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Complete List of Authors:	Mohd Ibrahim, Hishamshah; Women's and Children's Hospital Kuala Lumpur, Department of Paediatrics Muda, Zulaiha ; Women's and Children's Hospital Kuala Lumpur, Department of Paediatrics Othman, Ida Shahnaz ; Women's and Children's Hospital Kuala Lumpur, Department of Paediatrics Mohamed Unni, Mohamed Najib ; Women's and Children's Hospital Kuala Lumpur, Department of Paediatrics Teh, Kok Hoi ; Women's and Children's Hospital Kuala Lumpur, Department of Paediatrics Thevarajah, Asohan ; Sabah Women & Children Hospital, Department of Paediatrics Gunasagaran, Kogilavani ; Sabah Women & Children Hospital, Department of Paediatrics Ong, Gek Bee ; Hospital Umum Sarawak, Department of Paediatrics Yeoh, Seoh Leng ; Hospital Pulau Pinang, Department of Paediatrics Muhammad Rivai, Aisyah ; Hospital Raja Permaisuri Bainun, Department of Paediatrics Che Mohd Razali, Che Hadibiah ; Hospital Sultan Ismail, Department of Paediatrics Din, Nazzlin Dizana ; Hospital Sultanah Nur Zahirah Kuala Terengganu, Department of Paediatrics Alias, Hamidah ; Hospital Canselor Tuanku Muhriz UKM, Department of Paediatrics Abdul Latiff, Zarina ; Hospital Canselor Tuanku Muhriz UKM, Department of Paediatrics A Jamal, A Rahman ; Hospital Canselor Tuanku Muhriz UKM, Department of Paediatrics Mohamad, Norsarwany ; Hospital Universiti Sains Malaysia, Department of Paediatrics Mohd Ariffin, Hany ; University of Malaya Medical Centre, Department of Paediatrics
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The current scenario of thalassaemia in Malaysia through the Malaysian Thalassaemia Registry

Hishamshah Mohd Ibrahim*[1], Zulaiha Muda[1], Ida Shahnaz Othman[1], Mohamed Najib Mohamed Unni[1], Kok Hoi Teh[1], Asohan Thevarajah[2], Kogilavani Gunasagaran[2], Gek Bee Ong[3], Seoh Leng Yeoh[4], Aisyah Muhammad Rivai[5], Che Hadibiah Che Mohd Razali[6], Nazzlin Dizana Din[7], Hamidah Alias[8], Zarina Abdul Latiff[8], A Rahman A Jamal[8], Norsarwany Mohamad[9] and Hany Mohd Ariffin[10]

[1]Department of Paediatrics, Women's & Children's Hospital Kuala Lumpur, Kuala Lumpur, Malaysia

[2]Department of Paediatrics, Sabah Women & Children Hospital, Likas, Kota Kinabalu, Sabah, Malaysia

[3]Department of Paediatrics, Hospital Umum Sarawak, Kuching, Sarawak, Malaysia

[4]Department of Paediatrics, Hospital Pulau Pinang, George Town, Pulau Pinang, Malaysia

[5]Department of Paediatrics, Hospital Raja Permaisuri Bainun, Ipoh, Perak, Malaysia

[6]Department of Paediatrics, Hospital Sultan Ismail, Johor Bahru, Johor, Malaysia

[7]Department of Paediatrics, Hospital Sultanah Nur Zahirah, Kuala Terengganu, Terengganu, Malaysia

[8]Department of Paediatrics, Hospital Canselor Tuanku Muhriz UKM, Cheras, Kuala Lumpur, Malaysia

[9]Department of Paediatrics, Hospital Universiti Sains Malaysia, Kubang Kerian, Kota Bharu, Kelantan, Malaysia

[10]Department of Paediatrics, University Malaya Medical Centre, Kuala Lumpur, Malaysia

Running Heads: Current Scenario of Thalassaemia in Malaysia

***Corresponding Author**

Dr Hishamshah Mohd Ibrahim

Women's & Children's Hospital Kuala Lumpur, Jalan Raja Muda Abdul Aziz, Kampung Baru, 50300 Kuala Lumpur, Malaysia

Tel: +603-2615 5555 ext 5640/6418

Email: drhishamshah@moh.gov.my/ hishamshahibrahim@gmail.com

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Abstract

Objective: This study aims to report the data obtained from the Malaysian Thalassaemia Registry and use it to describe the current scenario and provide a comprehensive understanding of thalassaemia in Malaysia.

Design: Data were extracted from the Malaysian Thalassaemia Registry, a web-based system accessible to enrolled users through www.mytalasemia.net.my.

Setting: The Malaysian Thalassaemia Registry data was recorded from reports obtained from 110 participating government and university hospitals in Malaysia.

Participants: The patients were those attending the 110 participating hospitals for thalassaemia treatment.

Intervention: Data was collected from the Malaysian Thalassaemia Registry from 2007 until the fourth quarter of 2018.

Primary Outcome Measure: Out of 8681 thalassaemia patients registered in the Malaysian Thalassaemia Registry, 7984 were reported still alive.

Results: From the registry, most of the patients were reported in Sabah (22.72%); the largest age group was 5.0-24.9 years (64.45%); the largest ethnic group was Malay (63.95%); and the major diagnosis was haemoglobin E/β-thalassaemia (34.37%). From the 7984 patients, only 56.72% were on regular transfusion and 61.72% were on chelation therapy. A small fraction (14.23%) has undergone splenectomy, while the percentage of high-risk patients (serum ferritin ≥ 5000 µg/L)

is reducing. However, cardiac complications are still the main cause of death in thalassaemia patients.

Conclusion: Data gathered into the registry can be used to understand the progression of the disorder and to improve the outcomes of treatment, monitor iron overload management, enhance preventive strategies and reduce healthcare burden.

Keywords: Healthcare burden; Iron chelation therapy; Iron overload management; Thalassaemia cause of death; Thalassaemia serum ferritin

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The Malaysian Thalassaemia Registry is the first online registry in Malaysia, which aggregates data from all participating hospitals and allows real-time data analysis.
- The report provides an overall distribution of thalassaemia patient on a wider, national scale instead of area or state level.
- The report generated also provides the current status of thalassaemia patients and the progress of patient management in Malaysia.
- Limitations of the Malaysian Thalassaemia Registry include incomplete records as certain information is inaccessible, evaluation was not yet completed on the whole population or the data is not yet captured in the current year.
- Figures might differ dramatically from time to time due to the dynamic nature of the registry.

INTRODUCTION

Thalassaemia is one of the most common autosomal recessive disorders and is highly prevalent in countries within the tropical belt including Malaysia.[1, 2] Current estimation shows that 6.8% of Malaysians are thalassaemia carriers who might be affected with various degrees of anaemia.[3] A thalassaemia carrier couple has a 25% chance of producing a thalassaemia major progeny.

Caused by a wide spectrum of point mutations and gene deletions, thalassaemia leads to a reduced or zero formation of the α- or β-globin chain sub-units of the adult haemoglobin (Hb) molecule.[3] The deficiency produces fragile erythrocytes and haemolytic anaemia. The affected babies will eventually develop progressively severe anaemia and require life-long blood transfusions to meet their daily physiological needs.[4] Iron chelation therapy must accompany the monthly transfusions to reduce iron overload, allow normal growth and improve the survival rates of thalassaemia patients.[5, 6]

Although it is the most common hereditary haematological disorder in this country, information on its presence in certain areas and ethnicities as well as the outcomes of its therapy in Malaysia is still lacking. The Malaysian Cabinet endorsed a national comprehensive programme on 25th August 2004, consisting of health education and population awareness drive, thalassaemia screening initiative, comprehensive clinical management of thalassaemia patient and the Malaysian Thalassaemia Registry (MTR). The registry was launched on 12th May 2007, to store data on thalassaemia patients who received treatment at government hospitals under the Ministry of Health and university hospitals. The registry is the first online registry

featuring real-time data analysis in Malaysia, which allows enrolled users to observe the aggregated data at any point of time.

The registry records updated patients' information including their socio-demographical data, clinical records, treatments received, death records and complications. It is a web-based system accessible to enrolled users through www.mytalasemia.net.my (MyTalasemia). MTR collects data from 110 participating government hospitals and three university hospitals located in 13 states and three Federal Territories of Malaysia: Kuala Lumpur, Labuan and Putrajaya.

In this article, we aim to report the data obtained from the MTR and use it to describe the current scenario and provide a comprehensive understanding of thalassaemia in Malaysia involving a bigger population.

METHODS

This study utilised secondary data from the MTR, combining retrospective data (data of all thalassaemia patients enrolled from 2007 obtained from the registry up to current date) and prospective data (including patients' follow-up up to November 2018).

The data were collected by research assistants in various regional centres, supervised and verified by clinicians and then manually recorded into MyTalasemia. The types of data to be collected were guided by the registry's design. Data elements can be grouped into several categories including socio-demography, clinical characteristics, laboratory test results, type of treatment received, death record and other complications of thalassaemia patients. The data were further verified and discussed centrally during the annual National Thalassaemia Meeting.

In this report, the data was first separated into two groups: 1) surviving and 2) deceased patients. The surviving patients were analysed according to 1) demography (location, gender, age groups and ethnicity), 2) clinical diagnosis, 3) receipt of regular transfusion, 4) receipt of chelation therapy, 5) history of splenectomy and 6) serum ferritin level. In deceased patients, the cause of death (CoD) was also reported.

Results were presented as fractions and percentages over the total number of reported cases. For sections involving sub-groups (i.e. regions, age groups and ethnicity), the fractions and percentages were calculated against the total number of reported cases in the respective sub-groups.

This study has obtained the ethics approval from Medical Research and Ethics Committee, Ministry of Health Malaysia (National Medical Research Register ID: NMRR-17-2410-37653).

