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# BMJ Open

## The current scenario of thalassaemia in Malaysia through the Malaysian Thalassaemia Registry

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3 **1 The current scenario of thalassaemia in Malaysia through the Malaysian**  
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5 **2 Thalassaemia Registry**  
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14 25 **Running Heads:** Current Scenario of Thalassaemia in Malaysia  
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3 34 **Abstract**  
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6 35 **Objective:** This study aims to report the data obtained from the Malaysian  
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9 36 Thalassaemia Registry and use it to describe the current scenario and provide a  
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11 37 comprehensive understanding of thalassaemia in Malaysia.  
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14 38 **Design:** Data were extracted from the Malaysian Thalassaemia Registry, a web-  
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17 39 based system accessible to enrolled users through [www.mytalasemia.net.my](http://www.mytalasemia.net.my).  
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20 40 **Setting:** The Malaysian Thalassaemia Registry data was recorded from reports  
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23 41 obtained from 110 participating government and university hospitals in Malaysia.  
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26 42 **Participants:** The patients were those attending the 110 participating hospitals for  
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29 43 thalassaemia treatment.  
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32 44 **Intervention:** Data was collected from the Malaysian Thalassaemia Registry from  
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35 45 2007 until the fourth quarter of 2018.  
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38 46 **Primary Outcome Measure:** Out of 8681 thalassaemia patients registered in the  
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41 47 Malaysian Thalassaemia Registry, 7984 were reported still alive.  
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44 48 **Results:** From the registry, most of the patients were reported in Sabah (22.72%);  
45  
46 49 the largest age group was 5.0-24.9 years (64.45%); the largest ethnic group was  
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48 50 Malay (63.95%); and the major diagnosis was haemoglobin E/ $\beta$ -thalassaemia  
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50 51 (34.37%). From the 7984 patients, only 56.72% were on regular transfusion and  
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53 52 61.72% were on chelation therapy. A small fraction (14.23%) has undergone  
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55 53 splenectomy, while the percentage of high-risk patients (serum ferritin  $\geq$  5000  $\mu\text{g/L}$ )  
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3 54 is reducing. However, cardiac complications are still the main cause of death in  
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5 55 thalassaemia patients.  
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9 56 **Conclusion:** Data gathered into the registry can be used to understand the  
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11 57 progression of the disorder and to improve the outcomes of treatment, monitor iron  
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13 58 overload management, enhance preventive strategies and reduce healthcare  
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16 59 burden.  
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19 60 **Keywords:** Healthcare burden; Iron chelation therapy; Iron overload management;  
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21 61 Thalassaemia cause of death; Thalassaemia serum ferritin  
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## 63 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

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

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## 76 INTRODUCTION

77 Thalassaemia is one of the most common autosomal recessive disorders and is  
78 highly prevalent in countries within the tropical belt including Malaysia.[1, 2] Current  
79 estimation shows that 6.8% of Malaysians are thalassaemia carriers who might be  
80 affected with various degrees of anaemia.[3] A thalassaemia carrier couple has a  
81 25% chance of producing a thalassaemia major progeny.

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

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

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3 99 featuring real-time data analysis in Malaysia, which allows enrolled users to observe  
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5 100 the aggregated data at any point of time.  
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9 101 The registry records updated patients' information including their socio-  
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11 102 demographical data, clinical records, treatments received, death records and  
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13 103 complications. It is a web-based system accessible to enrolled users through  
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15 104 www.mytalasemia.net.my (MyTalasemia). MTR collects data from 110 participating  
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17 105 government hospitals and three university hospitals located in 13 states and three  
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19 106 Federal Territories of Malaysia: Kuala Lumpur, Labuan and Putrajaya.  
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24 107 In this article, we aim to report the data obtained from the MTR and use it to describe  
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26 108 the current scenario and provide a comprehensive understanding of thalassaemia in  
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28 109 Malaysia involving a bigger population.  
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## 31 32 110 **METHODS** 33 34

35 111 This study utilised secondary data from the MTR, combining retrospective data (data  
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37 112 of all thalassaemia patients enrolled from 2007 obtained from the registry up to current  
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39 113 date) and prospective data (including patients' follow-up up to November 2018).  
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43 114 The data were collected by research assistants in various regional centres, supervised  
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45 115 and verified by clinicians and then manually recorded into MyTalasemia. The types of  
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47 116 data to be collected were guided by the registry's design. Data elements can be  
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49 117 grouped into several categories including socio-demography, clinical characteristics,  
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51 118 laboratory test results, type of treatment received, death record and other  
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53 119 complications of thalassaemia patients. The data were further verified and discussed  
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55 120 centrally during the annual National Thalassaemia Meeting.  
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3 121 In this report, the data was first separated into two groups: 1) surviving and 2)  
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5 122 deceased patients. The surviving patients were analysed according to 1)  
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7 123 demography (location, gender, age groups and ethnicity), 2) clinical diagnosis, 3)  
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9 124 receipt of regular transfusion, 4) receipt of chelation therapy, 5) history of  
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11 125 splenectomy and 6) serum ferritin level. In deceased patients, the cause of death  
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13 126 (CoD) was also reported.  
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18 127 Results were presented as fractions and percentages over the total number of  
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20 128 reported cases. For sections involving sub-groups (i.e. regions, age groups and  
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22 129 ethnicity), the fractions and percentages were calculated against the total number of  
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24 130 reported cases in the respective sub-groups.  
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28 131 This study has obtained the ethics approval from Medical Research and Ethics  
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30 132 Committee, Ministry of Health Malaysia (National Medical Research Register ID:  
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32 133 NMRR-17-2410-37653).  
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### 36 134 **Patient and Public Involvement**

  
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40 135 This report was prepared without patient and public involvement. Patients and the  
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42 136 public were not invited to comment on the database and study design or to  
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44 137 contribute to the writing or editing of this report.  
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## 48 138 **RESULTS**

  
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51 139 As of 28<sup>th</sup> November 2018, 8681 thalassaemia patients have been registered in the  
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53 140 MTR. Only 7984 patients were reported still alive; of these, 130 were reported cured  
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55 141 by stem cell transplant and another 614 were lost to follow-up. The remaining 697  
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57 142 patients were reported as deceased.  
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## 143 **Location**

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

147 The patient distribution was also analysed based on regional division: Peninsular  
148 Malaysia (which includes all states and Federal Territories except for Sabah,  
149 Sarawak and Labuan), Sabah (combining Sabah and Labuan) and Sarawak.

150 Peninsular Malaysia recorded 5922 registered patients (74.17%), while Sabah and  
151 Sarawak have registered 1839 (23.03%) and 223 (2.79%) patients, respectively.

