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Malaysian socio-demographic characteristics, mean haemoglobin levels and BMI distribution of the monthly transfused group (MTG) and non-monthly transfused group (NMTG) thalassemia patients

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***Abstract*---**Background: Thalassemia is a genetic blood disorder characterized by insufficient haemoglobin level due to mutation in the globin chains causing anaemia with iron overload and the most common genetic haemoglobinopathy in Malaysia. They are grouped as transfusion dependent and non-dependent according to their transfusion requirement. The frequency of thalassemia transfusions can be discriminated further into monthly to non-monthly transfusion group. Objective: To analyze the socio-demographic characteristic, haemoglobin levels and BMI distribution after classifying the thalassemia patients according to monthly transfused group (MTG), non-monthly transfused group (NMTG) and comparing to a healthy individual control group. Methods and Materials: This was a prospective cross-sectional study gathering data on socio-demographic characteristic, haemoglobin levels and BMI distribution

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of patients with MTG and NMTG thalassemia patients from a thalassemia clinic in Ampang Hospital and comparing them to healthy individuals in Faculty of Medicine and Health Sciences, Universiti Putra Malaysia. The study embarked between August to October 2020. Results: Our study clearly shows in adult thalassemia MTG are predominantly in Malay ethnicity and younger in comparison to NMTG. The mean Hb levels of MTG is lower compared to NMTG regardless of the genotype and phenotype characteristics. In MTG, they have a mean BMI of 21.16 ± SD 3.88, NMTG of 22.37 ± SD 4.73 with highest BMI in healthy controls of 26.07 ±SD 0.7 ($p < 0.00001$). Conclusion: We believe this is the first ever study to look into the socio-demographic, mean Hb levels and BMI of thalassemia patients grouped differently as MTG and NMTG alongside with normal healthy controls. Adult thalassemia MTG group has lower mean Hb levels in comparison to NMTG by approximately 2 g/dL and healthy individuals by 5 g/dL apart. There is a significant relationship between Hb and BMI, whereby MTG are underweight in reference to the WHO BMI classification. We also found that our healthy individual controls have a mild anaemia with lower Hb range according to WHO anaemia classification, indicating that there is a need for a wider screen for thalassemia gene carriers.

***Keywords*---**thalassemia, socio-demographic, body mass index, haemoglobin, monthly-transfused group, non-monthly-transfused group.

Introduction

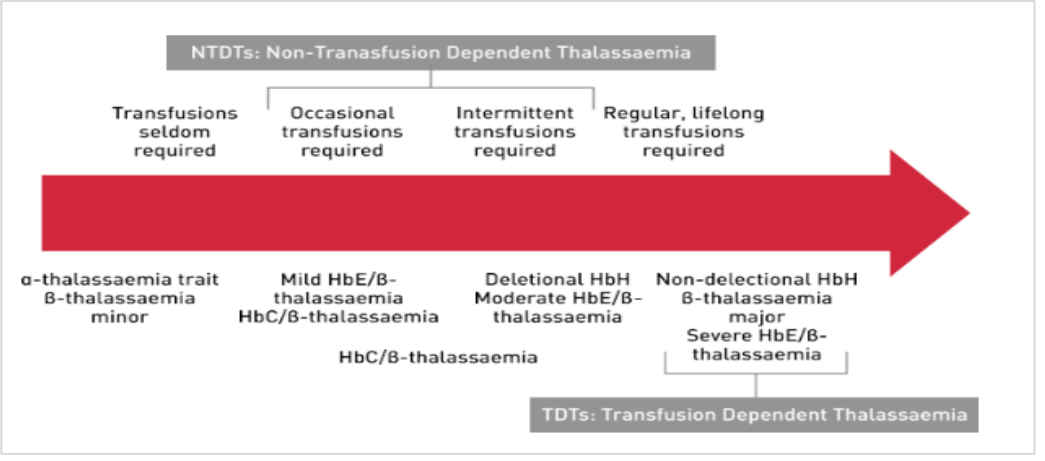
Almost 60,000 individuals are born globally with thalassemia, with b-thalassemia to be most common in 2020 [1], [2] . It is also the commonest blood disorder in Malaysia, with β-thalassemia being the most common genotype in the carriers [3]. Thalassemia is a recognized debilitating disease of globin gene mutation rendering the imbalance synthesis in one or more of the globin chains with an impact on red blood cell maturation to form aggregates that cause ineffective erythropoiesis, and consequently shortening the cells' survival, oxidative stress and peripheral hemolysis and leading to anaemia [4].

