

ORIGINAL ARTICLE

Demographic and Socioeconomic Profile of Transfusion Dependent Beta-Thalassemia Major Patients in Sabah

Jenet Guan Chin¹, Intan Juliana Abd Hamid², Kogilavani Gunasagaran³, Julaiha Amir⁴, Primus John⁵, Anisah Azmi⁵, Ernest Mangantig²

¹ Hospital Queen Elizabeth II, Ministry of Health Malaysia, 88300, Kota Kinabalu, Sabah, Malaysia

² Regenerative Medicine Cluster, Advanced Medical and Dental Institute, Universiti Sains Malaysia, 13200, Kepala Batas, Pulau Pinang, Malaysia

³ Hospital Wanita dan Kanak-Kanak Kuala Lumpur, Ministry of Health Malaysia, 50586, Kuala Lumpur, Malaysia

⁴ Hospital Wanita dan Kanak-Kanak Sabah, Ministry of Health Malaysia, 88996, Kota Kinabalu, Sabah, Malaysia

⁵ Hospital Kota Belud, Ministry of Health Malaysia, 89158, Kota Belud, Sabah, Malaysia

ABSTRACT

Introduction: Thalassemia prevalence in Malaysia is highest in Sabah. This study was conducted to characterize the demographic and socioeconomic profile of transfusion-dependent β -thalassemia major patients in Sabah, to explore their parents' background, and to identify factors associated with having more than one thalassemia major children in the family. **Methods:** This was a cross-sectional study conducted in Hospital Wanita dan Kanak-Kanak Sabah and Hospital Kota Belud Sabah between February 2018 and Jun 2019. A total of 108 patients attending Thalassemia Treatment Clinic at both centers were selected randomly for interview. **Results:** β -thalassemia major patients in this study were majority from the indigenous ethnic groups (Kadazan, Dusun, Murut, Rungus, Sungai). Parents of the thalassemia patients mostly had low education level and socioeconomic status. Thirty-seven percent of parents have more than one children with thalassemia major and a high proportion (41.7%) have intermarriages. Parents with a higher number of children in the family are associated with having more than one thalassemia major children (OR: 2.1, 95% CI: 1.5, 2.9, P-value = 1.3×10^{-5}). **Conclusions:** A considerably high proportion of parents have more than one children with thalassemia major in this study. Knowledge and counselling are important to parents with low educational level and socioeconomic status to ensure their understanding of thalassemia risk and prevention.

Keywords: Beta-Thalassemia Major, Demography, Socioeconomic, Sabah, Malaysia

Corresponding Author:

Ernest Mangantig, PhD

Email: e.mangantig@usm.my

Tel: +604-5622289

INTRODUCTION

Thalassemia is an inherited disorder of red blood cells with high prevalence in the Middle East, Indian subcontinent, and South East Asia countries (1). It is the commonest inherited blood disorder in Malaysia, and about 4.5% of the Malaysian population are carriers for β -thalassemia (2). Records from the 2018 Malaysian Thalassemia Registry showed a total of 7,984 registered thalassemia patients in Malaysia (3). Patients with β -thalassemia major are dependent on life-long blood transfusion treatment and iron chelation therapy which includes long term monitoring of treatment side effects (4). Moreover, with regular blood transfusion, patients are also at risk for complications such as transmission of infection through blood, alloimmunization, and iron overload in various organs (4).

In some of the countries with high thalassemia

prevalence such as Saudi Arabia, India, and Iran, high consanguineous marriage rates play a role in the high birth rate of thalassemia (5-7) as consanguinity increases the gene frequency of any recessively inherited disorders such as thalassemia (8). In Malaysia, Sabah has the highest number of thalassemia patients (1,819 of 7,984 registered patients), with almost half of the affected individuals were from the indigenous ethnic group Kadazandusun (3, 4). The population in Sabah is made up of multi-ethnic indigenous and non-indigenous groups with its own languages and cultures. The largest ethnic group are Kadazan-dusun (25%), followed by Bajau (15%), Murut (3%) and other minority ethnics such as Rungus, Sungai, Lundayeh, Kedayan, Brunei, Suluk and others (9). The median monthly household income in Sabah is Ringgit Malaysia 4,110, which is below the national level median monthly household income of Ringgit Malaysia 5,228 (10). Previous study have suggested that marital consanguinity among the indigenous population in Sabah may contribute to the β -thalassemia problem in this population (11) although there are no publish data on the rates of consanguineous marriage among parents of thalassemia patients in Sabah.