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

## 157 **Gender**

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

## 160 **Age groups**

161 Majority of the patients were of 5.0-24.9 years of age (5146/7984 patients,  
162 collectively, 64.45%), with the largest population being patients aged between 10.0-  
163 14.9 years (17.46%). The number of patients decreased steadily in the subsequent

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3 164 age groups, from 790 patients in the 25.0-29.9 years age group to 5 patients in the  
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5 165 85.0-89.9 years age group.  
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9 166 With the passage of time, there is a change in the survival trend of thalassaemia  
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11 167 patients. The registry showed an increasing number of patients aged  $\geq 40.0$  years,  
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13 168 showing that the survival graph is currently shifting to the right (Figure 1). The  
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15 169 survival shift was more distinguishable in Peninsular Malaysia. This is generally true  
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17 170 for the more affluent states here that have better access to treatment regime  
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19 171 compared to Sabah and Sarawak regions. Table 1 summarises the findings on  
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21 172 location, region and age groups of the patients.  
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174 **Table 1** Summary of thalassaemia patient distribution according to state, region and age group

| <b>Distribution of patient according to state</b> |              |              |              |              |              |                 |              |  |  |  |  |  |  |  |  |  |  |  |  |
|---|--------------|--------------|--------------|--------------|--------------|-----------------|--------------|--|--|--|--|--|--|--|--|--|--|--|--|
| <b>State</b>                                      | <b>n (%)</b> | <b>State</b> | <b>n (%)</b> | <b>State</b> | <b>n (%)</b> | <b>State</b>    | <b>n (%)</b> |  |  |  |  |  |  |  |  |  |  |  |  |
| 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)    |  |  |  |  |  |  |  |  |  |  |  |  |

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

175 <sup>a</sup> Peninsular Malaysia region: Including all states and Federal Territories, except for the states of Sabah and Sarawak and the Federal Territory  
 176 of Labuan; <sup>b</sup> Sabah region: Combining the state of Sabah and the Federal Territory of Labuan; <sup>c</sup> Sarawak region: The state of Sarawak.

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## 178 **Ethnicity**

179 The majority of thalassaemia patients were Malays (5106/7984, 63.95%), followed  
180 by Chinese (938, 11.75%) and Kadazan-Dusuns (907, 11.36%). Other specified  
181 ethnicities include Pribumi Sabah (213, 2.67%), Bajau (196, 2.45%), Murut (147,  
182 1.84%), Rungus (112, 1.40%) and Indian (43, 0.54%). The remaining ethnicities  
183 such as Orang Asli, Thais, Iban, Bidayuh, Sino Kadazan and Melanau (322, 4.03%)  
184 are listed as 'Others', along with 68 patients from foreign countries.

185 Comparison was also made according to regional division, focusing on the four  
186 major ethnicities (Malay, Chinese, Indian and Kadazan-Dusun). Data showed that  
187 the Malays made up 85.45% of registered patients from these important ethnicities in  
188 Peninsular Malaysia (4904 out of 5739 patients). Patients in Sarawak, on the other  
189 hand, were mostly Malays (95/186, 51.08%) and Chinese (86/186, 46.24%).  
190 Conversely, patients in Sabah comprised mainly of Kadazan-Dusun patients  
191 (864/1069, 80.82%) instead (Figure 2).

## 192 **Clinical diagnosis**

193 Majority of the patients were diagnosed as haemoglobin E (HbE)/ $\beta$ -thalassaemia  
194 (2744/7984, 34.37%), followed by  $\beta$ -thalassaemia major (2676, 33.52%),  
195 haemoglobin H (HbH) disease (1458, 18.26%),  $\beta$ -thalassaemia intermedia (748,  
196 9.37%) and 'Others' (358, 4.48%). The 'Others' group includes other forms of HbH  
197 disease, Hb Lepore Hollandia,  $\alpha$ -thalassaemia syndrome,  $\delta\beta$ -thalassaemia and other  
198 thalassaemia disorders requiring regular packed cell transfusion.



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3 199 Patterns can be observed in age groups and ethnicity. Patients aged < 15.0 years  
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6 200 were commonly reported with  $\beta$ -thalassaemia major (1186/3201 cases collectively,  
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8 201 37.05%). On the other hand, patients aged 25.0-44.9 years were commonly reported  
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10 202 with HbE/ $\beta$ -thalassaemia (707/1873, 37.75%), while patients aged  $\geq$  55.0 years were  
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12 203 commonly diagnosed with HbH disease (86/180, 47.78%). These observations were  
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14 204 consistent with the presentation of the clinical diagnoses. Beta-thalassaemia major  
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16 205 symptoms would present early in life and are mostly transfusion dependent, which  
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18 206 affects their survival in the later decades of life. The severity of HbE/ $\beta$ -thalassaemia  
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20 207 broadly ranges from mild to severe. HbH disease, on the other hand, is non-  
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22 208 transfusion dependent thalassaemia and patients might survive longer due to the  
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24 209 lower risk of iron overload.

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30 210 In relation to ethnicity, HbE/ $\beta$ -thalassaemia was frequently reported in Malay patients  
31  
32 211 (2441 patients, 47.81% of 5106 Malay patients and 88.96% of 2744 HbE/ $\beta$ -  
33  
34 212 thalassaemia cases), while  $\beta$ -thalassaemia major was predominant in the Kadazan-  
35  
36 213 Dusuns (783/907, 86.33%). Another interesting note is that there was a high  
37  
38 214 proportion of Chinese patients diagnosed with HbH disease (297/938, 31.66%) in  
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40 215 comparison to the other ethnicities (Figure 3).

### 216 **Regular transfusion**

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

## 222 **Chelation therapy**

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

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

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

## 238 **History of splenectomy**

239 To date, splenectomy was performed on 1235 out of 8681 registered patients  
240 (14.23%). This is mainly in the older cohort, which did not undergo iron chelation  
241 therapy, to reduce their transfusion requirement.

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3 242 The current trend is not to recommend splenectomy or defer it to selected cases as it  
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5 243 may lead to more central nervous system (CNS) events and fulminant post-  
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7 244 splenectomy sepsis.  
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### 10 11 245 **Serum ferritin level** 12 13

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15 246 Patients were classified into five groups of serum ferritin level (in  $\mu\text{g/L}$ ):  $\leq 1000$ ;  
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17 247  $1000-2499$ ;  $2500-4999$ ;  $5000-9999$ ; and  $\geq 10000$  (high-risk patients). In 2018, serum  
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19 248 ferritin level was only reported for 3091 patients (38.71%). As the number of patients  
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21 249 with reported serum ferritin level varies each year, the difference is best presented in  
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23 250 percentage.  
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28 251 The percentage of patients with serum ferritin level  $\leq 2499 \mu\text{g/L}$  was increasing and  
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30 252 was most pronounced in the  $1000-2499 \mu\text{g/L}$  group. On the contrary, the percentage  
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32 253 started to reduce in the groups with serum ferritin level  $\geq 5000 \mu\text{g/L}$ , which was most  
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34 254 remarkable in the  $5000-9999 \mu\text{g/L}$  group (Figure 4).  
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### 38 255 **Deceased patients** 39 40