The thalassemia syndrome can range from mild anaemia to monthly transfusion since birth or death in utero (hydrops fetalis), causing off-guards to parents bearing the thalassemia genes without knowing they are carrying the genes. The evolution of thalassemia classifications has been a challenge but settled into transfusion-dependent thalassemia (TDT; regular lifelong blood transfusions starting before the age of 2 years) and non-transfusion-dependent thalassemia (NTDT) are those with occasional blood transfusions or limited periods of transfusion, such as for pregnancy or surgery [5], [6].

These phenotypic divisions translate the transfusion-dependent-thalassemia (TDT) group as those in dire need of regular blood transfusion for a prolonged period due to moderately severe to severe anaemia and the non-transfusion-

dependent thalassemia (NTDT) who does not usually demand the blood transfusion, but in specific manners, maintain the haemoglobin levels where a few patients may receive transfusions occasionally. The illustration is as shown in Figure 1 [7], [6].

Figure 1. Phenotype classification of thalassemia syndromes based on the clinical severity and transfusion requirement



It is important to note that there are two different guidelines for the two phenotypes. In 2013 and 2017, Taher et al defined non-transfusion-dependent thalassemia (NTDT) as a term used to label patients who do not require such lifelong regular transfusions for survival, although they may require occasional or even frequent transfusions in certain clinical settings and for defined periods of timeas shown in Figure 2. As for NTDT, it includes three clinically distinct forms: β-thalassemia intermedia, haemoglobin E/β-thalassemia (mild and moderate forms), and α-thalassemia intermedia (he-moglobin H disease) [8], [6]. It has to be noted that although patients with haemoglobin S/β-thalassemia and haemoglobin C/β-thalassemia may have transfusion requirements similar to NTDT patients, these genetic mutations have other specific characteristics and management peculiarities in real life.

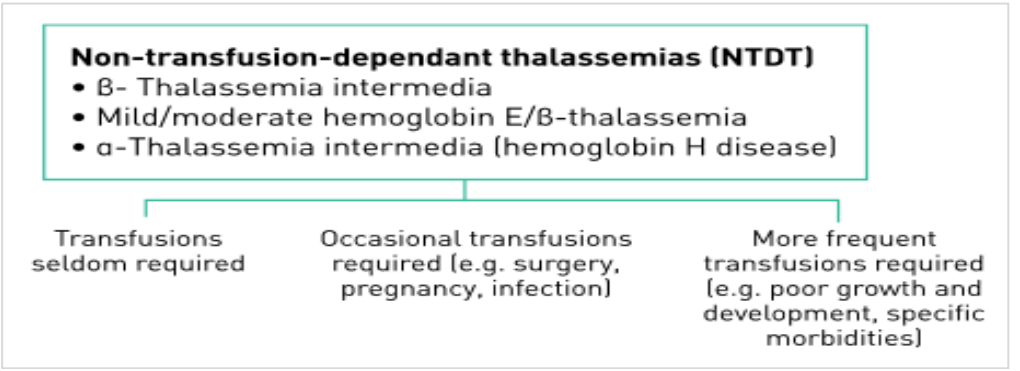


Figure 2. Transfusion requirement in non-transfusion-dependent thalassemia (NTDT)

The TDTs on the other hand, requires regular blood transfusion to survive and without adequate transfusion support, they would suffer several complications and a shortened life span. This category includes patients with genotypes of β thalassemia major, severe HbE/β thalassemia transfusion -dependent Hb H disease or HbH hydrops fetalis and surviving Hb Bart's hydrops fetalis. Generally, in all healthcare centers, the thalassemia patients who need transfusions monthly (MTG) for lifelong are considered dependent on them for survival in comparison to non-monthly transfused thalassemia patients (NMTG) who may have longer lifespan and mild to moderate anaemia. This is a universal presentation of thalassemia patients in any healthcare facility treating thalassemia patients that chronically under the healthcare visitations and a general outlook in this classification will make it easier for the front-liners in healthcare, paramedics and public to be aware of the effects of monthly transfusion and non-monthly transfusion thalassemia in our community for early detection of complications.