Although Sabah has the highest prevalence of thalassemia in Malaysia, epidemiological studies to understand the sociodemographic profile of this high risk population is still lacking. Knowing the sociodemographic characteristics is important as this may aid in the planning of preventive measures to reduce thalassemia cases in Sabah. To date, previous studies in Sabah were mostly to characterize the molecular genetics of thalassemia (11-15). Moreover, the factors that contribute to the high prevalence in Sabah is still not explored.

Hence, this study aims to characterize the demographic and socioeconomic profile of β -thalassemia major patients in Sabah and to explore their parents' background. Additionally, we determine the sociodemographic factors that associated with family having more than one β -thalassemia major children.

MATERIALS AND METHODS

A cross-sectional study was conducted at the thalassemia treatment clinic (TTC) in Hospital Wanita dan Kanak-Kanak Sabah (HWKKS) and Hospital Kota Belud (HKB) Sabah between February 2018 and Jun 2019. Patients attending the TTC for their review were randomly selected based on the list of appointment. Patients with diagnosis of transfusion-dependent β -thalassemia major, aged 7 years and older, and accompanied by either one of parent were selected for interview while those who are unwell and unaccompanied by parents were excluded. The selected patients and their parents were informed about the study and invited to participate voluntarily. Assent consent and informed consent were obtained from both patients and parents if they agreed to be interviewed.

One of the factor of interest in this study is the proportion of marital consanguinity among parents of thalassemia patients in Sabah. Hence, the proportion of thalassemia patients with parents who had marital consanguinity in other countries with high thalassemia prevalence (16) was used for reference in sample size calculation using single proportion formula. With a true population proportion of 50%, precision of 10%, and 20% non-response rate, the total sample required was 115 patients.

A structured interview was conducted with both patients and parents. A data collection form was created to record patients' demographic (age, gender, ethnicity, town/district of residence, father's age, and mother's age) and socioeconomic (schooling status, education level, education level of father and mother, employment status of father and mother, total monthly household income, and receiving financial aids) information. For parents' background, several questions were asked including the total number of children in the family, number of children with thalassemia carrier status, number of

children with β -thalassemia major, have heard about thalassemia before the birth of first affected child, aware of thalassemia carrier status before marriage, have undergone pre-marital thalassemia screening before marriage, blood relationship between husband and wife, and ethnicity of husband and wife.

Data analysis was performed using IBM SPSS version 24.0. Descriptive statistics was performed to obtain the frequency and its percentage for categorical variables, and mean and its standard deviation (or median and its interquartile range for variables with skewed distribution) for numerical variables. In addition, logistic regression was performed to identify factors associated with family having more than one β -thalassemia children. Variables with P-value less than 0.25 at univariable analysis were chosen for inclusion in multivariable analysis. Variable selection was performed using both forward and backward (likelihood ratio) method.

This study was approved by the Human Research Ethics Committee of Universiti Sains Malaysia (USM/JEPeM/18010008) and the Medical Research and Ethics Committee (MREC) Ministry of Health Malaysia [NMRR-18-218-39524].

RESULTS

Demographic and socioeconomic profile of patients

A total of 115 transfusion-dependent β -thalassemia major patients and parents were included in the study. However, there were 7 pairs of siblings identified and one of the siblings were excluded from the analyses, leaving a total sample of 108 patients. The majority patients (N=91) were from HWKKS and the remaining 17 patients from HKB. Tables I and II shows the demographic and socioeconomic profile of patients. The ages of the patients ranged from seven to seventeen years with mean age of 12 years. The majority was in the age group between 7 to 12 years (60.2%), and all patients included in the study were born between the year 2001 and 2011. There is an equal number of male and female patients in this study. Most of the patients (45.4%) were of Dusun ethnicity and reside in the west coast of Sabah, mainly in Kota Kinabalu.