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42 256 There were 697 deaths recorded, of which 89 had incomplete data. The leading CoD  
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44 257 among the 608 thalassaemia patients with verifiable data in Malaysia were cardiac  
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46 258 failures (254 cases, 41.78%) and infections (232 cases, 38.16%). Other specified  
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48 259 causes were motor vehicle accidents (18 cases, 2.96%), liver diseases (16, 2.63%),  
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50 260 tumour and malignancies (15, 2.47%), endocrine complications (13, 2.14%), multiple  
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52 261 organ dysfunction (7, 1.15%), surgical complications (7, 1.15%), thrombosis (6,  
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54 262 0.99%), CNS events (5, 0.82%) and other causes (35, 5.75%). The case records for  
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3 263 deaths with incomplete data were unavailable and may have been archived, leaving  
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5 264 the details unrecorded in the registry.  
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9 265 **Birth summary**

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12 266 Currently, the highest reported number of thalassaemia birth was in 2014 with 207  
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14 267 thalassaemia babies born. Sabah has recorded the highest number of reported  
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16 268 thalassaemia babies born compared to others. Accessibility to antenatal diagnosis  
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18 269 and family planning considerations are among the current challenges in reducing  
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20 270 thalassaemia birth rate.  
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25 271 However, the exact number of births in the recent years might not represent the  
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27 272 current birth rate. This is notable in the number of births from 2016 onwards, which  
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29 273 declined from 105 (2016) to 70 (2017) and 3 (2018). Patients are only registered in  
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31 274 the MTR after the manifestations of the disorder instead of on the year of birth. Thus,  
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33 275 the recent years' data might only be fully updated in the future years.  
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38 276 **DISCUSSION**

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41 277 This study highlights the current scenario of thalassaemia in Malaysia through the  
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43 278 data obtained from MTR. The MTR congregates data on thalassaemia patients  
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45 279 seeking treatment at participating government and university hospitals nationwide.  
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47 280 Through the report, more comprehensive data on patient population, location, age  
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49 281 groups, ethnicity and clinical diagnosis can be obtained. In addition, information on  
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51 282 transfusion and chelation therapy outcomes obtained from MTR can be studied to  
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53 283 monitor the efficacy of treatment. Indirectly, the data on the outcome of therapy can  
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55 284 be used to help improve patient management.  
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3 285 Before and during the early development of MTR in 2007, researchers only  
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5 286 estimated the prevalence of thalassaemia and other figures related to the disorder in  
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7 287 Malaysia based on a small, single-centered population and previous reports. Reports  
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9 288 were mainly focused on molecular characterisation of thalassaemia or evaluation of  
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11 289 quality of life according to state, centre or ethnicity. Published reports did mention  
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13 290 the significance of thalassaemia in a region, yet they lacked the exact figure of  
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15 291 reported cases in the respective region where the study was conducted.[7, 8] Certain  
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17 292 reports only referred to old data when estimating the thalassaemia carrier rate in  
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19 293 Malaysia.[9-11] Other than that, other references used to describe the thalassaemia  
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21 294 scenario in Malaysia include the Ministry of Health annual report[12] and news  
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23 295 articles.[4]

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29 296 The current estimate of the population of Malaysia is 32.4 million,[13] with  
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31 297 Bumiputera (including Malay and indigenous people of Sabah and Sarawak, such as  
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33 298 Kadazan-Dusun) comprising 69.1% of the entire population. This is followed by  
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35 299 Chinese (23.0%), Indian (6.9%) and 'Others' (1.0%).[14] Patients of Indian ethnicity  
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37 300 are low in this study as the Malaysian Indians' ancestors, who were mostly from  
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39 301 South India, rarely presented with  $\alpha$ - or  $\beta$ -thalassaemia.[10, 15-17]

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44 302 Malay thalassaemia patients have a higher prevalence of HbE/ $\beta$ -thalassaemia. Point  
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46 303 mutation at CD26, the  $\beta$ -globin gene mutation causing HbE disease, is commonly  
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48 304 detected in Malaysian Malay patients during molecular characterisation.[10, 18] The  
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50 305 highest proportion of HbE/ $\beta$ -thalassaemia in the current study were found in  
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52 306 Selangor, Kuala Lumpur, Kelantan and Kedah. The plausible factors are due to  
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54 307 centralisation of thalassaemia referral centre (in the case of Selangor and Kuala  
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56 308 Lumpur), being close to the capital or centre of migration (Selangor in relation to

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3 309 Kuala Lumpur) and being the border states (such as Kedah and Kelantan, which  
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5 310 promotes interaction between the populations of Thailand and Peninsular Malaysia).

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9 311 Beta-thalassaemia major is important, especially in the Kadazan-Dusuns due to the  
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11 312 higher prevalence of Filipino  $\beta$ -thalassaemia deletion in the ethnicity.[15, 19]  
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13 313 Comprising 24.5% out of the Bumiputera population,[20] the registered cases in the  
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15 314 MTR signifies that a large proportion of Kadazan-Dusuns are affected by  $\beta$ -  
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17 315 thalassaemia major.

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21 316 On the other hand, HbH disease, which is commonly caused by the deletion of three  
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23 317  $\alpha$ -globin genes ( $--/\alpha$ ), is predominant in the Malaysian Chinese.[16, 17] Although  
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25 318 single  $\alpha$ -globin gene deletions like the  $-\alpha^{3.7}$  rightward single  $\alpha$ -globin gene deletion ( $-$   
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27 319  $\alpha^{3.7}/\alpha\alpha$ ) are also present in the Malays and Indians, the Southeast Asian double  $\alpha$ -  
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29 320 globin gene deletion ( $--^{SEA}/\alpha\alpha$ ) that is common in the Malaysian Chinese is  
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31 321 responsible for the development of this disease.[16]

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36 322 Clinicians are encouraged to prescribe iron chelator monotherapy whenever possible  
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38 323 unless the chelation is inadequate, or patients are not compliant. An example is non-  
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40 324 compliance or intolerance towards DFO, which is administered subcutaneously for 8-  
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42 325 12 hours,[21] leading to the change to oral chelators DFX or DFP. DFX is the more  
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44 326 popular option in the current study as it can be prescribed to younger patients  
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46 327 (minimum 2 years old, in the form of dispersible tablets, once daily) compared to  
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48 328 DFP (6 years and older, in the form of tablets or capsule, three times daily).[21, 22]  
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50 329 Older patients might have started off with DFP earlier before the approval of DFX in  
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52 330 2005[21] and might have been compliant with the treatment. Combination therapy, in  
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3 331 contrast, will only be initiated when intensive therapy is needed to overcome severe  
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5 332 iron overload.