Frequently, the caring clinicians are required to re-evaluate transfusion requirements because they can transform from an NTDT phenotype to a TDT phenotype over time. The unpredictable nature of the upregulation of thalassemia genes is due to multifactorial reasons. According to WHO classification, anaemia is defined as a condition where the erythrocytes number or the haemoglobin levels are under the normal average. WHO considered about 42% of the world's children aged 5 years old and 40% of pregnant women as anaemic [16]. Severity of anaemia categorized into three groups: mild with haemoglobin level of 11-11.9 g/dL; moderate (8-10.9 g/dL) and lastly the severe level of anaemia which ranges less than 8 g/dL [9]. The mean Hb levels are peculiar from NTDT and TDT, with reports of heterogeneous parameters in the red cell indices when compared between each genetic mutation [6].

As thalassemia is known to be associated with poor growth, the body mass index (BMI) is considered an important contributor to be associated with a significant risk of medical problems particularly if they were in the extreme polar of underweight or overweight group. WHO classified obesity to Type I, II and III and included underweight specification is ideal to be used in thalassemia patients[10]. It is well known that BMI findings in thalassemia major children has a significant impact in causing failure to thrive and earlier epiphyseal end fusion of the long bones which consequently cause retardation of the growth process, although, a diagnostic tool is deem required to determine the associated malnutrition status in these patients. Hence early intervention is needed [11]. The difference was more marked between thalassemic boys and girls aged 10 years or older where they were mostly underweight or have less BMI index in comparison with the healthy individuals [Figure 3, 12, 13].

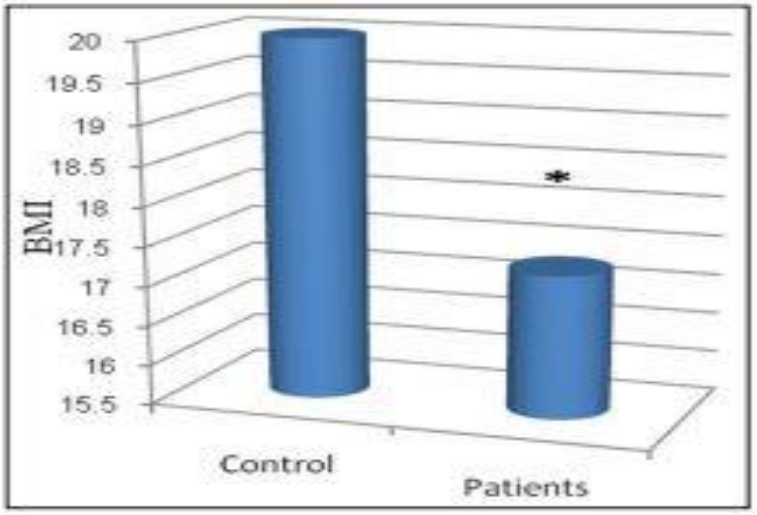


Figure 3. Comparison of BMI in thalassemics and health group with the age group of 10-19 years

Little information can be found with regards to the haemoglobin levels in relation to the BMI in adult NMTG and MTG thalassemia patients [14]. Therefore, we embarked our study to understand further the socio-demographic, mean haemooglobin levels and the BMI differences in monthly-transfused group (MTG) and non-monthly transfused group (NMTG) that present in thalassemia clinic in our center.

Methods and Materials

Study population

The sample of thalassemia population was recruited from thalassemia clinic of Ampang Hospital and the healthy individuals were from the Faculty of Medicine and Health Sciences, Universiti Putra Malaysia. Both centers were from the same state of Selangor Darul Ehsan, Malaysia approximately 25 km apart.

This study was embarked to understand the socio-demographic differences by categorized thalassemia patients according to transfusion frequency into two:

a. Monthly-transfused group (MTG) involving patients became blood dependent (once every month) as early an at birth, and
b. Non-monthly transfused group (NMTG) was composed of patients who were occasionally blood dependent (once every 5 to 6 months) when commenced the blood transfusion, particularly after the age of 2 years old, and blood independent prior.

We recruited only Malaysian citizens diagnosed with thalassemia between the age of 18-64 years old with the exclusion of lactating and pregnant thalassemics. As for the healthy individual's group, we selected Malaysians without definite history of thalassemia or other known genetic disorders, without other known medical

illness and any form of treatment prescription between the age of 18-64 years old. We matched the thalassemia and healthy individuals according to age and gender. The study was approved by Medical Research and Ethics Committee (MREC), Ministry of Health, Malaysia (Reference number: NMRR-19-3918-51308) in conjunction with the notification and endorsement of Ethics Committee for Research Involving Human Subject (JKEUPM). The study instrument and assessment, proforma was designed to gather the demographic data of participants' such as age, gender and ethnicity etc. There were other blood parameters such as haemoglobin, the frequency of blood transfusion, complications and other data were obtained through the medical records. Each participant was examined for BMI calculation and recorded for this study.