Majority of patients (93.5%) in this study are still attending school and currently in primary school (55.6%). Most of the patients' father and mother completed secondary school education (70.4% and 65.7%, respectively). Majority patients' father were employed (63.9%) but mothers were mostly housewife (59.3%). The median monthly total household income in Malaysian Ringgit (MYR) was 1500 and majority (75.9%) are considered as bottom 40% (B40) group with income less than MYR 3000 per month. Only 30.6% of the patients received financial aids from the government and non-governmental organization.

Table I: Demographic profile of patients (N=108)

Demographic profile	n (%)
Age group (years)	11.9 ± 2.9 ^a
7 – 12	65 (60.2)
13 – 17	43 (39.8)
Gender	
Male	54 (50.0)
Female	54 (50.0)
Ethnicity	
Dusun	49 (45.4)
Kadazan	24 (22.2)
Bajau	7 (6.5)
Brunei	7 (6.5)
Murut	6 (5.6)
Rungus	4 (3.7)
Sungai	2 (1.9)
Sino	2 (1.9)
Kedayan	1 (0.9)
Lundayeh	1 (0.9)
Chinese	2 (0.9)
Malay	2 (1.9)
Jawa	1 (0.9)
District of residence	
West coast division:	
Kota Kinabalu	40 (37.0)
Kota Belud	18 (16.7)
Tuaran	12 (11.1)
Penampang	12 (11.2)
Papar	11 (10.2)
Ranau	3 (2.8)
Interior division: Keningau and Beaufort	3 (2.8)
Kudat division: Kudat, Kota Marudu, and Pitas	3 (2.8)
Father's age	44.5 ± 0.7 ^a
Mother's age	40.8 ± 0.7 ^a

^a Mean ± Standard deviation

Parents' background

Table III provide the information for parents' background. The total number of children in the family ranged from 1 to 12, with median of 4 children. Whereas, the number of children with beta-thalassemia major ranged from 1 to 4, with median of 1 children. Majority parents (n=68, 63%) have only one child with β-thalassemia major, followed by 27.8% have 2 β-thalassemia children, 8.3% have 3 β-thalassemia children, and only 1% have 4 β-thalassemia children. Out of 108 parents, 40 (37%) have more than one β-thalassemia major children in the family.

When the parents were asked if they have heard about thalassemia before the birth of first affected child, only 13.9% responded 'yes'. Most of the parents (91.7%) were also not aware of their thalassemia carrier status before marriage, and majority (94.4%) did not undergone pre-marital thalassemia screening before marriage. Regarding blood relationship between husband and wife, 21.3% were married between relatives and 78.7% were not relatives. In terms of ethnic composition,

Table II: Socioeconomic profile of patients (N=108)

Socioeconomic profile	n (%)
Schooling status	
Still attending school	101 (93.5)
Quit school	2 (1.9)
Did not answer	4 (3.7)
Education level	
Primary school	60 (55.6)
Secondary school	44 (40.7)
Did not answer	4 (3.7)
Education level of father	
No formal education	2 (1.9)
Primary school	17 (15.7)
Secondary school	76 (70.4)
Tertiary education	13 (12.0)
Education level of mother	
No formal education	5 (4.6)
Primary school	14 (13.0)
Secondary school	71 (65.7)
Tertiary education	18 (16.7)
Employment status of father	
Employed	69 (63.9)
Self-employed	31 (28.7)
Unemployed	2 (3.7)
Retired	4 (3.7)
Did not answer	2 (1.9)
Employment status of mother	
Employed	37 (34.3)
Self-employed	6 (5.6)
Housewife	64 (59.3)
Retired	1 (0.9)
Total household income (MYR)	1500 (950 – 3000) ^a
≤ 3000 (B40 group)	82 (75.9)
> 3000 (M40 group)	19 (17.6)
Did not answer	7 (6.5)
Receiving financial aids	
No	71 (65.7)
Yes	33 (30.6)
Did not answer	4 (3.7)