Patient and Public Involvement

This report was prepared without patient and public involvement. Patients and the public were not invited to comment on the database and study design or to contribute to the writing or editing of this report.

RESULTS

As of 28th November 2018, 8681 thalassaemia patients have been registered in the MTR. Only 7984 patients were reported still alive; of these, 130 were reported cured by stem cell transplant and another 614 were lost to follow-up. The remaining 697 patients were reported as deceased.

Location

The largest number of registered thalassaemia cases came from Sabah (1814/7984 cases, 22.72% of total reported cases), followed by the states of Selangor (14.64%), Kedah (8.69%), Johor (7.98%) and Perak (7.06%).

The patient distribution was also analysed based on regional division: Peninsular Malaysia (which includes all states and Federal Territories except for Sabah, Sarawak and Labuan), Sabah (combining Sabah and Labuan) and Sarawak. Peninsular Malaysia recorded 5922 registered patients (74.17%), while Sabah and Sarawak have registered 1839 (23.03%) and 223 (2.79%) patients, respectively.

Hospital Ampang, Selangor, recorded the highest number of patients (703 patients) as the hospital also serves as the referral centre for adult thalassaemia cases, including patients from the capital of Malaysia, Kuala Lumpur. Hospital Queen Elizabeth (370 patients) and Hospital Wanita Dan Kanak-Kanak Likas (300 patients), both located in Sabah, also recorded high number of patients.

Gender

Gender distribution among the recorded thalassaemia patients was almost equal, with a male to female ratio of 49.60:50.40 (3960 versus 4024).

Age groups

Majority of the patients were of 5.0-24.9 years of age (5146/7984 patients, collectively, 64.45%), with the largest population being patients aged between 10.0-14.9 years (17.46%). The number of patients decreased steadily in the subsequent

age groups, from 790 patients in the 25.0-29.9 years age group to 5 patients in the 85.0-89.9 years age group.

With the passage of time, there is a change in the survival trend of thalassaemia patients. The registry showed an increasing number of patients aged ≥ 40.0 years, showing that the survival graph is currently shifting to the right (Figure 1). The survival shift was more distinguishable in Peninsular Malaysia. This is generally true for the more affluent states here that have better access to treatment regime compared to Sabah and Sarawak regions. Table 1 summarises the findings on location, region and age groups of the patients.

Table 1 Summary of thalassaemia patient distribution according to state, region and age group

Distribution of patient according to state							
State	**n (%)**	**State**	**n (%)**	**State**	**n (%)**	**State**	**n (%)**
Sabah	1814 (22.72)	Perak	564 (7.06)	Pahang	437 (5.47)	Negeri Sembilan	181 (2.27)
Selangor	1169 (14.64)	Kuala Lumpur	535 (6.70)	Terengganu	344 (4.31)	Perlis	128 (1.60)
Kedah	694 (8.69)	Kelantan	486 (6.09)	Melaka	226 (2.83)	Putrajaya	41 (0.51)
Johor	637 (7.98)	Pulau Pinang	480 (6.01)	Sarawak	223 (2.79)	Labuan	25 (0.31)

Distribution of patient according to region																			
Region	**Total no of patients (n)**	**Age group (year)**																	
		0.0-4.9	**5.0-9.9**	**10.0-14.9**	**15.0-19.9**	**20.0-24.9**	**25.0-29.9**	**30.0-34.9**	**35.0-39.9**	**40.0-44.9**	**45.0-49.9**	**50.0-54.9**	**55.0-59.9**	**60.0-64.9**	**65.0-69.9**	**70.0-74.9**	**75.0-79.9**	**80.0-84.9**	**85.0-89.9**
Peninsular Malaysia[a]	5922	351	859	962	923	906	636	444	277	192	133	83	59	44	26	10	9	3	5
Sabah[b]	1839	167	379	397	330	246	138	80	41	17	13	11	1	0	10	2	1	0	0
Sarawak[c]	223	17	34	35	33	42	16	21	9	2	6	4	1	1	0	1	1	0	0

[a] Peninsular Malaysia region: Including all states and Federal Territories, except for the states of Sabah and Sarawak and the Federal Territory of Labuan; [b] Sabah region: Combining the state of Sabah and the Federal Territory of Labuan; [c] Sarawak region: The state of Sarawak.

Ethnicity

The majority of thalassaemia patients were Malays (5106/7984, 63.95%), followed by Chinese (938, 11.75%) and Kadazan-Dusuns (907, 11.36%). Other specified ethnicities include Pribumi Sabah (213, 2.67%), Bajau (196, 2.45%), Murut (147, 1.84%), Rungus (112, 1.40%) and Indian (43, 0.54%). The remaining ethnicities such as Orang Asli, Thais, Iban, Bidayuh, Sino Kadazan and Melanau (322, 4.03%) are listed as 'Others', along with 68 patients from foreign countries.

Comparison was also made according to regional division, focusing on the four major ethnicities (Malay, Chinese, Indian and Kadazan-Dusun). Data showed that the Malays made up 85.45% of registered patients from these important ethnicities in Peninsular Malaysia (4904 out of 5739 patients). Patients in Sarawak, on the other hand, were mostly Malays (95/186, 51.08%) and Chinese (86/186, 46.24%). Conversely, patients in Sabah comprised mainly of Kadazan-Dusun patients (864/1069, 80.82%) instead (Figure 2).

Clinical diagnosis

Majority of the patients were diagnosed as haemoglobin E (HbE)/β-thalassaemia (2744/7984, 34.37%), followed by β-thalassaemia major (2676, 33.52%), haemoglobin H (HbH) disease (1458, 18.26%), β-thalassaemia intermedia (748, 9.37%) and 'Others' (358, 4.48%). The 'Others' group includes other forms of HbH disease, Hb Lepore Hollandia, α-thalassaemia syndrome, δβ-thalassaemia and other thalassaemia disorders requiring regular packed cell transfusion.

Patterns can be observed in age groups and ethnicity. Patients aged < 15.0 years were commonly reported with β-thalassaemia major (1186/3201 cases collectively, 37.05%). On the other hand, patients aged 25.0-44.9 years were commonly reported with HbE/β-thalassaemia (707/1873, 37.75%), while patients aged ≥ 55.0 years were commonly diagnosed with HbH disease (86/180, 47.78%). These observations were consistent with the presentation of the clinical diagnoses. Beta-thalassaemia major symptoms would present early in life and are mostly transfusion dependent, which affects their survival in the later decades of life. The severity of HbE/β-thalassaemia broadly ranges from mild to severe. HbH disease, on the other hand, is non-transfusion dependent thalassaemia and patients might survive longer due to the lower risk of iron overload.

In relation to ethnicity, HbE/β-thalassaemia was frequently reported in Malay patients (2441 patients, 47.81% of 5106 Malay patients and 88.96% of 2744 HbE/β-thalassaemia cases), while β-thalassaemia major was predominant in the Kadazan-Dusuns (783/907, 86.33%). Another interesting note is that there was a high proportion of Chinese patients diagnosed with HbH disease (297/938, 31.66%) in comparison to the other ethnicities (Figure 3).

Regular transfusion

Only 4529 patients (56.72%) were on regular transfusion, requiring packed cell transfusions biweekly or up to once every 12 weeks. The remaining patients were classified as non-transfusion dependent thalassaemia, which consists of patients who were on irregular packed cell transfusion (> 16 weeks intervals) or who had never undergone transfusion therapy.

Chelation therapy

Only 4928 patients (61.72%) were on iron chelation therapy. The most common iron chelator prescribed was deferasirox (DFX) (1645/4928 patients, 33.38%), followed by deferiprone (DFP) (1107, 22.46%) and desferrioxamine (DFO) (963, 19.54%). Combination therapies of DFO+DFP (910, 18.47%), DFO+DFX (169, 3.43%), DFP+DFX (92, 1.87%) and DFO+DFP+DFX (42, 0.85%) were prescribed for the remaining patients.

Therapy using DFX was common in patients aged < 15.0 years old; DFX was prescribed to 1231 out of 1836 patients (67.05%) from the age group. On the contrary, adults aged ≥ 30.0 years were mostly prescribed DFP (457/888, 51.46%).

Overall, majority of the patients (3715 out of 4928, 75.39%) were on single chelation therapy. There is an increase in number of patients from the older age groups who were prescribed with combination therapy, which peaked at the 20.0-24.9 years age group (330/4928 patients, 6.70%). However, the number started to reduce again in the groups of patients above 25.0 years old as more were prescribed single chelation therapy.

History of splenectomy

To date, splenectomy was performed on 1235 out of 8681 registered patients (14.23%). This is mainly in the older cohort, which did not undergo iron chelation therapy, to reduce their transfusion requirement.

The current trend is not to recommend splenectomy or defer it to selected cases as it may lead to more central nervous system (CNS) events and fulminant post-splenectomy sepsis.

Serum ferritin level

Patients were classified into five groups of serum ferritin level (in μg/L): ≤ 1000; 1000-2499; 2500-4999; 5000-9999; and ≥ 10000 (high-risk patients). In 2018, serum ferritin level was only reported for 3091 patients (38.71%). As the number of patients with reported serum ferritin level varies each year, the difference is best presented in percentage.

The percentage of patients with serum ferritin level ≤ 2499 μg/L was increasing and was most pronounced in the 1000-2499 μg/L group. On the contrary, the percentage started to reduce in the groups with serum ferritin level ≥ 5000 μg/L, which was most remarkable in the 5000-9999 μg/L group (Figure 4).