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9 333 Iron chelation therapy in the current population shows positive impact in decreasing  
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11 334 the serum ferritin level. Although high-risk patients with serum ferritin level above  
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13 335 10000 µg/L are still present, the decline in their numbers indicate improvement in  
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15 336 patient management. Nevertheless, cardiac complications due to iron overload is still  
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17 337 the leading CoD among thalassaemia patients. Thus, participating centres might  
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19 338 need to improve on iron overload monitoring and chelation therapy, especially in  
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21 339 high-risk patients. In addition, the assessment of ferritin level might not be specific,  
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23 340 causing clinicians to move towards the use of magnetic resonance imaging (MRI)  
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25 341 T2\* to assess iron deposition in tissue.[23, 24] Nevertheless, the MRI T2\* data  
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27 342 collection for the MTR has not started.

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33 343 Although MTR was able to gather most information on thalassaemia patients  
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35 344 nationwide, certain records are still incomplete. Among the notable limitations in this  
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37 345 report are records of serum ferritin level, death record and birth summary, as certain  
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39 346 information might not be accessible, or the evaluation was not completed on the  
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41 347 whole population. Data on thalassaemia births in 2017 and 2018, for instance, may  
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43 348 only be captured after the patient presents the symptoms of thalassaemia.  
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45 349 Laboratory data on serum ferritin, on the other hand, might not be recorded in the  
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47 350 patient's notes and thus unavailable.

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53 351 In addition, MTR is a dynamic database, where the number of reported cases might  
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55 352 change rapidly through time. Thus, the figures might differ remarkably following  
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3 353 periodical update of the report. A clear cut-off point is needed every time a report is  
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5 354 generated to identify the most updated version.  
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## 8 9 355 **CONCLUSION**

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12 356 The MTR describes the current and evolving scenario of thalassaemia in Malaysia  
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14 357 over the past decade. The landscape has changed dramatically where patients are  
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16 358 now living past the second decade of life with improvement of patient management.  
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18 359 Data gathered into MTR can also be used to understand the progression of the  
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20 360 disorder and to improve the outcomes of treatment, monitor iron overload  
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22 361 management, enhance preventive strategies and reduce healthcare burden.  
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18  
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21

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23  
24 371 ARAJ, NM and HMA designed the study and provided intellectual input along with  
25  
26 372 data validation for the report. All authors contributed to drafting, revising and final  
27  
28 373 approval of the submitted manuscript.  
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31  
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50  
51 380 The authors have no competing interests  
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54 381 **PATIENT CONSENT**  
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3 382 The study utilises secondary data from a database, thus no informed consent was  
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5 383 required.  
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9 384 **ETHICAL APPROVAL**  
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11  
12 385 This study has been approved by Medical Research and Ethics Committee, Ministry  
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14 386 of Health Malaysia (National Medical Research Register ID: NMRR-17-2410-37653).  
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18 387 **DATA AVAILABILITY STATEMENT**  
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21 388 The data in this report were collected from the Malaysian Thalassaemia Registry.  
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23 389 Any request to access the data must be made to the Ministry of Health, Malaysia.  
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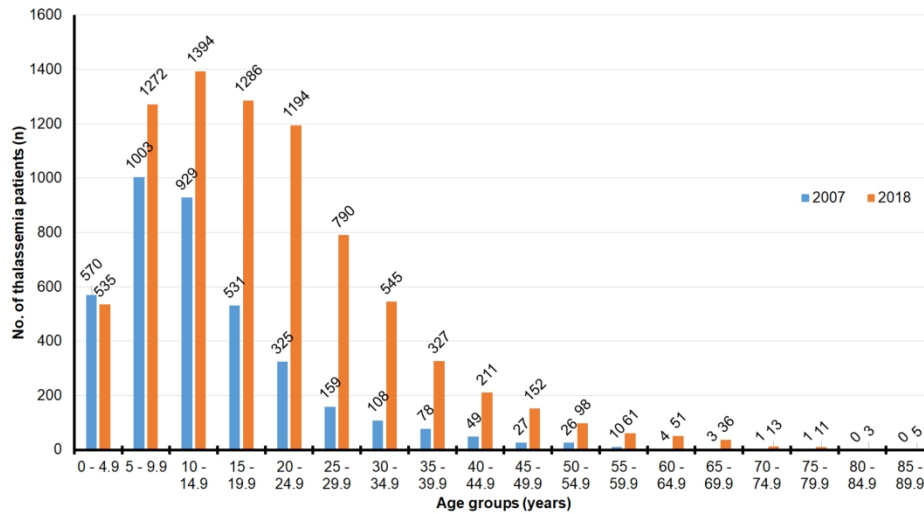
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3 472 **FIGURE LEGEND(S)**  
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7 473 **Figure 1 Comparison of survival trends of thalassaemia patients in Malaysia**  
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9 474 **between the years 2007 and 2018.** The survival trend of thalassaemia patient in  
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11 475 Malaysia is currently shifting towards the right, indicating an increase in the number  
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13 476 of patients aged 40 years and above.

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17 477 **Figure 2 Distribution of thalassaemia patients of four major ethnicities**  
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19 478 **according to geographical region.** The percentage was calculated against the total  
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21 479 number of patients of these ethnicities (Malay, Chinese, Indian and Kadazan-Dusun)  
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23 480 in each respective geographical region.

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27 481 **Figure 3 Percentage of clinical diagnosis of thalassaemia according to the**  
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29 482 **major ethnic groups in Malaysia.** The highest percentage of patients diagnosed  
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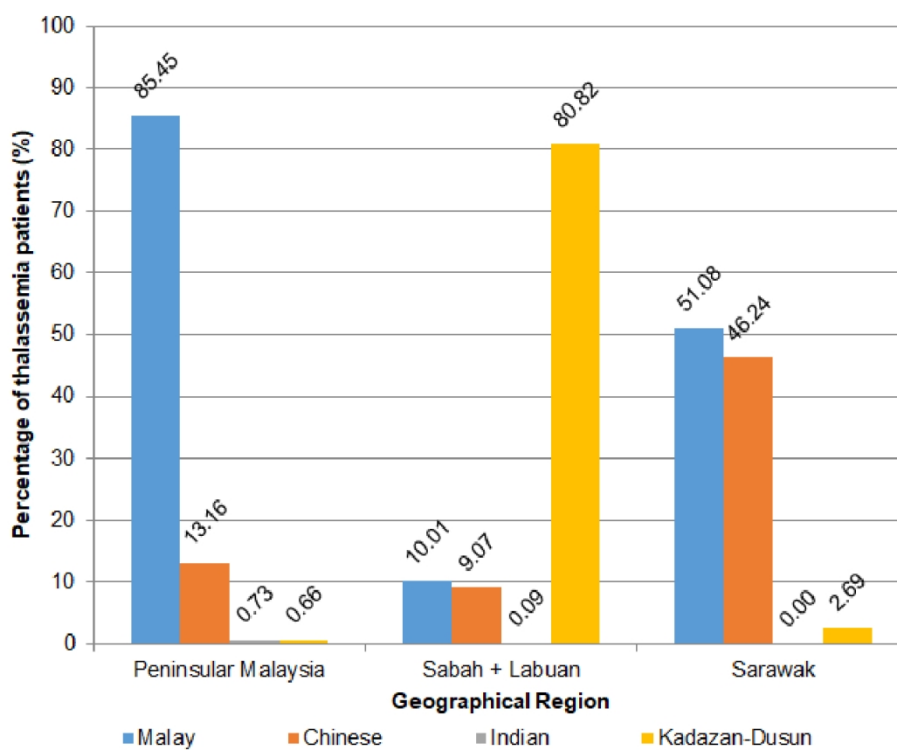
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37 485 **Figure 4 Reported serum ferritin level of regularly transfused thalassaemia**  
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39 486 **patients in Malaysia (2007-2018).** The number of patients with an acceptable level  
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41 487 of serum ferritin ( $\leq 2499$   $\mu\text{g/L}$ ) was increasing over time.  
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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.