^a Median (Interquartile range) MYR: Malaysian Ringgit
Income group categorization is based on Department of Statistics Malaysia (Report of Household Income and Basic Amenities Survey 2016) for bottom 40% (B40 group) (median income of ≤3000) and middle 40% (M40 group) (median income of >3000)

majority 36.1% were Dusun couples, 10.2% Kadazan couples, 18.5% intermarriage between different KDM (indigenous population comprising of Kadazan, Dusun, Murut, Rungus, Sungai, etc) ethnic groups, and 10.5% intermarriage between KDM ethnic groups and non-KDM ethnic groups such as Bajau, Suluk, Chinese, Brunei, and Jawa. This study also found high proportion (N=45, 41.7%) of intermarriages with other ethnic groups among parents of thalassemia patients in this study.

Demographic profile of parents with blood relationship

Table IV summarizes the demography profile of parents who were married between relatives. Out of the 23 parents, 4 had marriage between uncle and niece, 6

Table III: Parents' background (N=108)

Parents' profile	n (%)
Total number of children	4 (2 – 5) ^a
Total number of children with thalassemia carrier status	1 (0 – 2) ^a
Total number of children with beta-thalassemia major	1 (1 – 2) ^a
1	68 (63.0)
2	30 (27.8)
3	9 (8.3)
4	1 (0.9)
Have heard about thalassemia before the birth of first affected child	
No	93 (86.1)
Yes	15 (13.9)
Aware of thalassemia carrier status before marriage	
No	99 (91.7)
Yes	9 (8.3)
Undergone pre-marital thalassemia screening before marriage	
No	102 (94.4)
Yes	6 (5.6)
Blood relationship between husband and wife	
Not related	85 (78.7)
Related	23 (21.3)
Ethnicity of husband and wife	
Dusun – Dusun	39 (36.1)
Kadazan – Kadazan	11 (10.2)
Murut – Murut	3 (2.8)
Rungus – Rungus	2 (1.9)
Sungai – Sungai	2 (1.9)
Bajau – Bajau	4 (3.7)
Brunei – Brunei	1 (0.9)
Malay – Malay	1 (0.9)
Intermarriage between different KDM ethnic groups	20 (18.5)
Intermarriage between KDM and other ethnics (Bajau, Suluk, Chinese, Brunei, and Jawa)	19 (10.5)
Intermarriage between Brunei and other ethnics (Sino, Iranun, and Malay)	3 (2.8)
Intermarriage between Bajau and Kedayan	3 (2.8)

^a Median (Interquartile range)

KDM: Indigenous ethnic group comprising of Kadazan, Dusun, Murut, Rungus, Sungai etc

had second cousin marriages, and 13 had third cousin marriages. Ten parents (9.2%) in this study have marital consanguinity (defined as “marriage between two individuals who are related as second cousins or closer”) (17). The majority 11 of the parents were Dusun couples, 5 Kadazan couples, 2 Bajau couples, 1 Murut couple, 1 Sungai couple, and 3 intermarriages.

Factors associated with family having more than one β-thalassemia major children

In univariable analysis, nine sociodemographic factors were analyzed using logistic regression to determine its association with family having more than one thalassemia major children: total number of children, age of mother, age of father, education level of mother (no formal education/primary school/secondary school/tertiary education), education level of father (no formal education/primary school/secondary school/tertiary education), ethnicity group (KDM/non-KDM), income group (≤3000/>3000), receiving financial aids (no/yes), and residing in Kota Kinabalu city (no/yes). At 5% level of

Table IV: Demographic profile of parents with blood relationship (N=23)