Statistical analysis

Statistical Analysis Data were analyzed using the Statistical Package of the Social Sciences (SPSS) version 25 (IBM, IL, USA). Variables data presented in mean ± standard deviation, range (minimum-maximum) and percentages. Pearson Chi-square test performed for two or more categorical data (frequencies) comparison. Student t-test performed for two continuous data group comparisons. The differences among three or more groups were for nonparametric tests obtained using One Way ANOVA or Kruskal–Wallis analysis. The Pearson or Spearman correlation for correlation analysis. In all the statistical tests, the significant level (p-value) was set at <0.05.

Results

Socio-demographic data of the patients according to the frequency of transfusion in comparison to healthy subjects

We were able to recruit 75 thalassemia patients and 75 healthy control subjects between the study period where 58 (77.3%) of them are categorized as MTG which phenotypically are thalassemia majors (TMajor) whereas the NMTG group consist of 10 (13.3%) thalassemia minor (TMinor) and 7 (9.3%) of thalassemia intermedia (TI). There was almost equal distribution in gender in our study cohort. The predominant ethnic group of the human subjects in both thalassemia patient groups and controls were Malays, followed by Chinese and a few Indians (P=0.00003) where there were no Indian subjects recruited in both MTG and NMTG. (Table 1). According to their genotype, there were a total of 27 cases β-thalassemia, 24 cases HbE/β, while the remaining were 7 of α-thalassemia in the MTG. As for the NMTG, there were 8 cases with β-thalassemia, and 9 cases with α-thalassemia.

Table 1: Demographic data of thalassemia patients alongside the healthy control group according to the frequency of transfusion

Variable	MTG TM (n=58)	NMTG TI (n=7) and T. Minor (n=10)	Control	*p*-value
N	58	17	75	
Female n (%)	28 (48.28 %)	10 (58.82 %)	38 (50.67 %)	

Male n (%)	30 (51.72 %)	7 (41.18 %)	37 (49.33 %)	0.74634
Median age (range), years	29 (18 – 64)	35 (18 – 45)	35 (23 – 59)	0.02636
Ethnicity				
Malay	40 (68.97%)	11 (64.71%)	68 (90.67%)	
Chinese	18 (31.03%)	6 (35.29%)	1 (1.33%)	0.00003
Indian	0 (0%)	0 (0%)	6 (8%)	

Abbreviation: MTG Implies to Monthly Transfused Group; NMTG: Non-Monthly Transfused Group; TI: Thalassemia Intermedia; T. Minor: Thalassemia Minor and BMI: Body Mass Index. Data presented by Numbers (Percentage) adding to Mean ± Standard Deviation for BMI profile. One Way ANOVA was performed to determine the age and BMI classification, and Pearson Chi-square test for ethnicity. * P-value set at <0.05

The pre-transfusion means Hb levels interpretations in MTG, NMTG and control

The pre-transfusion mean Hb levels of MTG/T major was at the range of 4.4 - 9.6 g/dL which is significantly lower than NMTG/T minor and NMTG/T intermedia combined with a range of 7.4 – 12.4 g/dL. Collectively the mean Hb levels are 7.82 ± SD 1.16 in MTG and 9.08 ± SD 1.43 in NMTG (Table 2).

Table 2: The mean Hb levels comparison between MTG, NMTG and control

Parameters	MTG (n=58)	NMTG (n=17)	Control (n=75)	*p*-value
Haemoglobin (Hb g/dL)	7.82 ± 1.16	9.08 ± 1.43	12.72 ± 1.22	< 0.00001

Abbreviation: MTG Implies to Monthly Transfused Group; NMTG: Non-Monthly Transfused Group and ND: Not Determined. Data presented by Mean ± SD and Range (minimum-maximum), adding to Percentage for LIC & Cardiac T2* * Kruskal-Wallis test for significant difference among three means at 0.05.