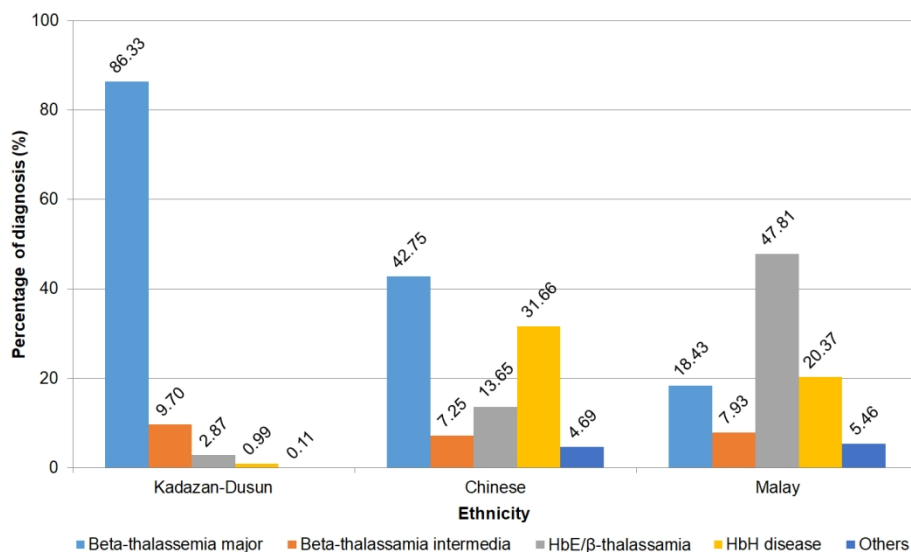
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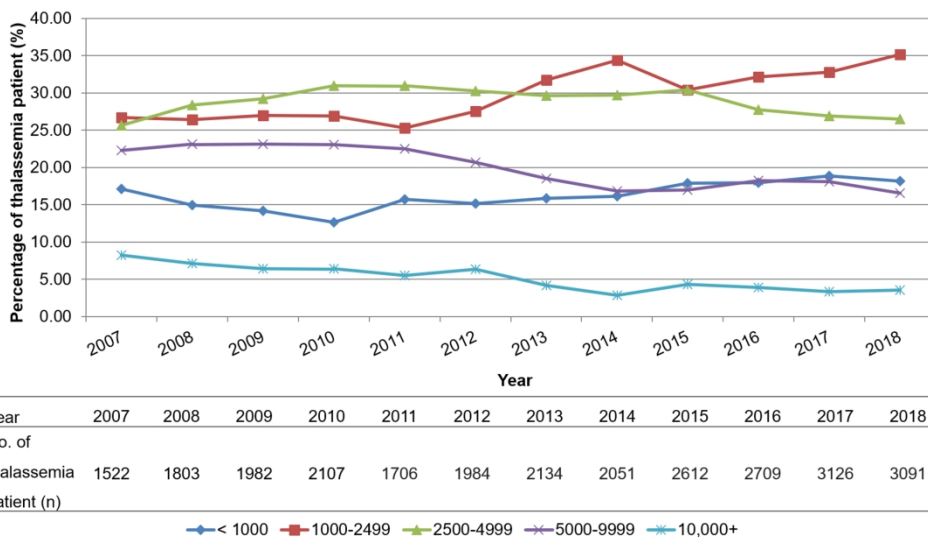
Distribution of thalassaemia patients of four major ethnicities according to geographical region. The percentage was calculated against the total number of patients of these ethnicities (Malay, Chinese, Indian and Kadazan-Dusun) in each respective geographical region.

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

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Reported serum ferritin level of regularly transfused thalassaemia patients in Malaysia (2007-2018). The number of patients with an acceptable level of serum ferritin ( $\leq 2499 \mu\text{g/L}$ ) was increasing over time.

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# BMJ Open

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

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| Article Type:                   | Original research   |
| Date Submitted by the Author:   | 12-May-2020   |
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3 **1 An observational study on the current status of thalassaemia in Malaysia: a**  
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11 4 Najib Mohamed Unni<sup>2</sup>, Kok Hoi Teh<sup>2</sup>, Asohan Thevarajah<sup>3</sup>, Kogilavani  
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14 25 **Running Heads:** Current Trend of Thalassaemia in Malaysia  
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## 37 **Abstract**

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

42 **Design:** Data were extracted from the Malaysian Thalassaemia Registry, a web-  
43 based system accessible to enrolled users through [www.mytalasemia.net.my](http://www.mytalasemia.net.my).

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

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

48 **Intervention:** Data was collected from the Malaysian Thalassaemia Registry from  
49 2007 until the fourth quarter of 2018.

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

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

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3 58 (serum ferritin  $\geq$  5000  $\mu\text{g/L}$ ) reduced over time. However, cardiac complications are  
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5 59 still the main cause of death in thalassaemia patients.  
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9 60 **Conclusion:** Data gathered into the registry can be used to understand the  
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11 61 progression of the disorder, to monitor iron overload management and to improve  
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13 62 the outcomes of treatment, to enhance preventive strategies, reduce healthcare  
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15 63 burden and improve the quality of life. Sustainability of the MTR is important for  
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17 64 surveillance of thalassaemia management in the country and help the national health  
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19 65 authorities to develop more effective policies.  
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24 66 **Keywords:** Healthcare burden; thalassaemia; haemoglobinopathy; database;  
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26 67 registry; Malaysia  
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## 69 STRENGTHS AND LIMITATIONS OF THIS STUDY

- 70 • The Malaysian Thalassaemia Registry is the first online patient registry in  
71 Malaysia, which aggregates data from all participating hospitals and allows real-  
72 time data analysis.
- 73 • This is the largest nationwide report that describes the overall distribution, current  
74 disease status and the progress of management of thalassaemia patients in  
75 Malaysia.
- 76 • Some missing data in a few variables during data collection and non-participating  
77 centres that treat a small number of thalassaemia patients made this survey  
78 susceptible to reporting bias.
- 79 • Data presented describes the findings of study as at fourth quarter of the year  
80 2018. Figures might differ at different time points due to the dynamic nature of the  
81 registry.