No.	Blood relationship	Ethnicity of husband and wife	Home-town of husband and wife	Total no. of children	No. of thalassemia carrier children	No. of thalassemia major children
1	Uncle and nieces	Dusun – Dusun	Kota Belud – Kota Belud	5	3	1
2		Kadazan – Kadazan	Menggatal – Penampang	2	0	1
3		Murut – Murut	Tenom – Tenom	2	1	1
4		Dusun – Rungus	Pitas – Pitas	3	2	1
5	Second cousins	Dusun – Dusun	Kota Belud – Kota Belud	3	0	2
6		Dusun – Dusun	Kota Belud – Kota Belud	7	2	2
7		Dusun – Dusun	Menggatal – Menggatal	4	1	1
8		Kadazan – Kadazan	Menggatal – Menggatal	4	1	1
9		Rungus – Dusun	Inanam – Inanam	2	1	1
10		Rungus – Brunei	Kudat – Kudat	2	0	2
11	Third cousins	Dusun – Dusun	Kota Belud – Kota Belud	12	3	2
12		Dusun – Dusun	Kota Belud – Kota Belud	8	2	3
13		Dusun – Dusun	Kota Belud – Kota Belud	7	3	2
14		Dusun – Dusun	Ranau – Ranau	3	2	1
15		Dusun – Dusun	Tamparuli – Tamparuli	1	0	1
16		Dusun – Dusun	Penampang – Penampang	3	1	2
17		Dusun – Dusun	Keningau – Keningau	6	2	4
18		Kadazan – Kadazan	Kinarut – Kinarut	3	1	1
19		Kadazan – Kadazan	Papar – Papar	4	0	1
20		Kadazan – Kadazan	Penampang – Penampang	5	1	3
21		Bajau – Bajau	Menumbok – Kota Belud	3	1	2
22		Bajau – Bajau	Kuala Penyu – Kuala Penyu	2	1	1
23		Sungai – Sungai	Kota Marudu – Kota Marudu	6	3	3

significance, only total number of children (P-value=1.5 x 10⁻⁵) and mother's education level (P-value of tertiary education vs no formal education=0.04) showed significant association. Whereas, age of mother showed

borderline significance (P-value=0.06).

In multivariable analysis, six factors (total number of children, age of mother, education level of mother, ethnicity group, receiving financial aids, and residing in Kota Kinabalu city) were included in the logistic regression analysis considering the importance of the variables. Only total number of children remained significant (P-value=1.3 x 10⁻⁵; OR=2.1; 95% CI 1.5, 2.9) at multivariable analysis and receiving financial aids showed borderline significance (P-value=0.06) (Table V).

Table V. Factors associated with family having more than one beta-thalassemia major children (N=108)

Factors	Univariable logistic regression		Multivariable logistic regression	
	Crude OR (95% CI)	P-value	Adjusted OR* (95% CI)	P-value
Number of children	2.0 (1.5, 2.8)	1.5 x 10 ⁻⁵	2.1 (1.5, 2.9)	1.3 x 10 ⁻⁵
Receiving financial aids				
No	1	-	1	-
Yes	2.0 (0.8, 4.6)	0.12	2.6 (0.9, 7.0)	0.06

*Variable selection using forward (LR) method
Multicollinearity was checked and not found
Hosmer-Lemeshow test (P-value=0.369) and classification table (overall correctly classified percentage=78%) were applied to check model fitness

DISCUSSION

Beta-thalassemia major is highly prevalent in Sabah. In this study, β -thalassemia major patients were majority from the indigenous KDM ethnic groups (Kadazan, Dusun, Murut, Rungus, Sungai), consistent with reports from previous studies in Sabah that identified Kadazandusun with highest thalassemia major compared to other ethnics (11-15, 18). The predominance of indigenous patients in this study is related to the high indigenous population in Sabah which comprised of more than 30 heterogeneous ethnic groups that make up about 60% of the total Sabah population (9).