The mean Hb levels were found to be not statistically significantly different in the MTG when dissected between their genotypes which are reflecting the phenotypes of major thalassemia have no significant difference in their mean Hb levels regardless β, α or HbE/β that was found in our cohort (Table 3). Similarly in the NMTG, the mean pre-transfusion Hb levels comparison according to their β and α genotypes shows no major significant difference statistically (Table 4 & Table 5).

Table 3: Comparison of the mean Hb levels in MTG in terms of the genotypes and phenotypes

Parameters	β-thal major; n= 27	α-thal major; n= 7	HbE/β –thal major; n=24	α-thal major

				(*p*-v
			(*p*-value with β-thal major)	HbE maj
Haemoglobin (Hb g/dL)	8.10 ± SD 1.043	7.742 ± SD 1.219	7.541 ± SD 1.242	
p-value	0.487941		0.08711	0.7

Abbreviation: MTG implies to Monthly-Transfused Group; β-thal major: Beta T Major; α-thal major: Alpha Thalassemia Major and HbE/β major: HbE/Beta T (Major). Data presented by the Mean values ± Standard Deviation
* Student t-test for significant difference between two means at 0.05

Table 4: The mean Hb levels of NMTG in terms of the genotypes

	β-thal (n=8)	α-thal (n=9)	*p*-value
Haemoglobin (Hb g/dL)	9.55 ± SD1.722	8.66 ±SD 1.065	0.235189

Abbreviation: NMTG implies to Non-Monthly Transfused Group; β-thal: Beta-Thalassemia and α-thal: Alpha-Thalassemia. Data presented by the Mean values ± Standard Deviation.
* Student t-test for significant difference between two means at 0.05

Table 5: The mean Hb levels in NMTG in terms of the phenotypes

Variables	Thalassemia Intermedia (n=7)	Thalassemia Minor (n=10)	*p*-value
Haemoglobin (Hb g/dL)	8.7 ± SD1.09	9.35 ± SD 1.63	0.343144

Data presented by the Mean values ± Standard Deviation
* Student t-test for significant difference between two means at 0.05.

BMI interpretations

The statistical analysis of BMI revealed a highly significant difference among the three groups showing the MTG a mean BMI of 21.16 ± SD 3.88, NMTG with a mean BMI of 22.37 ± SD 4.73 and highest BMI in healthy controls of 26.07 ±SD 0.7 ($p < 0.00001$). By computing the Spearman rho correlation test with correlation coefficient, there was a significant positive relationship between BMI and Hb levels among the three main groups (Controls: r = 0.2770, P= 0,0161*; MTG: r = 0.2604, P= 0.0487* and MNTG: r =0.4898, P=0.0463) which seemingly indicated that healthy normal individuals who intended to have normal levels of Hb also have normal-weight BMI. The thalassemia patients who seemed to have lower Hb levels, in turn are underweight (Figure 4, Table 6).

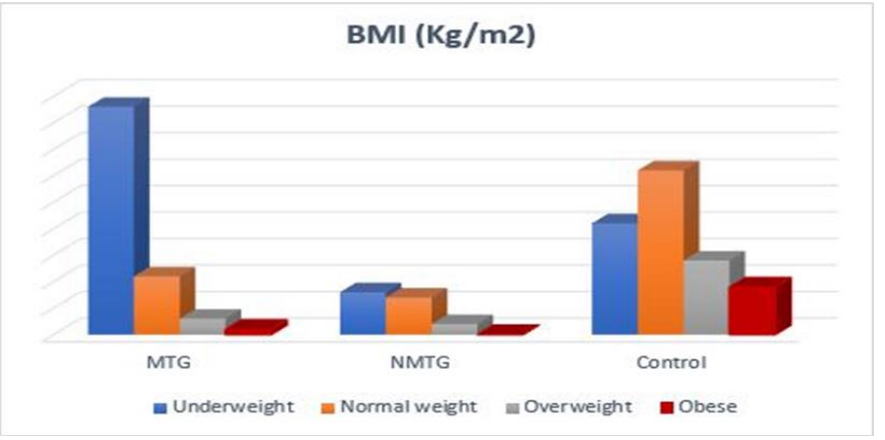


Figure 4: Histogram showing the BMI distribution of adult MTG, NMTG thalassemia and the healthy control group

Table 6: BMI distribution of adult thalassemia patients according to the frequency of transfusion and the healthy control group using WHO BMI classification

Variable	MTG TM (n=58)	NMTG TI (n=7); T. Minor (n=10)	Control	*p*-value
N	58	17	75	
BMI (kg/m^2)	21.16 ± SD3.88	22.37 ±SD 4.73	26.07 ±SD 0.7	
Underweight	43 (74.14%)	8 (47.06%)	21 (28%)	< 0.00001
Normal weight	11 (18.96%)	7 (41.18%)	31 (41.33%)	
Overweight	3 (5.18%)	2 (11.76%)	14 (18.67)	
Obese	1 (1.72%)	0 (0%)	9 (12%)	

Data presented by the Mean values ± Standard Deviation and Numbers (Percentage).
* One Way ANOVA for significant difference among three means at 0.05.