82

## 83 INTRODUCTION

84 Thalassaemia is one of the most common autosomal recessive disorders and is  
85 highly prevalent in countries within the tropical belt, including Malaysia.[1, 2] Current  
86 estimation shows that 6.8% of Malaysians are thalassaemia carriers who might be  
87 affected with various degrees of anaemia.[3] A thalassaemia carrier couple has a  
88 25% chance of producing a thalassaemia major progeny.

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

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

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3 106 patients from all over the country who received treatment at government hospitals  
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5 107 under the Ministry of Health (MOH) and university hospitals under the Ministry of  
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7 108 Education. The registry is the first online patient registry in Malaysia featuring real-  
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10 109 time data entry, facilitates update and data reporting, and allows enrolled users to  
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12 110 observe the aggregated data at any point of time. The core data set of essential data  
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14 111 elements was predefined by a team of experts including clinicians and the  
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16 112 completeness and validity of data collection was ensured by joined cooperation  
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18 113 between the company in charge and MOH, Malaysia. Site visits to ensure accuracy  
19  
20 114 and completeness of the data were carried out by a team of research assistants  
21  
22 115 appointed by the MOH and working in collaboration with the company. A regular  
23  
24 116 internal audit for quality control of the MTR is performed by the company in charge.  
25  
26 117 The web-based system is accessible to enrolled users through  
27  
28 118 [www.mytalasemia.net.my](http://www.mytalasemia.net.my) (MyTalasemia). It is user friendly and can be managed  
29  
30 119 from different locations. The MTR demonstrates the value of a continuously updated  
31  
32 120 registry for the surveillance of health services pertaining to thalassaemia in the  
33  
34 121 country. Patient registries, which include usage of large set of data, have been  
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36 122 reported to be helpful in mapping the functionalities and providing a positive return  
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38 123 on investment.[7]

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45 124 Herein, we report the data obtained from the MTR from 2007 to November 2018,  
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47 125 unravelling the current trend of thalassaemia in Malaysia. This work provides a near  
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49 126 comprehensive understanding of thalassaemia in Malaysia nationwide.

## 50 51 52 53 127 **METHODS**

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3 128 The updated MTR included all patients diagnosed with thalassaemia from 2007 to  
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5 129 November 2018 in 113 participating centres (110 government hospitals and three  
6  
7 130 university hospitals), located in 13 states and three Federal Territories of Malaysia  
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9 131 (Kuala Lumpur, Labuan and Putrajaya). The updated data from the registry was  
10  
11 132 retrieved in November 2018 for analysis. This study utilised secondary data,  
12  
13 133 involving data that have been gathered by the MOH for national census. The  
14  
15 134 patients' data from diagnosis to last follow-up or death were retrospectively collected  
16  
17 135 by research assistants in various regional centres in Malaysia. They were supervised  
18  
19 136 and all data were verified by clinicians and then manually entered into the  
20  
21 137 MyTalasemia system. All research assistants had centrally undergone training on  
22  
23 138 data collection and recording onto the web-based system. The types of data  
24  
25 139 collected were guided by the registry design. Data elements were grouped into  
26  
27 140 several categories including socio-demography, clinical characteristics, laboratory  
28  
29 141 test results, type of treatment received, death record and complications. Duplicate  
30  
31 142 registration was prevented. The updated data were further verified and discussed  
32  
33 143 centrally during the annual National Thalassaemia Meeting held in November.  
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35 144 In this report, the data was separated into two groups: 1) alive patients and 2)  
36  
37 145 deceased patients. In the alive patient group the following variables were analysed:  
38  
39 146 1) demography (location, gender, age groups and ethnicity); 2) clinical diagnosis; 3)  
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41 147 receipt of regular blood transfusions; 4) receipt of chelation therapy; 5) history of  
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43 148 splenectomy; and 6) serum ferritin levels. In deceased patients, the causes of death  
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45 149 were reported.  
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56 150 Results were presented as fractions and percentages over the total number of  
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58 151 reported cases. For demographic characteristics of regions, age groups and  
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3 152 ethnicity, the fractions and percentages were calculated against the total number of  
4  
5 153 reported cases in the respective groups.  
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9 154 This study has obtained the ethics approval from Medical Research and Ethics  
10  
11 155 Committee, Ministry of Health Malaysia (National Medical Research Register ID:  
12  
13 156 NMRR-17-2410-37653).  
14  
15

### 16 157 **Patient and Public Involvement**

17  
18  
19  
20 158 This report was prepared without patients and public involvement. Patients and the  
21  
22 159 public were not invited to comment on the database and study design or to  
23  
24 160 contribute to the writing or editing of this report.  
25  
26  
27

## 28 161 **RESULTS**

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31 162 As of 28<sup>th</sup> November 2018, 8681 thalassaemia patients have been registered in the  
32  
33 163 MTR. Out of 8681 patients, 7984 (91.97%) were reported to be alive and 130 of  
34  
35 164 those alive (1.63%) were reported cured by stem cell transplantation. Another 614  
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37 165 patients (7.69%) were lost to follow-up. The remaining 697 patients (8.03%) had  
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39 166 deceased.  
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### 43 167 **Geography**

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47 168 The largest number of registered thalassaemia patients came from state Sabah  
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49 169 (1814/7984 cases, 22.72%), followed by state Selangor (14.64%), Kedah (8.69%),  
50  
51 170 Johor (7.98%) and Perak (7.06%). Figure 1 shows the map of Malaysia with the  
52  
53 171 cumulative numbers of registered thalassaemia patients in each state of Peninsular  
54  
55 172 Malaysia, Sabah and Sarawak.  
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3 173 The patient geographic distribution was also analysed based on regional division:  
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5 174 Peninsular Malaysia (which includes 11 states and the Federal Territory of Kuala  
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7 175 Lumpur and Putrajaya); Sabah (Sabah and the Federal Territory of Labuan); and  
8  
9 176 Sarawak. Peninsular Malaysia recorded a 5922 (74.17%) registered patients, while  
10  
11 177 Sabah and Sarawak had registered 1839 (23.03%) and 223 (2.79%) patients,  
12  
13 178 respectively.

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18 179 Hospital Ampang in state Selangor, recorded the highest number of patients (703,  
19  
20 180 8.81%) seen since the hospital serves as a referral centre for adult thalassaemia  
21  
22 181 patients, including patients from the capital of Malaysia, Kuala Lumpur. Hospital  
23  
24 182 Queen Elizabeth and Hospital Wanita dan Kanak-Kanak Likas, both located in  
25  
26 183 Sabah, also recorded a high number of patients (370, (4.63%) and 300, (3.76%),  
27  
28 184 respectively).