Patients in this study mostly living in the west coast of Sabah. This was expected as data collection were mainly conducted at HWKSS, the main referral center for thalassemia pediatric and adolescent patients in Sabah. As such, all patients included in this study were those age 17 years and below. Majority parents in this study have low education level and socioeconomic status. The low education level among parents of thalassemic children were also observed in other studies in Malaysia (19, 20). Therefore, special attention should be given to counsel at-risk families with low education and socioeconomic background to ensure their understanding of future thalassemia major risk in the family.

In this study, 37% of parents were found to have more than one thalassemia major children in the family, with highest up to four thalassemic children. In Malaysia, the initiative by the Ministry of Health for thalassemia control strategy includes genetic counseling, voluntary

screening, cascade screening of an index case, and prenatal diagnosis (4). The prenatal diagnosis was only available in Sabah in 2013 and the high cost for the diagnosis should be paid by the parents. Given the low socioeconomic status among the parents of thalassemia patients in this study, many would not be able to afford the cost and it is unlikely for the parents undergone the prenatal diagnosis.

This study found that only 13.9% of the parents have heard about thalassemia before the birth of first affected child, and majority (91.7%) of the parents were not aware of their thalassemia carrier status before marriage. This reflect the lack of awareness about thalassemia among the local population. Successful thalassemia control in countries such as Cyprus, Greece and Italy implemented multi-disciplinary approach which includes mandatory premarital screening, prenatal diagnosis, genetic counselling, and termination of affected pregnancies (21). In Malaysia, premarital screening is not mandatory and termination of pregnancy is not favourable due to religious reasons (19). Hence, the current population screening program among adolescents at secondary schools in Malaysia which started in 2016 will be beneficial for future preventive measures in addition to the cascade screening (18).

In the present study, 9.2% of the parents had marital consanguinity. Marital consanguinity in Sabah is not uncommon among the indigenous population although this was rarely reported. Living in small communities or isolated areas might contribute to marital consanguinity among the indigenous or pooling of similar gene in a small population due to geographical isolation. The proportion of marital consanguinity in this study is much lower compared to other thalassemia prevalent countries such as Iran, Saudi Arabia, Iran, and Pakistan (7, 16, 22). However, as data collection was conducted mainly in Kota Kinabalu city, the proportion of marital consanguinity in this study is likely to be underestimated. In addition, there is a high proportion (41.7%) of intermarriages among parents of thalassemia patients in this study. Intermarriages in Sabah is common and the rate was reported to be highest in Malaysia compared to other states (23).

This study identified significant association between increased number of children and having more than one β -thalassemia major children in the family. This was expected as thalassemia carrier couples have 25% chance of having a thalassemia major baby in each pregnancy due to the autosomal recessive pattern of inheritance (15). Hence, genetic counselling is crucial for known thalassemia carrier couples to ensure their understanding of thalassemia risk and prevention. However, with the high carrier rate of β -thalassemia in Sabah (15, 18), thalassemia educational and awareness programme should be extended to communities outside hospital.

Certain limitations of the current study should be taken into account. First, data was collected in two thalassemia treatment centers in the west coast of Sabah and include only pediatric and adolescent patients. Hence, this may limit the generalizability of the study findings. Second, certain important factors that may contribute to having more than one thalassemia major children in the family such as history of prenatal screening, method of family planning, and religious belief was not asked during the interview. An in-depth interview session will be more suitable to ask these sensitive questions. Nevertheless, this study provide insights on both patients and their parents' sociodemographic characteristics in Sabah in which published study is still lacking.

CONCLUSION

Beta-thalassemia major patients in this study were majority from the indigenous KDM ethnic groups (Kadazan, Dusun, Murut, Rungus, Sungai) and parents mostly have low education level and socioeconomic status. A considerably high proportion of parents have more than one children with β -thalassemia major and parents with higher number of children in the family is associated with having more than one thalassemia major children. Knowledge and counselling is important to these parents to ensure their understanding of thalassemia major risk and prevention. Demographic characteristics and socioeconomic status of parents should be taken into account when planning an effective educational program and counselling.

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