Deceased patients

There were 697 deaths recorded, of which 89 had incomplete data. The leading CoD among the 608 thalassaemia patients with verifiable data in Malaysia were cardiac failures (254 cases, 41.78%) and infections (232 cases, 38.16%). Other specified causes were motor vehicle accidents (18 cases, 2.96%), liver diseases (16, 2.63%), tumour and malignancies (15, 2.47%), endocrine complications (13, 2.14%), multiple organ dysfunction (7, 1.15%), surgical complications (7, 1.15%), thrombosis (6, 0.99%), CNS events (5, 0.82%) and other causes (35, 5.75%). The case records for

deaths with incomplete data were unavailable and may have been archived, leaving the details unrecorded in the registry.

Birth summary

Currently, the highest reported number of thalassaemia birth was in 2014 with 207 thalassaemia babies born. Sabah has recorded the highest number of reported thalassaemia babies born compared to others. Accessibility to antenatal diagnosis and family planning considerations are among the current challenges in reducing thalassaemia birth rate.

However, the exact number of births in the recent years might not represent the current birth rate. This is notable in the number of births from 2016 onwards, which declined from 105 (2016) to 70 (2017) and 3 (2018). Patients are only registered in the MTR after the manifestations of the disorder instead of on the year of birth. Thus, the recent years' data might only be fully updated in the future years.

DISCUSSION

This study highlights the current scenario of thalassaemia in Malaysia through the data obtained from MTR. The MTR congregates data on thalassaemia patients seeking treatment at participating government and university hospitals nationwide. Through the report, more comprehensive data on patient population, location, age groups, ethnicity and clinical diagnosis can be obtained. In addition, information on transfusion and chelation therapy outcomes obtained from MTR can be studied to monitor the efficacy of treatment. Indirectly, the data on the outcome of therapy can be used to help improve patient management.

Before and during the early development of MTR in 2007, researchers only estimated the prevalence of thalassaemia and other figures related to the disorder in Malaysia based on a small, single-centered population and previous reports. Reports were mainly focused on molecular characterisation of thalassaemia or evaluation of quality of life according to state, centre or ethnicity. Published reports did mention the significance of thalassaemia in a region, yet they lacked the exact figure of reported cases in the respective region where the study was conducted.[7, 8] Certain reports only referred to old data when estimating the thalassaemia carrier rate in Malaysia.[9-11] Other than that, other references used to describe the thalassaemia scenario in Malaysia include the Ministry of Health annual report[12] and news articles.[4]

The current estimate of the population of Malaysia is 32.4 million,[13] with Bumiputera (including Malay and indigenous people of Sabah and Sarawak, such as Kadazan-Dusun) comprising 69.1% of the entire population. This is followed by Chinese (23.0%), Indian (6.9%) and 'Others' (1.0%).[14] Patients of Indian ethnicity are low in this study as the Malaysian Indians' ancestors, who were mostly from South India, rarely presented with α- or β-thalassaemia.[10, 15-17]

Malay thalassaemia patients have a higher prevalence of HbE/β-thalassaemia. Point mutation at CD26, the β-globin gene mutation causing HbE disease, is commonly detected in Malaysian Malay patients during molecular characterisation.[10, 18] The highest proportion of HbE/β-thalassaemia in the current study were found in Selangor, Kuala Lumpur, Kelantan and Kedah. The plausible factors are due to centralisation of thalassaemia referral centre (in the case of Selangor and Kuala Lumpur), being close to the capital or centre of migration (Selangor in relation to

Kuala Lumpur) and being the border states (such as Kedah and Kelantan, which promotes interaction between the populations of Thailand and Peninsular Malaysia).

Beta-thalassaemia major is important, especially in the Kadazan-Dusuns due to the higher prevalence of Filipino β-thalassaemia deletion in the ethnicity.[15, 19] Comprising 24.5% out of the Bumiputera population,[20] the registered cases in the MTR signifies that a large proportion of Kadazan-Dusuns are affected by β-thalassaemia major.

On the other hand, HbH disease, which is commonly caused by the deletion of three α-globin genes (--/-α), is predominant in the Malaysian Chinese.[16, 17] Although single α-globin gene deletions like the $-\alpha^{3.7}$ rightward single α-globin gene deletion ($-\alpha^{3.7}/\alpha\alpha$) are also present in the Malays and Indians, the Southeast Asian double α-globin gene deletion ($--^{SEA}/\alpha\alpha$) that is common in the Malaysian Chinese is responsible for the development of this disease.[16]

Clinicians are encouraged to prescribe iron chelator monotherapy whenever possible unless the chelation is inadequate, or patients are not compliant. An example is non-compliance or intolerance towards DFO, which is administered subcutaneously for 8-12 hours,[21] leading to the change to oral chelators DFX or DFP. DFX is the more popular option in the current study as it can be prescribed to younger patients (minimum 2 years old, in the form of dispersible tablets, once daily) compared to DFP (6 years and older, in the form of tablets or capsule, three times daily).[21, 22] Older patients might have started off with DFP earlier before the approval of DFX in 2005[21] and might have been compliant with the treatment. Combination therapy, in

contrast, will only be initiated when intensive therapy is needed to overcome severe iron overload.

Iron chelation therapy in the current population shows positive impact in decreasing the serum ferritin level. Although high-risk patients with serum ferritin level above 10000 µg/L are still present, the decline in their numbers indicate improvement in patient management. Nevertheless, cardiac complications due to iron overload is still the leading CoD among thalassaemia patients. Thus, participating centres might need to improve on iron overload monitoring and chelation therapy, especially in high-risk patients. In addition, the assessment of ferritin level might not be specific, causing clinicians to move towards the use of magnetic resonance imaging (MRI) T2* to assess iron deposition in tissue.[23, 24] Nevertheless, the MRI T2* data collection for the MTR has not started.

Although MTR was able to gather most information on thalassaemia patients nationwide, certain records are still incomplete. Among the notable limitations in this report are records of serum ferritin level, death record and birth summary, as certain information might not be accessible, or the evaluation was not completed on the whole population. Data on thalassaemia births in 2017 and 2018, for instance, may only be captured after the patient presents the symptoms of thalassaemia. Laboratory data on serum ferritin, on the other hand, might not be recorded in the patient's notes and thus unavailable.

In addition, MTR is a dynamic database, where the number of reported cases might change rapidly through time. Thus, the figures might differ remarkably following

periodical update of the report. A clear cut-off point is needed every time a report is generated to identify the most updated version.

CONCLUSION

The MTR describes the current and evolving scenario of thalassaemia in Malaysia over the past decade. The landscape has changed dramatically where patients are now living past the second decade of life with improvement of patient management. Data gathered into MTR can also be used to understand the progression of the disorder and to improve the outcomes of treatment, monitor iron overload management, enhance preventive strategies and reduce healthcare burden.

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STATEMENT OF AUTHORS' CONTRIBUTION

HMI, ZM, ISO, MNMU, KHT, AT, KG, GBO, SLY, AMR, CHCMR, NDD, HA, ZAL, ARAJ, NM and HMA designed the study and provided intellectual input along with data validation for the report. All authors contributed to drafting, revising and final approval of the submitted manuscript.

All authors contributed equally to the development of this work. MediConnexions Consulting Sdn Bhd provided writing assistance.

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CONFLICT OF INTERESTS

The authors have no competing interests

PATIENT CONSENT

The study utilises secondary data from a database, thus no informed consent was required.

ETHICAL APPROVAL

This study has been approved by Medical Research and Ethics Committee, Ministry of Health Malaysia (National Medical Research Register ID: NMRR-17-2410-37653).

DATA AVAILABILITY STATEMENT

The data in this report were collected from the Malaysian Thalassaemia Registry. Any request to access the data must be made to the Ministry of Health, Malaysia.

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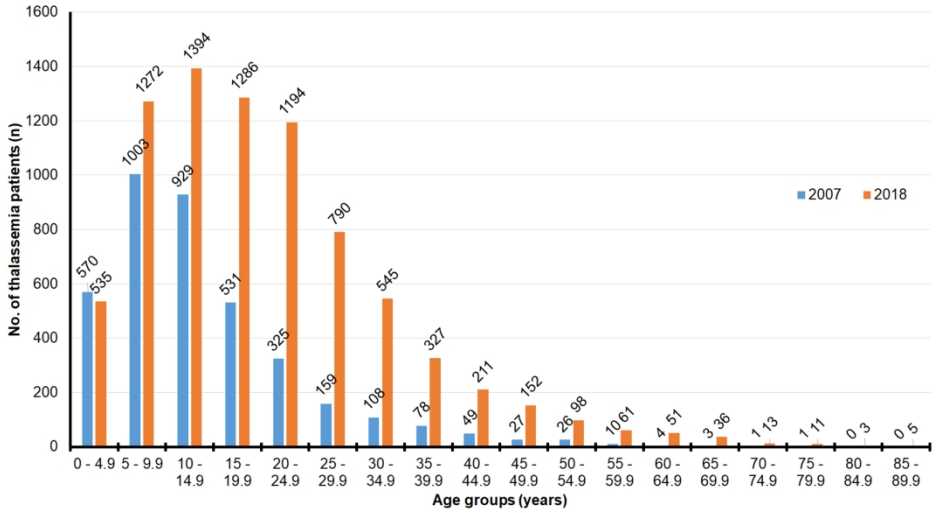
FIGURE LEGEND(S)

Figure 1 Comparison of survival trends of thalassaemia patients in Malaysia between the years 2007 and 2018. The survival trend of thalassaemia patient in Malaysia is currently shifting towards the right, indicating an increase in the number of patients aged 40 years and above.

Figure 2 Distribution of thalassaemia patients of four major ethnicities according to geographical region. The percentage was calculated against the total number of patients of these ethnicities (Malay, Chinese, Indian and Kadazan-Dusun) in each respective geographical region.