### 185 **Gender**

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

### 188 **Age groups**

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



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195 1 shows the distribution of registered cases according to age groups and the three  
196 main geographical regions in Malaysia.

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198

For peer review only

199 **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 <sup>a</sup>             | 5922                     | 351              | 859     | 962       | 923       | 906       | 636       | 444       | 277       | 192       | 133       | 83        | 59        | 44        | 26        | 10        | 9         | 3         | 5         |
| Sabah <sup>b</sup>                           | 1839                     | 167              | 379     | 397       | 330       | 246       | 138       | 80        | 41        | 17        | 13        | 11        | 1         | 6         | 10        | 2         | 1         | 0         | 0         |
| Sarawak <sup>c</sup>                         | 223                      | 17               | 34      | 35        | 33        | 42        | 16        | 21        | 9         | 2         | 6         | 4         | 1         | 1         | 0         | 1         | 1         | 0         | 0         |
| TOTAL  | 7984                     | 535              | 127     | 139       | 128       | 119       | 790       | 545       | 327       | 211       | 152       | 98        | 61        | 51        | 36        | 13        | 11        | 3         | 5         |
|  |                          |                  | 2       | 4         | 6         | 4         |           |           |           |           |           |           |           |           |           |           |           |           |           |

200 <sup>a</sup> Peninsular Malaysia region: Includes all states and Federal Territories, except the states of Sabah, Sarawak and the Federal Territory  
 201 Labuan; <sup>b</sup> Sabah region: Combining the state of Sabah and the Federal Territory Labuan; <sup>c</sup> Sarawak region: The state of Sarawak.

## 203 **Ethnicity**

204 The majority of the registered thalassaemia patients were Malay (5106/7984,  
205 63.95%), followed by Chinese (938, 11.75%) and Kadazan-Dusuns (907, 11.36%).  
206 Other specified ethnicities include Pribumi Sabah (213, 2.67%), Bajau (196, 2.45%),  
207 Murut (147, 1.84%), Rungus (112, 1.40%) and Indian (43, 0.54%). The remaining  
208 ethnicities such as Orang Asli, Thais, Iban, Bidayuh, Sino Kadazan and Melanau  
209 (322, 4.03%) are listed as 'Others', along with 68 patients from foreign countries.  
210 Comparison was also made according to regional division. The data showed that the  
211 Malay made up 82.81% of registered patients in Peninsular Malaysia (4904/5922  
212 patients). Patients in Sarawak, on the other hand, were mostly Malay (95/223,  
213 42.60%) and Chinese (86/223, 38.57%), while patients in Sabah comprised mainly of  
214 Kadazan-Dusun (864/1839, 46.98%) and other Sabah's Indigenous (673/1839,  
215 36.60%) (Figure 3).

## 216 **Clinical diagnosis**

217 Majority of the patients were diagnosed with haemoglobin E (HbE)/ $\beta$ -thalassaemia  
218 (2744/7984, 34.37%), followed by  $\beta$ -thalassaemia major (TM) (2676, 33.52%),  
219 haemoglobin H (HbH) disease (1458, 18.26%),  $\beta$ -thalassaemia intermedia (748,  
220 9.37%) and 'others' (358, 4.48%). The 'others' group includes other forms of HbH  
221 disease, Hb Lepore Hollandia,  $\alpha$ -thalassaemia syndrome,  $\delta\beta$ -thalassaemia and other  
222 thalassaemia disorders requiring regular blood transfusions.

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

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2  
3 225 diagnosed with TM (37.05%). Patients aged 25.0-44.9 years old were commonly  
4  
5 226 reported with HbE/ $\beta$ -thalassaemia (707/1873, 37.75%), while patients aged  $\geq$  55.0  
6  
7  
8 227 years old were commonly diagnosed with HbH disease (86/180, 47.78%). These  
9  
10 228 observations were consistent with the presentation of the clinical diagnosis; TM  
11  
12 229 presents early in life, the severity of HbE/ $\beta$ -thalassaemia ranges from mild to severe,  
13  
14 230 while HbH disease is non-transfusion dependent thalassaemia (non-TDT) and  
15  
16 231 patients are most likely to survive longer due to the lower risk of iron overload. Figure  
17  
18 232 2 shows the peak of patient distribution corresponds to the age group of 10-14.9  
19  
20 233 years for TM, 15-19.9 years for HbE/ $\beta$ -thalassaemia, and 10-14.9 years for HbH  
21  
22 234 disease and  $\beta$ -thalassaemia intermedia, respectively.

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

### 241 **Regular transfusion**

242 4529 out of 7984 (56.73%) patients require regular blood transfusions. Regular blood  
243 transfusions is defined as requiring red blood cell transfusions biweekly or up to once  
244 every 12 weeks. The remaining patients were classified as non-TDT, which consists  
245 of patients who were on irregular blood transfusions ( $>$  16 weeks intervals) or who  
246 had never needed transfusion therapy.

### 247 **Chelation therapy**

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3 248 There was 4928 of 7984 patients (61.72%) on iron chelation therapy. The most  
4  
5 249 common iron chelator monotherapy prescribed was deferasirox (DFX) (1645/4928  
6  
7 250 patients, 33.38%), followed by deferiprone (DFP) (1107, 22.46%) and  
8  
9 251 desferrioxamine (DFO) (963, 19.54%). Combination therapies were prescribed for  
10  
11 252 the remaining patients: DFO and DFP (910, 18.47%); DFO and DFX (169, 3.43%);  
12  
13 253 DFP and DFX (92, 1.87%); and DFO, DFP and DFX (42, 0.85%).  
14  
15  
16  
17  
18 254 Oral iron chelator, DFX was commonly prescribed for the young patients aged < 15.0  
19  
20 255 years old (1231/1836, 67.05%). Meanwhile oral DFP was commonly prescribed for  
21  
22 256 the adult patients aged  $\geq$  30.0 years (457/888, 51.46%).  
23  
24  
25  
26 257 Overall, majority of the patients (3715/4928, 75.39%) were given single chelation  
27  
28 258 therapy. There was a higher number of patients in the age group 20.0-24.9 years old  
29  
30 259 (330/4928, 6.70%) who were prescribed combination therapy but patients above  
31  
32 260 25.0 years old were commonly prescribed single chelation therapy.  
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### 261 **History of splenectomy**

36  
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38  
39 262 Splenectomy was performed in 1235 out of 8681 patients (14.23%). This was  
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41 263 performed mainly in the older aged patients, who were not on iron chelation therapy  
42  
43 264 or had chronic iron overload. Almost 80% of the splenectomy were carried out in  
44  
45 265 those with TM (43.15%) and HbE/ $\beta$ -thalassaemia (41.78%), followed by  
46  
47 266 thalassaemia intermedia and HbH disease (7.61%).  
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### 51 267 **Serum ferritin levels**

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55 268 Data on ferritin levels were available for 3091 (38.71%) of the registered cases. As  
56  
57 269 there were many missing data on ferritin levels despite multiple or serial results  
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3 270 entered for individual patients, the registry could only generate report on the most  
4  
5 271 recent ferritin levels recorded for each patient. Overall, 562 (18.18%) patients had  
6  
7 272 ferritin levels < 1000 µg/L; 1087 (35.17%) patients had ferritin levels between 1000-  
8  
9 273 2499 µg/L; 820 (26.53%) patients had ferritin levels between 2500-4999 µg/L; 511  
10  
11 274 (16.53%) patients had ferritin levels between 5000-9999 µg/L; and 111 (3.59%)  
12  
13  
14 275 patients had ferritin levels ≥ 10000 µg/L.