Discussion

A larger number and a longer period of a cohort study by having equal numbers of MTG, NMTG and healthy controls comparison is recommended to overcome the bias and other limitations. Our study may not reflect the NMTG well due to a small number of cases. This is most likely that they are not regularly seen monthly in the hospital and can be functional as normal individuals. Genotype and phenotype of other classes are not studied or included due the design of cross-sectional study. It will be interesting to see other factors that may contribute to pre-transfusion requirement or transfusion requirement in terms of host decompensatory response to the severe anaemia or lower Hb levels. Our findings show a difference with a report from Sardina where the haemoglobin ranges in patients with thalassemia was between 7- <7 g/d which was lower than our study cohort. Similarly, a previous study revealed that most patients with thalassemia major can have reduced Hb levels that vary from 7 g/dL and less [1].

The thalassemia intermedia and minor mean Hb levels in Malaysia was not in our scope of study. We have also not included hydrops fetalis in our study. We recommend doing genetic screening for asymptomatic thalassemia gene carriers along with other workups for causes of anaemia. It is imperative to mention that our healthy control group clearly shows evidence of lower range Hb which fulfills the definition of anaemia following WHO anaemia classification. The spleen and liver sizes, the degree of chronic hemolysis in MTG and NMTG group along with other transfusion and non-transfusion related thalassemia treatment and complication data will be interesting to be analyzed for the associated factors that contributes to the monthly and non-monthly transfusion nature. The available data may help to intervene as necessary and as urgently needed in order to improve the quality of life of these patients. Dietician referral for low iron diet has become obsolete to thalassemia patients, nevertheless our study shows the majority of MTG are underweight. A change in the outlook of high carbohydrate and low iron diet coupled with iron chelators by the dietician perhaps is advisable for MTG. This study agrees with a prospective study that conducted particularly over thalassemia patients who were majorly affected by the disease where low food carbohydrates and diets with poor iron were necessarily considered to avoid diabetes or the impaired glucose tolerance [17].

Albeit the curative therapy has advanced from only hematopoietic cell transplantation to a sophisticated gene therapy, just a minority of patients would be able to undergo such a procedure. It requires many protocols, for example, searching for an ideal stem cell donor without the thalassemia genes, a transplant center with the expertise and other factors to establish success in the procedure. There were other reports highlighting the advantages of this method which are used to generate stabilized genes of the patient's hematopoietic stem cell (HSC) that lead to effective erythropoiesis and avoid the haemolytic anaemia in thalassemia patients thus there is no need for blood transfusions. Two main obstacles while implementing a secured and efficient gene therapy are by providing an adequate amount of HSC cells as well as ensuring a safe transduce of CD34+ HSCs cells among the different levels of gene therapy [15].

Conclusions

We believe this is the first ever study to look into the socio-demographic, mean Hb levels and BMI of thalassemia patients grouped differently as MTG and NMTG alongside with normal healthy controls. Our study clearly shows in adult thalassemia MTG are predominantly in Malay ethnicity and younger in comparison to NMTG. Adult thalassemia MTG group has lower mean Hb levels in comparison to NMTG by approximately 2 g/dL and healthy individuals by 5 g/dL apart. There is a significant relationship between Hb and BMI, where our study proves that adult thalassemia patients with severe anaemia are underweight in reference to the WHO BMI classification. We also found that our healthy individual controls have a mild anaemia with lower Hb range according to WHO anaemia classification, indicating that there is a need for a wider screen for thalassemia gene carriers.

Author Contributions

All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Medical Research and Ethics Committee (MREC), Ministry of Health, Malaysia (reference number: NMRR-19-3918-51308) and Ethics Committee of University Putra Malaysia (JKEUPM).

Informed Consent Statement: “Not applicable”.
Data Availability Statement: “Not applicable”.

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