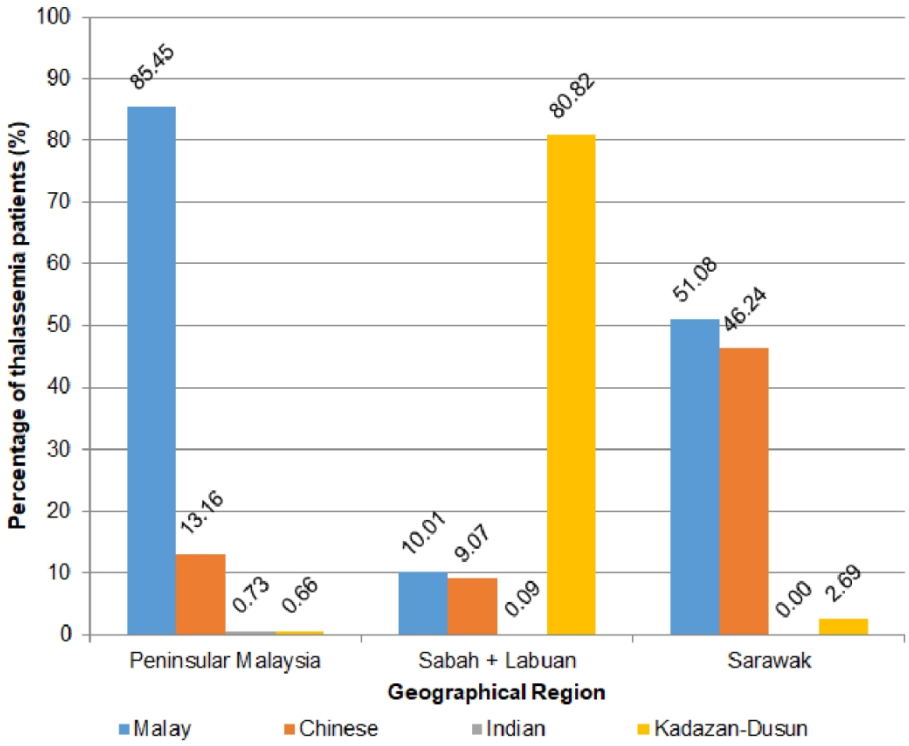
Figure 3 Percentage of clinical diagnosis of thalassaemia according to the major ethnic groups in Malaysia. The highest percentage of patients diagnosed with β-thalassaemia major, HbE/β-thalassaemia and HbH disease were found in the Kadazan-Dusun, Malay and Chinese ethnicities, respectively.

Figure 4 Reported serum ferritin level of regularly transfused thalassaemia patients in Malaysia (2007-2018). The number of patients with an acceptable level of serum ferritin (≤ 2499 µg/L) was increasing over time.



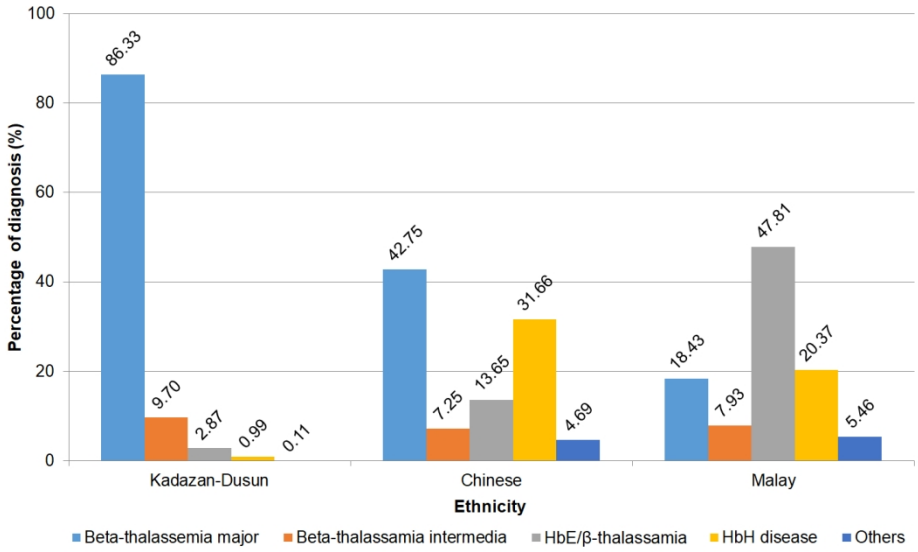
Comparison of survival trends of thalassaemia patients in Malaysia between the years 2007 and 2018. The survival trend of thalassaemia patient in Malaysia is currently shifting towards the right, indicating an increase in the number of patients aged 40 years and above.

320x184mm (300 x 300 DPI)



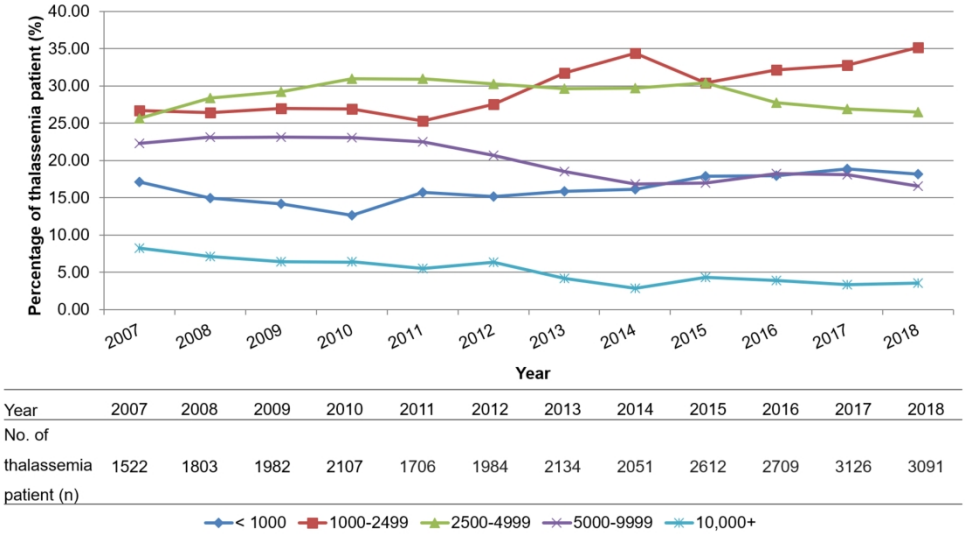
Distribution of thalassaemia patients of four major ethnicities according to geographical region. The percentage was calculated against the total number of patients of these ethnicities (Malay, Chinese, Indian and Kadazan-Dusun) in each respective geographical region.

120x97mm (300 x 300 DPI)



Percentage of clinical diagnosis of thalassaemia according to the major ethnic groups in Malaysia. The highest percentage of patients diagnosed with β-thalassaemia major, HbE/β-thalassaemia and HbH disease were found in the Kadazan-Dusun, Malay and Chinese ethnicities, respectively.

282x174mm (144 x 144 DPI)



Year	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
No. of thalassemia patient (n)	1522	1803	1982	2107	1706	1984	2134	2051	2612	2709	3126	3091

Reported serum ferritin level of regularly transfused thalassaemia patients in Malaysia (2007-2018). The number of patients with an acceptable level of serum ferritin (≤ 2499 µg/L) was increasing over time.

338x190mm (300 x 300 DPI)

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An observational study on the current status of thalassaemia in Malaysia: a report from the Malaysian Thalassaemia Registry

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An observational study on the current status of thalassaemia in Malaysia: a report from the Malaysian Thalassaemia Registry

Hishamshah Mohd Ibrahim[1,2], Zulaiha Muda[2], Ida Shahnaz Othman[2], Mohamed Najib Mohamed Unni[2], Kok Hoi Teh[2], Asohan Thevarajah[3], Kogilavani Gunasagaran[3], Gek Bee Ong[4], Seoh Leng Yeoh[5], Aisyah Muhammad Rivai[6], Che Hadibiah Che Mohd Razali[7], Nazzlin Dizana Din[8], Zarina Abdul Latiff[9], A Rahman A Jamal[9], Norsarwany Mohamad[10], Hany Mohd Ariffin[11], and Hamidah Alias*[9]

[1]Division for Research and Technical Support, Ministry of Health, Malaysia

[2]Department of Paediatrics, Hospital Tunku Azizah, Kuala Lumpur, Malaysia

[3]Department of Paediatrics, Sabah Women & Children Hospital, Likas, Kota Kinabalu, Sabah, Malaysia

[4]Department of Paediatrics, Hospital Umum Sarawak, Kuching, Sarawak, Malaysia

[5]Department of Paediatrics, Hospital Pulau Pinang, George Town, Pulau Pinang, Malaysia

[6]Department of Paediatrics, Hospital Raja Permaisuri Bainun, Ipoh, Perak, Malaysia

[7]Department of Paediatrics, Hospital Sultan Ismail, Johor Bahru, Johor, Malaysia

[8]Department of Paediatrics, Hospital Sultanah Nur Zahirah, Kuala Terengganu, Terengganu, Malaysia

[9]Department of Paediatrics, Hospital Canselor Tuanku Muhriz UKM, Cheras, Kuala Lumpur, Malaysia

[10]Department of Paediatrics, Hospital Universiti Sains Malaysia, Kubang Kerian, Kota Bharu, Kelantan, Malaysia

[11]Department of Paediatrics, University Malaya Medical Centre, Kuala Lumpur, Malaysia

Running Heads: Current Trend of Thalassaemia in Malaysia

***Corresponding Author**

Dr Hamidah Alias

Department of Paediatrics

Hospital Canselor Tuanku Muhriz,

The National University of Malaysia

56000 Cheras, Kuala Lumpur, Malaysia,

Tel: +603-91455396,

Email: midalias@ppukm.ukm.edu.my

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Abstract

Objective: Thalassaemia is the most common inherited blood disorder in Malaysia. This study aims to report the current status of thalassaemia in Malaysia and provide a comprehensive understanding of the disease through data obtained from the Malaysian Thalassaemia Registry.

