows 92–95% HbA, over 3.8% HbA2, and variable amounts of HbF ranging

from 0.5% to 4% (Cao & Galanello, 2010). In our study, hemoglobin electrophoresis played a crucial role in identifying hemoglobinopathies by detecting elevated levels of HbA2 and HbF.

Elevated HbA2 levels play a crucial role in diagnosing beta-thalassemia, a condition marked by an imbalance in globin chain production. Carriers of beta-thalassemia generally exhibit HbA2 levels above 3.5%. They are easily detected through routine hematological methods, often showing microcytosis (small red blood cells) and occasionally mild anemia (Wonke et al., 2007).

While some laboratories consider HbA2 levels of 4.0% or higher diagnostic for β-thalassemia, others use thresholds of 3.3% or 3.5%. Levels below these thresholds are often classified as "borderline." Accurate detection of borderline beta-thalassemia carriers requires a comprehensive molecular analysis of the β-globin gene, ensuring precise identification where standard cut-offs may not be sufficient (Colaco & Nadkarni, 2021).

In HbE/β-thalassemia and other β-thalassemia syndromes, high levels of fetal hemoglobin (HbF) are generally due to increased erythropoietin levels, leading to bone marrow expansion and potentially enhanced F-cell production. This, combined with ineffective erythropoiesis, provides a survival advantage to F-cells, allowing them to persist and function under these conditions (Rees et al.,1999).

The presence of microcytes and hypochromic red cells in blood films is a key indicator of hemoglobinopathies, including thalassemia and other variants. These red blood cell morphologies indicate abnormalities in hemoglobin synthesis and serve as diagnostic markers for these conditions. In our study, adolescents with hemoglobinopathies showed reduced hemoglobin levels, increased red blood cell counts, and elevated platelet counts. A descriptive cross-sectional study that screened students for beta-thalassemia found that affected individuals typically exhibited microcytic hypochromic red blood cells, including the presence of target cells (Qazi et al., 2014). Reactive thrombocytosis can result from conditions such as acute hemorrhage, malignancy, chronic inflammation, iron deficiency anemia, and hemolytic anemia (Tailor et al., 2015). Additionally, β-thalassemia is associated with anemia and hypercoagulability, increasing the risk of thromboembolic events and underscoring the need for early identification and management of this state (Vasilopoulou et al., 2022).

Our study is limited by a relatively small sample size of 149 adolescents, which may impact the generalizability of the carrier frequency of hemoglobinopathies. Additionally, the absence of molecular analysis limits the ability to achieve detailed genetic characterization and confirm hemoglobinopathies or thalassemia traits, which may be overlooked during mass screening. We adopted the questionnaire as described but did not include a cross-validation component. This study directed to the prevalence of hemoglobinopathy and did not aim to explore absenteeism in the National Thalassemia Screening Program.

CONCLUSION

In regions with a high prevalence of beta-thalassemia, such as Kota Kinabalu, Sabah, the prevalence of hemoglobinopathies among adolescents is significant, particularly among genetically predisposed ethnic groups like the Kadazandusuns. Those identified with hemoglobinopathies were generally younger. Our findings underscore the critical importance of comprehensive screening and counseling programs to improve adolescents' awareness of their carrier status. That will minimize missed cases in the National Thalassemia Prevention and Control Program. Moreover, we plan to extend the research to include molecular studies in the future to enhance the

accuracy of diagnosing hemoglobinopathies, particularly for differentiating variants and confirming specific traits that may not be fully resolved through HPLC alone.

CONFLICT OF INTEREST

The authors declare no conflict of interest regarding the publication of this manuscript. All authors have reviewed and approved the final version of the manuscript, and there are no financial, personal, or professional relationships that could inappropriately influence or appear to influence the content of this research.

ACKNOWLEDGMENT

We would like to express our sincere gratitude to Prof Mohammad Saffree Bin Jeffree (Former Dean of FPSK) for allowing us to conduct this research and to Universiti Malaysia Sabah for the financial support. We also thank all Medical Laboratory Technicians and participants involved in this study.

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