Design: Data were extracted from the Malaysian Thalassaemia Registry, a web-based system accessible to enrolled users through www.mytalasemia.net.my.

Setting: The Malaysian Thalassaemia Registry data was recorded from reports obtained from 110 participating government and university hospitals in Malaysia.

Participants: The patients were those attending the 110 participating hospitals for thalassaemia treatment.

Intervention: Data was collected from the Malaysian Thalassaemia Registry from 2007 until the fourth quarter of 2018.

Primary Outcome Measure: 7984 out of 8681 thalassaemia patients registered in the Malaysian Thalassaemia Registry, were reported alive.

Results: Majority of the patients were reported in state Sabah (22.72%); the largest age group affected was 5.0-24.9 years old(64.45%); the largest ethnic group involved was Malay (63.95%); and the major diagnosis was haemoglobin E/β-thalassaemia (34.37%). From the 7984 patients, 56.72% were on regular blood transfusions and 61.72% were on chelation therapy. A small fraction (14.23%) has undergone splenectomy, while the percentage of patients with severe iron overload

(serum ferritin ≥ 5000 µg/L) reduced over time. However, cardiac complications are still the main cause of death in thalassaemia patients.

Conclusion: Data gathered into the registry can be used to understand the progression of the disorder, to monitor iron overload management and to improve the outcomes of treatment, to enhance preventive strategies, reduce healthcare burden and improve the quality of life. Sustainability of the MTR is important for surveillance of thalassaemia management in the country and help the national health authorities to develop more effective policies.

Keywords: Healthcare burden; thalassaemia; haemoglobinopathy; database; registry; Malaysia

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The Malaysian Thalassaemia Registry is the first online patient registry in Malaysia, which aggregates data from all participating hospitals and allows real-time data analysis.
- This is the largest nationwide report that describes the overall distribution, current disease status and the progress of management of thalassaemia patients in Malaysia.
- Some missing data in a few variables during data collection and non-participating centres that treat a small number of thalassaemia patients made this survey susceptible to reporting bias.
- Data presented describes the findings of study as at fourth quarter of the year 2018. Figures might differ at different time points due to the dynamic nature of the registry.

INTRODUCTION

Thalassaemia is one of the most common autosomal recessive disorders and is highly prevalent in countries within the tropical belt, including Malaysia.[1, 2] Current estimation shows that 6.8% of Malaysians are thalassaemia carriers who might be affected with various degrees of anaemia.[3] A thalassaemia carrier couple has a 25% chance of producing a thalassaemia major progeny.

Caused by a wide spectrum of point mutations and gene deletions, thalassaemia leads to a reduced or zero formation of the α- or β-globin chain sub-units of the adult haemoglobin (Hb) molecule.[3] The deficiency produces fragile erythrocytes and haemolytic anaemia. The affected babies will eventually develop progressively severe anaemia and require life-long blood transfusions to meet their daily physiological needs.[4] Iron chelation therapy must accompany the regular transfusions to reduce iron overload, allow normal growth and improve the survival rates of thalassaemia patients.[5, 6]

Although thalassaemia is the most common hereditary haematological disorder in Malaysia, information on nationwide geographic distribution of patients, socioeconomic and clinical data including treatment outcomes is still lacking. Due to concern over its public health burden on the country, the Malaysian Cabinet endorsed a national comprehensive thalassaemia programme on 25th August 2004, consisting of health education and population awareness drive, screening initiative, comprehensive clinical management and establishing a Malaysian Thalassaemia Registry (MTR). The registry was officially launched on 12th May 2007, an initiative to identify and collect detailed epidemiological and clinical data of thalassaemia

patients from all over the country who received treatment at government hospitals under the Ministry of Health (MOH) and university hospitals under the Ministry of Education. The registry is the first online patient registry in Malaysia featuring real-time data entry, facilitates update and data reporting, and allows enrolled users to observe the aggregated data at any point of time. The core data set of essential data elements was predefined by a team of experts including clinicians and the completeness and validity of data collection was ensured by joined cooperation between the company in charge and MOH, Malaysia. Site visits to ensure accuracy and completeness of the data were carried out by a team of research assistants appointed by the MOH and working in collaboration with the company. A regular internal audit for quality control of the MTR is performed by the company in charge. The web-based system is accessible to enrolled users through www.mytalasemia.net.my (MyTalasemia). It is user friendly and can be managed from different locations. The MTR demonstrates the value of a continuously updated registry for the surveillance of health services pertaining to thalassaemia in the country. Patient registries, which include usage of large set of data, have been reported to be helpful in mapping the functionalities and providing a positive return on investment.[7]

Herein, we report the data obtained from the MTR from 2007 to November 2018, unravelling the current trend of thalassaemia in Malaysia. This work provides a near comprehensive understanding of thalassaemia in Malaysia nationwide.

METHODS

The updated MTR included all patients diagnosed with thalassaemia from 2007 to November 2018 in 113 participating centres (110 government hospitals and three university hospitals), located in 13 states and three Federal Territories of Malaysia (Kuala Lumpur, Labuan and Putrajaya). The updated data from the registry was retrieved in November 2018 for analysis. This study utilised secondary data, involving data that have been gathered by the MOH for national census. The patients' data from diagnosis to last follow-up or death were retrospectively collected by research assistants in various regional centres in Malaysia. They were supervised and all data were verified by clinicians and then manually entered into the MyTalasemia system. All research assistants had centrally undergone training on data collection and recording onto the web-based system. The types of data collected were guided by the registry design. Data elements were grouped into several categories including socio-demography, clinical characteristics, laboratory test results, type of treatment received, death record and complications. Duplicate registration was prevented. The updated data were further verified and discussed centrally during the annual National Thalassaemia Meeting held in November.

In this report, the data was separated into two groups: 1) alive patients and 2) deceased patients. In the alive patient group the following variables were analysed: 1) demography (location, gender, age groups and ethnicity); 2) clinical diagnosis; 3) receipt of regular blood transfusions; 4) receipt of chelation therapy; 5) history of splenectomy; and 6) serum ferritin levels. In deceased patients, the causes of death were reported.

Results were presented as fractions and percentages over the total number of reported cases. For demographic characteristics of regions, age groups and

ethnicity, the fractions and percentages were calculated against the total number of reported cases in the respective groups.

This study has obtained the ethics approval from Medical Research and Ethics Committee, Ministry of Health Malaysia (National Medical Research Register ID: NMRR-17-2410-37653).

Patient and Public Involvement

This report was prepared without patients and public involvement. Patients and the public were not invited to comment on the database and study design or to contribute to the writing or editing of this report.

RESULTS

As of 28th November 2018, 8681 thalassaemia patients have been registered in the MTR. Out of 8681 patients, 7984 (91.97%) were reported to be alive and 130 of those alive (1.63%) were reported cured by stem cell transplantation. Another 614 patients (7.69%) were lost to follow-up. The remaining 697 patients (8.03%) had deceased.

Geography

The largest number of registered thalassaemia patients came from state Sabah (1814/7984 cases, 22.72%), followed by state Selangor (14.64%), Kedah (8.69%), Johor (7.98%) and Perak (7.06%). Figure 1 shows the map of Malaysia with the cumulative numbers of registered thalassaemia patients in each state of Peninsular Malaysia, Sabah and Sarawak.

The patient geographic distribution was also analysed based on regional division: Peninsular Malaysia (which includes 11 states and the Federal Territory of Kuala Lumpur and Putrajaya); Sabah (Sabah and the Federal Territory of Labuan); and Sarawak. Peninsular Malaysia recorded a 5922 (74.17%) registered patients, while Sabah and Sarawak had registered 1839 (23.03%) and 223 (2.79%) patients, respectively.

Hospital Ampang in state Selangor, recorded the highest number of patients (703, 8.81%) seen since the hospital serves as a referral centre for adult thalassaemia patients, including patients from the capital of Malaysia, Kuala Lumpur. Hospital Queen Elizabeth and Hospital Wanita dan Kanak-Kanak Likas, both located in Sabah, also recorded a high number of patients (370, (4.63%) and 300, (3.76%), respectively).

Gender

Gender distribution among the recorded thalassaemia patients was almost equal, with a male to female ratio of 49.60:50.40 (3960 versus 4024).

Age groups

Majority of the patients were in the group of 5.0-24.9 years of age (5146/7984 patients, 64.45%), and the largest number of patients were aged between 10.0-14.9 years (1394,17.46%). The number of patients decreased in the older age groups, from 790 patients (9.89%) in the 25.0-29.9 years age group to 5 patients (0.06%) in the 85.0-89.9 years age group. Figure 2 depicts the distribution of cumulative number of registered cases in year 2018 in the MTR according to age groups. Table

1 shows the distribution of registered cases according to age groups and the three main geographical regions in Malaysia.

Table 1 Summary of thalassaemia patient distribution according to three main geographical regions and age group

Distribution of patients according to region																			
Region	**Total no of patients (n)**	**Age group (year)**																	
		0.6-4.9	**5.0-9.9**	**10.0-14.9**	**15.0-19.9**	**20.0-24.9**	**25.0-29.9**	**30.0-34.9**	**35.0-39.9**	**40.0-44.9**	**45.0-49.9**	**50.0-54.9**	**55.0-59.9**	**60.0-64.9**	**65.0-69.9**	**70.0-74.9**	**75.0-79.9**	**80.0-84.9**	**85.0-89.9**
Peninsular Malaysia[a]	5922	351	859	962	923	906	636	444	277	192	133	83	59	44	26	10	9	3	5
Sabah[b]	1839	167	379	397	330	246	138	80	41	17	13	11	1	6	10	2	1	0	0
Sarawak[c]	223	17	34	35	33	42	16	21	9	2	6	4	1	1	0	1	1	0	0
TOTAL	7984	535	1272	1394	1286	1194	790	545	327	211	152	98	61	51	36	13	11	3	5

[a] Peninsular Malaysia region: Includes all states and Federal Territories, except the states of Sabah, Sarawak and the Federal Territory Labuan; [b] Sabah region: Combining the state of Sabah and the Federal Territory Labuan; [c] Sarawak region: The state of Sarawak.

Ethnicity

The majority of the registered thalassaemia patients were Malay (5106/7984, 63.95%), followed by Chinese (938, 11.75%) and Kadazan-Dusuns (907, 11.36%). Other specified ethnicities include Pribumi Sabah (213, 2.67%), Bajau (196, 2.45%), Murut (147, 1.84%), Rungus (112, 1.40%) and Indian (43, 0.54%). The remaining ethnicities such as Orang Asli, Thais, Iban, Bidayuh, Sino Kadazan and Melanau (322, 4.03%) are listed as 'Others', along with 68 patients from foreign countries.

Comparison was also made according to regional division. The data showed that the Malay made up 82.81% of registered patients in Peninsular Malaysia (4904/5922 patients). Patients in Sarawak, on the other hand, were mostly Malay (95/223, 42.60%) and Chinese (86/223, 38.57%), while patients in Sabah comprised mainly of Kadazan-Dusun (864/1839, 46.98%) and other Sabah's Indigenous (673/1839, 36.60%) (Figure 3).

Clinical diagnosis

Majority of the patients were diagnosed with haemoglobin E (HbE)/β-thalassaemia (2744/7984, 34.37%), followed by β-thalassaemia major (TM) (2676, 33.52%), haemoglobin H (HbH) disease (1458, 18.26%), β-thalassaemia intermedia (748, 9.37%) and 'others' (358, 4.48%). The 'others' group includes other forms of HbH disease, Hb Lepore Hollandia, α-thalassaemia syndrome, δβ-thalassaemia and other thalassaemia disorders requiring regular blood transfusions.

A pattern of clinical diagnosis can be observed in certain age groups and ethnicity. Of the total registered patients aged < 15.0 years old (3201 patients), 1186 were

diagnosed with TM (37.05%). Patients aged 25.0-44.9 years old were commonly reported with HbE/β-thalassaemia (707/1873, 37.75%), while patients aged ≥ 55.0 years old were commonly diagnosed with HbH disease (86/180, 47.78%). These observations were consistent with the presentation of the clinical diagnosis; TM presents early in life, the severity of HbE/β-thalassaemia ranges from mild to severe, while HbH disease is non-transfusion dependent thalassaemia (non-TDT) and patients are most likely to survive longer due to the lower risk of iron overload. Figure 2 shows the peak of patient distribution corresponds to the age group of 10-14.9 years for TM, 15-19.9 years for HbE/β-thalassaemia, and 10-14.9 years for HbH disease and β-thalassaemia intermedia, respectively.

In relation to ethnicity, HbE/β-thalassaemia patients were frequently reported among the Malay. 2441/5106 (47.81%) of Malay patients were diagnosed with HbE/β-thalassaemia and 2441/2744 (88.96%) of the HbE/β-thalassaemia were of Malay patients. TM was predominant in the Kadazan-Dusuns (783/907, 86.33%). Another interesting note is a high proportion of Chinese patients were diagnosed with HbH disease (297/938, 31.66%) in comparison to the other ethnicities.

Regular transfusion

4529 out of 7984 (56.73%) patients require regular blood transfusions. Regular blood transfusions is defined as requiring red blood cell transfusions biweekly or up to once every 12 weeks. The remaining patients were classified as non-TDT, which consists of patients who were on irregular blood transfusions (> 16 weeks intervals) or who had never needed transfusion therapy.

Chelation therapy

There was 4928 of 7984 patients (61.72%) on iron chelation therapy. The most common iron chelator monotherapy prescribed was deferasirox (DFX) (1645/4928 patients, 33.38%), followed by deferiprone (DFP) (1107, 22.46%) and desferrioxamine (DFO) (963, 19.54%). Combination therapies were prescribed for the remaining patients: DFO and DFP (910, 18.47%); DFO and DFX (169, 3.43%); DFP and DFX (92, 1.87%); and DFO, DFP and DFX (42, 0.85%).

Oral iron chelator, DFX was commonly prescribed for the young patients aged < 15.0 years old (1231/1836, 67.05%). Meanwhile oral DFP was commonly prescribed for the adult patients aged ≥ 30.0 years (457/888, 51.46%).

Overall, majority of the patients (3715/4928, 75.39%) were given single chelation therapy. There was a higher number of patients in the age group 20.0-24.9 years old (330/4928, 6.70%) who were prescribed combination therapy but patients above 25.0 years old were commonly prescribed single chelation therapy.

History of splenectomy

Splenectomy was performed in 1235 out of 8681 patients (14.23%). This was performed mainly in the older aged patients, who were not on iron chelation therapy or had chronic iron overload. Almost 80% of the splenectomy were carried out in those with TM (43.15%) and HbE/β-thalassaemia (41.78%), followed by thalassaemia intermedia and HbH disease (7.61%).

Serum ferritin levels

Data on ferritin levels were available for 3091 (38.71%) of the registered cases. As there were many missing data on ferritin levels despite multiple or serial results

entered for individual patients, the registry could only generate report on the most recent ferritin levels recorded for each patient. Overall, 562 (18.18%) patients had ferritin levels < 1000 µg/L; 1087 (35.17%) patients had ferritin levels between 1000-2499 µg/L; 820 (26.53%) patients had ferritin levels between 2500-4999 µg/L; 511 (16.53%) patients had ferritin levels between 5000-9999 µg/L; and 111 (3.59%) patients had ferritin levels ≥ 10000 µg/L.

Birth summary

The updated data on affected births was retrieved on 22nd April 2020 during the revision of the writing. This is to obtain the actual numbers of affected births from 2007-2018, due to the dynamic nature of the database and patients were only registered in the MTR after diagnosis was made instead of on the year of birth. The total number of affected births was 1483, 1048, and 214 during 2007-2011, 2012-2016, and 2017-2018, respectively (online Supplementary Table 1). Overall, we observed a declining trend of affected birth from year 2015 onwards and this could likely explain the decreasing trend of total new cases between year 2016 and 2018 (388, 277 and 102 new cases, respectively) given the clinical manifestation of TDT. The highest reported number of thalassaemia birth was in 2008 with 334 babies were born and Sabah had the highest number of affected births compared to other states. From 2014 to 2018 new thalassaemia birth declined steadily especially in Sabah and this could be associated with increased public awareness due to initiatives carried out by the government besides screening of secondary school children. The causes of affected birth were not delineated.

Deceased patients

There were 697 (8.03%) recorded deaths out of 8681 patients, of which 89 (12.77%) had incomplete data. Overall, 72.31% death occurred in TM and 16.64% death in HbE/β-thalassaemia patients. The main causes of death among the 608 thalassaemia patients with verifiable data were cardiac failures (254, 41.78%) and infections (232, 38.16%). Other causes were motor vehicle accidents (18, 2.96%), liver diseases (16, 2.63%), malignancy (15, 2.47%), endocrine complications (13, 2.14%), multiple organs dysfunction (7, 1.15%), surgical complications (7, 1.15%), thrombosis (6, 0.99%), central nervous system events (5, 0.82%) and others (35, 5.75%).

183 of 252 deaths (72.61%) from cardiac causes were patients aged between 15 years old and 29.9 years old – 69 cases (27.38%) aged 15-19.9 years old; 73 cases (28.97%) aged 20-24.9 years old; and 41 cases (16.27%) aged 25-29.9 years old. The majority of death from cardiac failures were observed among patients with TM (190/254, 74.80%) between 20-24.9 years of age followed by the 15-19.9 years of age group. The HbE/β-thalassaemia patients recorded 38 deaths out of 254 (14.96%) and a similar age group to TM. The majority of deaths was associated with chronic iron overload. Among the 96 TM deaths with recorded ferritin level, 38 (39.58%) of them had ferritin level of 5000-9999 µg/L and 43 (44.79%) of them had ferritin level of ≥ 10000 µg/L. For the HbE/β-thalassaemia deaths, 28 patients had recorded ferritin levels and 8 (28.57%) of the 28 deaths were associated with both ferritin levels of 5000-9999 µg/L and ≥ 10000 µg/L, respectively. Overall, more than 50% of the cardiac deaths were associated with severe chronic iron overload.

For infection deaths, 229 patients had complete data; the mean age of death was 22.0 years old (SD ± 12.06) and those in age group 15.0-19.9 years old contributed

to the highest mortality numbers (57/229, 24.90%), followed by patients aged between 20.0-24.9 years old (49/229, 21.40%) and patients in age group 25.0-29.9 years old (28/229, 12.22%). Most of the death occurred among patients with TM (155, 66.81%) followed by the HbE/β-thalassaemia (50, 21.55%). Again, the majority of death was associated with chronic iron overload. Among the 81 TM deaths with recorded ferritin level, 25 (30.86%) and 23 (28.40%) of them had ferritin level of 5000-9999 µg/L and ≥ 10000 µg/L, respectively. For the HbE/β-thalassaemia deaths, 40 patients had recorded ferritin levels and 19 (47.50%) of the 40 deaths were associated with ferritin levels of 5000-9999 µg/L and 9 (22.50%) deaths had ferritin levels ≥ 10000 µg/L. Overall, more than 50% of the infection deaths were associated with severe chronic iron overload. We were not able to capture the commonest organisms responsible for the fatal outcome as this was not documented in the death certificate. All causes of death were obtained from the death certificates and for infection mortality it was often written as septicaemia/sepsis or pneumonia only.

Only one patient had history of splenectomy in the infection death group. Four patients died from complications related to stem cell transplantation. The case records for deaths with incomplete data were unavailable and may have been archived.

DISCUSSION

This study highlights the current trend of thalassaemia in Malaysia through the data obtained from MTR. The MTR congregates data on thalassaemia patients seeking treatment at the participating government hospitals and university hospitals nationwide. Through the report, comprehensive data on patient population,

geographic locations, age groups, ethnicity and clinical diagnosis can be obtained. Furthermore, information on blood transfusions and chelation therapy outcomes obtained from the MTR can be studied to evaluate the efficacy of treatment received. The interpretation of treatment outcome data can be used to help improve patient management.

Before and during the early development of MTR in year 2007, local researchers could only estimate the prevalence of thalassaemia and other figures related to the disorder based on small, single-centered population or previous reports. The previous reports were mainly focused on molecular characterisation of thalassaemia or evaluation of quality of life outcome according to state, centre or ethnicity and did not include the actual figure of reported cases in the respective region where the study was conducted.[8, 9] Reports on estimated thalassaemia carrier rate in Malaysia only referred to old data[10-12] and the previous works describing the thalassaemia scenario in Malaysia had utilised data from the MOH annual report.[13]

The current estimate of the population of Malaysia is 32.6 million with Bumiputera (including Malay and indigenous people of Sabah and Sarawak, such as Kadazan-Dusun) comprising 69.1% of the entire population. This is followed by Chinese (23.0%), Indian (6.9%) and 'Others' (1.0%).[14] In this study, patients of Indian ethnicity are small in number as the Malaysian Indians' ancestors, who were mostly from South India, rarely presented with α- or β-thalassaemia.[11, 15-17]

Malay ethnicity has a higher prevalence of HbE/β-thalassaemia. A point mutation at CD26, the β-globin gene mutation causing HbE disease, is commonly detected in Malaysian Malay patients during molecular characterisation.[11, 18] The highest

proportion of HbE/β-thalassaemia patients in the current study were found in Selangor, Kuala Lumpur, Kelantan and Kedah. The plausible factors are due to centralisation of thalassaemia referral centre (in the case of hospitals in Selangor and Kuala Lumpur), being close to the capital or centre of migration (Selangor in relation to Kuala Lumpur as capital of Malaysia) and being the border states (Kedah and Kelantan, which promotes interaction between the populations of Thailand and Peninsular Malaysia).

TM is more common in the Kadazan-Dusuns ethnicity in Sabah due to a higher prevalence of Filipino β-thalassaemia deletion in the ethnicity.[15, 19] Comprising 24.5% out of the Bumiputera population,[20] the registered cases in the MTR signifies that a large proportion of Kadazan-Dusuns are affected by TM.

HbH disease, which is commonly caused by the deletion of three α-globin genes (--/-α), is predominant in the Malaysian Chinese.[16, 17] Although a single α-globin gene deletion like the $-\alpha^{3.7}$ rightward single α-globin gene deletion ($-\alpha^{3.7}/\alpha\alpha$) are also present in the Malays and Indians, the Southeast Asian double α-globin gene deletion ($--^{SEA}/\alpha\alpha$) that is common in the Malaysian Chinese is responsible for the clinical manifestation of the disease.[16]

In all registered patients, serum ferritin levels have been traditionally used for monitoring iron overload. In general, we observed a remarkable improvement in the trend of ferritin levels during the 12 years. The percentage of patients with ferritin levels of ≤ 2499 µg/L has increased and was pronounced in the 1000-2499 µg/L group (from 406/1522 (26.68%) in 2007 to 1087/3091 (35.17%) in 2018) and the percentage of those with ferritin levels of ≥ 5000 µg/L has declined, which was most

remarkable in the 5000-9999 µg/L group (339/1522 (22.27%) in 2007 to 511/3091 (16.53%) in 2018) (Figure 4). The single measurement of ferritin levels reported here has limitation in overall interpretation of iron overload in the patients as the readings could be affected by inflammatory conditions. However, we believe that the overall report helps us to understand the status of management of iron overload in our patients over the years to enable planning for better monitoring.

In our report, 62% of TDT patients were on iron chelation therapy. Importantly, 61.7% of our patients had an iron overload of between 1000 and 4999 µg/L. Approximately 3.6% of our patients had very high levels of ferritin of ≥ 10000 µg/L and about 16% of the patients had ferritin levels of 5000-9999 µg/L, which underlines the need for optimisation of chelation therapy.

Early initiation of chelation therapy and close monitoring is paramount to prevent complications from iron overload. Here, clinicians are encouraged to prescribe iron chelator monotherapy whenever possible unless the chelation regime is inadequate to control the iron overload or patients are not compliant including intolerance towards subcutaneous infusion DFO of 8-12 hours.[21]. In such situations this could lead to a change from subcutaneous DFO to oral chelator DFX or DFP or a combination therapy. Oral chelator DFX, a dispersible tablet taken once daily is the preferred option observed in the current study as it is more feasible in younger patients as young as 2 years old compared to oral DFP, a tablet or capsule, taken 3 times daily.[21, 22]. In the analysis, the older patients were more likely have been started on DFP before the approval of DFX use in Malaysia in year 2005,[21] and then continue with the same medication. A combination therapy is usually initiated when intensive therapy is needed to overcome severe iron overload. Improvement in

management of iron overload and improved compliance to iron chelators especially the oral preparations could likely explain for the declined levels of serum ferritin observed in the past few years. The oral DFX monotherapy was mainly prescribed to the young patients and oral DFP was given to the adult patients. Overall, the above findings of ferritin levels trend should be interpreted with caution as cardiac complications due to iron overload is still the leading cause of death among the thalassaemia patients. Furthermore, the age groups with high mortality are rather young compared to other registry reports.[23] Other complications like endocrine dysfunction were not specifically recorded in the MTR. However, hypogonadism was found to occur in 22%[24] of young adults and adults with TDT and short stature has also been reported.[25, 26] Thus, intensification of chelation therapy, improvement on monitoring of iron overload, and compliance to chelation therapy is needed in all patients.

In recent years, the government started investing in magnetic resonance imaging (MRI) T2* sequence, to evaluate and monitor myocardial iron concentration specifically. Radiologists were trained and the service can be accessed in a few regions in the country. Clinicians managing TDT are now able to access MRI T2* for active surveillance of iron overload and this will help them to optimise chelation therapy for their patients.[27, 28] However, the MRI T2* data collection for the MTR has not started and the feasibility of entering the findings into the registry is underway.

Prevention of affected births is a challenge in Malaysia. To date, prenatal screening of thalassaemia is still very low although it can be conducted upon request and the cost is covered by the national health system if conducted in the government

hospitals. Despite multiple meetings and forums with medical and religious experts, which have been conducted since 2004, a policy on prenatal screening and diagnosis is yet to be developed. The multiethnic cultures and religions practised in the country play a huge role in prenatal diagnosis and therapeutic abortion. In a local study, majority of the study respondents were open to prenatal diagnosis, but less than one-third agreed to performing both prenatal diagnosis followed by termination of affected foetuses. More than 75% of those declining claimed that religious restriction is the main reason.[29] Accessibility to prenatal diagnosis in some regions and family planning consideration are also among the contributing factors.

In Malaysia, therapeutic abortion is permitted based on The Penal Code (Amendment) Act 1989 (Act A727), which allows abortion within 120 days of conception only if the continued pregnancy poses a greater threat to the mother's life or to her physical or mental health than would the termination of the pregnancy. Although this can affect the incidence of new TM cases, the current overall trend of affected births and newly diagnosed TDT cases suggests that the public awareness initiatives by MOH have given positive outcomes. Initiatives such as offering free early population screening, periodical health education and public awareness have helped to identify carriers and increased awareness on the risk of giving birth to a thalassaemic child. However, there were public concerns related to creating anxiety and stigmatising youth who are affected.

Overall, when we look at the trend of declining numbers of yearly new cases especially from 2015 onwards, we believe that continuous health education, public awareness programme and improved management of the thalassaemic in Malaysia over the last 10 years have provided positive return on the investment.

Although the MTR is able to identify and collect most of the important information on thalassaemia patients nationwide, certain records are still incomplete. A limitation of the MTR report may pertain to the missing data in several variables of the total number of registered patients; serum ferritin levels, MRI T2* findings, end organs complication, causes of death and birth summary, as some details were not accessible or not recorded in the patients' notes. Furthermore, as the MTR is a dynamic, real-time web system, the numbers of reported cases change through time hence the figures might differ following periodical update of the report. For instance, the total number of affected births in year 2017 or 2018, may only be captured when the patients present with symptoms related to thalassaemia later than the year of birth. Therefore, a definite cut-off point is needed each time a report is generated to ensure the most updated data is presented.

CONCLUSION

The MTR has successfully demonstrated the time trends and most recent update of thalassaemia patients in Malaysia over the past decade. We observed the disease landscape has changed significantly where many patients are now living past the second decade of life with improvement in patient management and quality of life. The continuously updated data entered into the MTR contributes to revealing the current disease status and to understand the progress of thalassaemia in Malaysia. Sustainability of the MTR is challenging as its maintenance requires ongoing support from the government, policy makers, research funding bodies and clinicians, however it provides a positive return on investment. It enables local health authorities and health providers to plan cost efficient services, improve treatment

outcomes, enhance preventive strategies, reduce healthcare burden and ultimately improve the quality of life of thalassaemia patients.

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STATEMENT OF AUTHORS' CONTRIBUTION

HMI, ZM, ISO, MNMU, KHT, AT, KG, GBO, SLY, AMR, CHCMR, NDD, ZAL, ARAJ, NM, HMA, and HA designed the study and provided intellectual input along with data validation for the report. All authors contributed to development and drafting of the work. HMI and HA revised, edited and made significant contributions to the final manuscript. All authors read and approved the final manuscript.

MediConnexions Consulting Sdn Bhd provided writing assistance.

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CONFLICT OF INTERESTS

The authors have no competing interests

PATIENT CONSENT

The study utilises secondary data from a database, thus no informed consent was required.

ETHICAL APPROVAL

This study has been approved by Medical Research and Ethics Committee, Ministry of Health Malaysia (National Medical Research Register ID: NMRR-17-2410-37653).

DATA AVAILABILITY STATEMENT

The data in this report were collected from the Malaysian Thalassaemia Registry. Data are available upon reasonable request. Any request to access the data must be made to the Ministry of Health, Malaysia.

WORD COUNT

4383 words

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FIGURE LEGEND(S)

Figure 1 Cumulative numbers of registered thalassaemia patients in each state of Malaysia.

Figure 2 Distribution of cumulative number of registered cases in year 2018 in the Malaysian Thalassaemia Registry (MTR) according to age groups.

Figure 3 Percentage of thalassaemia patients according to ethnicities and geographical region. The percentage was calculated against the total number of patients in each respective geographical region. 'Other Sabah's Indigenous' includes Pribumi Sabah, Bajau, Murut, Rungus and Sino Kadazan; 'Sarawak's Indigenous' includes Pribumi Sarawak, Iban, Bidayuh and Melanau; and 'Others' includes Orang Asli, Thais, mixed ethnicities, foreigners and other ethnicities.

Figure 4 Serum ferritin levels of regularly transfused thalassaemia patients between 2007 and 2018. The number of patients with ferritin level of ≤ 2499 µg/L have increased over time.

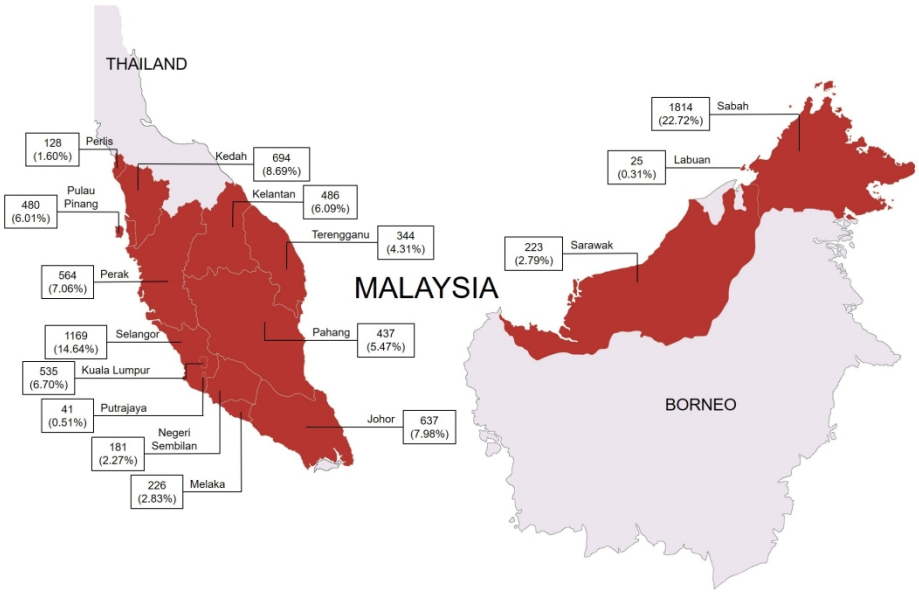

Figure 1 Cumulative numbers of registered thalassaemia patients in each state of Malaysia.

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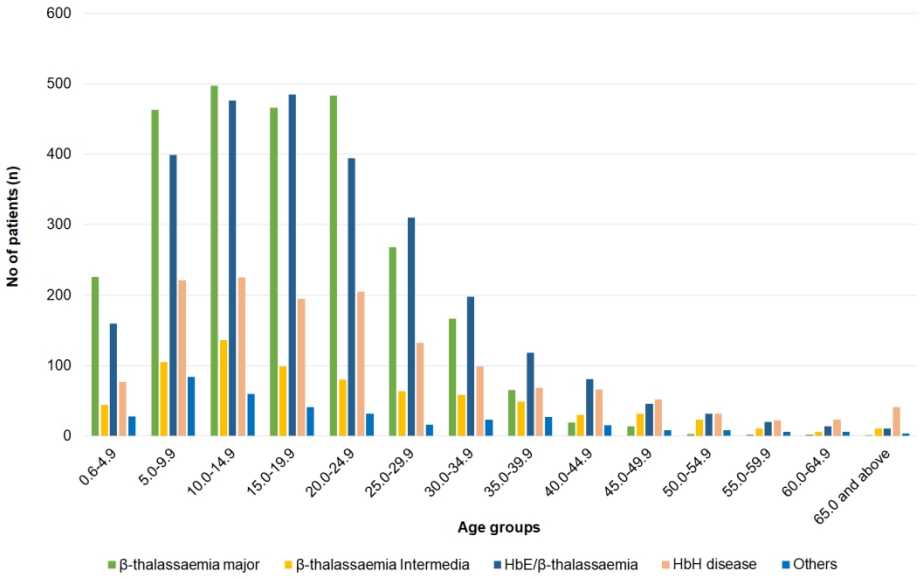

Figure 2 Distribution of cumulative number of registered cases in year 2018 in the Malaysian Thalassaemia Registry (MTR) according to age groups.

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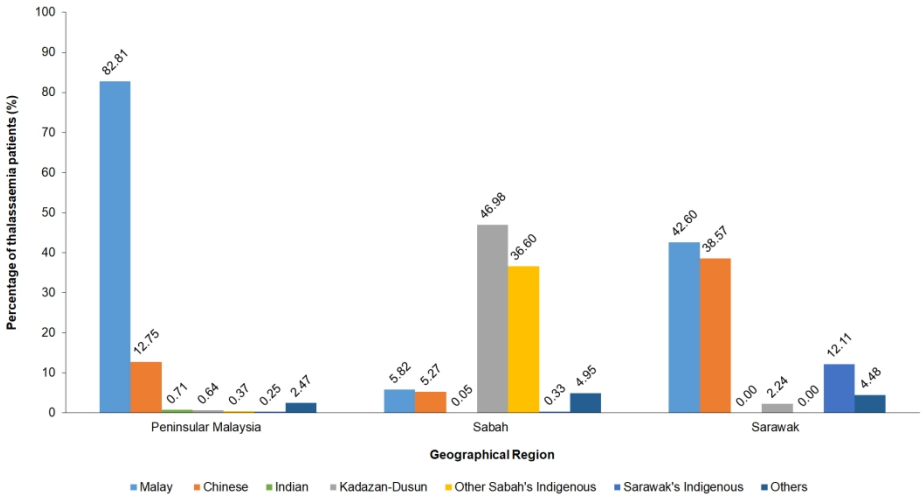

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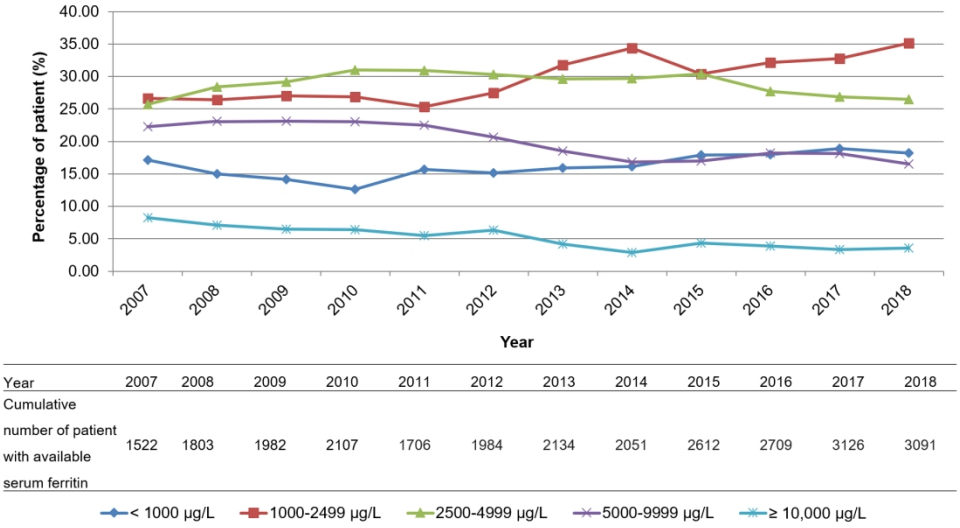
183x105mm (300 x 300 DPI)



Year	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Cumulative number of patient with available serum ferritin	1522	1803	1982	2107	1706	1984	2134	2051	2612	2709	3126	3091

Figure 4 Serum ferritin levels of regularly transfused thalassaemia patients between 2007 and 2018. The number of patients with ferritin level of ≤ 2499 µg/L have increased over time.

170x97mm (300 x 300 DPI)

Ibrahim et al Online Supplementary Data

Supplementary Table 1: Total number of new thalassaemia cases and total number of affected births per year from 2007 to 2018

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Total new cases/year[a]	N/A[b]	459	468	378	383	426	413	419	412	388	277	102
Total number of affected births/year	297	334	298	282	272	265	251	245	195	142	140	74

[a] Total new cases per year is generated by subtracting the total number of patients from each year with the previous year. E.g New case 2008 = total patients 2008 – total patients 2007.

[b] N/A – not available. The total new cases per year for 2007 could not be determined as there are no reference number of cases for 2006.