### 276 **Birth summary**

277 The updated data on affected births was retrieved on 22<sup>nd</sup> April 2020 during the  
278 revision of the writing. This is to obtain the actual numbers of affected births from  
279 2007-2018, due to the dynamic nature of the database and patients were only  
280 registered in the MTR after diagnosis was made instead of on the year of birth. The  
281 total number of affected births was 1483, 1048, and 214 during 2007-2011, 2012-  
282 2016, and 2017-2018, respectively (online Supplementary Table 1). Overall, we  
283 observed a declining trend of affected birth from year 2015 onwards and this could  
284 likely explain the decreasing trend of total new cases between year 2016 and 2018  
285 (388, 277 and 102 new cases, respectively) given the clinical manifestation of TDT.  
286 The highest reported number of thalassaemia birth was in 2008 with 334 babies  
287 were born and Sabah had the highest number of affected births compared to other  
288 states. From 2014 to 2018 new thalassaemia birth declined steadily especially in  
289 Sabah and this could be associated with increased public awareness due to  
290 initiatives carried out by the government besides screening of secondary school  
291 children. The causes of affected birth were not delineated.

### 292 **Deceased patients**

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3 293 There were 697 (8.03%) recorded deaths out of 8681 patients, of which 89 (12.77%)  
4  
5 294 had incomplete data. Overall, 72.31% death occurred in TM and 16.64% death in  
6  
7 295 HbE/ $\beta$ -thalassaemia patients. The main causes of death among the 608  
8  
9 296 thalassaemia patients with verifiable data were cardiac failures (254, 41.78%) and  
10  
11 297 infections (232, 38.16%). Other causes were motor vehicle accidents (18, 2.96%),  
12  
13 298 liver diseases (16, 2.63%), malignancy (15, 2.47%), endocrine complications (13,  
14  
15 299 2.14%), multiple organs dysfunction (7, 1.15%), surgical complications (7, 1.15%),  
16  
17 300 thrombosis (6, 0.99%), central nervous system events (5, 0.82%) and others (35,  
18  
19 301 5.75%).  
20  
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24

25 302 183 of 252 deaths (72.61%) from cardiac causes were patients aged between 15  
26  
27 303 years old and 29.9 years old – 69 cases (27.38%) aged 15-19.9 years old; 73 cases  
28  
29 304 (28.97%) aged 20-24.9 years old; and 41 cases (16.27%) aged 25-29.9 years old.  
30  
31 305 The majority of death from cardiac failures were observed among patients with TM  
32  
33 306 (190/254, 74.80%) between 20-24.9 years of age followed by the 15-19.9 years of  
34  
35 307 age group. The HbE/ $\beta$ -thalassaemia patients recorded 38 deaths out of 254  
36  
37 308 (14.96%) and a similar age group to TM. The majority of deaths was associated with  
38  
39 309 chronic iron overload. Among the 96 TM deaths with recorded ferritin level, 38  
40  
41 310 (39.58%) of them had ferritin level of 5000-9999  $\mu\text{g/L}$  and 43 (44.79%) of them had  
42  
43 311 ferritin level of  $\geq 10000 \mu\text{g/L}$ . For the HbE/ $\beta$ -thalassaemia deaths, 28 patients had  
44  
45 312 recorded ferritin levels and 8 (28.57%) of the 28 deaths were associated with both  
46  
47 313 ferritin levels of 5000-9999  $\mu\text{g/L}$  and  $\geq 10000 \mu\text{g/L}$ , respectively. Overall, more than  
48  
49 314 50% of the cardiac deaths were associated with severe chronic iron overload.  
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56 315 For infection deaths, 229 patients had complete data; the mean age of death was  
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58 316 22.0 years old (SD  $\pm 12.06$ ) and those in age group 15.0-19.9 years old contributed  
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3 317 to the highest mortality numbers (57/229, 24.90%), followed by patients aged  
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5 318 between 20.0-24.9 years old (49/229, 21.40%) and patients in age group 25.0-29.9  
6  
7 319 years old (28/229, 12.22%). Most of the death occurred among patients with TM  
8  
9 320 (155, 66.81%) followed by the HbE/ $\beta$ -thalassaemia (50, 21.55%). Again, the majority  
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11 321 of death was associated with chronic iron overload. Among the 81 TM deaths with  
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13 322 recorded ferritin level, 25 (30.86%) and 23 (28.40%) of them had ferritin level of  
14  
15 323 5000-9999  $\mu\text{g/L}$  and  $\geq 10000$   $\mu\text{g/L}$ , respectively. For the HbE/ $\beta$ -thalassaemia deaths,  
16  
17 324 40 patients had recorded ferritin levels and 19 (47.50%) of the 40 deaths were  
18  
19 325 associated with ferritin levels of 5000-9999  $\mu\text{g/L}$  and 9 (22.50%) deaths had ferritin  
20  
21 326 levels  $\geq 10000$   $\mu\text{g/L}$ . Overall, more than 50% of the infection deaths were associated  
22  
23 327 with severe chronic iron overload. We were not able to capture the commonest  
24  
25 328 organisms responsible for the fatal outcome as this was not documented in the death  
26  
27 329 certificate. All causes of death were obtained from the death certificates and for  
28  
29 330 infection mortality it was often written as septicaemia/sepsis or pneumonia only.  
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36  
37 331 Only one patient had history of splenectomy in the infection death group. Four  
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39 332 patients died from complications related to stem cell transplantation. The case  
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41 333 records for deaths with incomplete data were unavailable and may have been  
42  
43 334 archived.

## 44 45 46 335 **DISCUSSION**

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49  
50 336 This study highlights the current trend of thalassaemia in Malaysia through the data  
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52 337 obtained from MTR. The MTR congregates data on thalassaemia patients seeking  
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54 338 treatment at the participating government hospitals and university hospitals  
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56 339 nationwide. Through the report, comprehensive data on patient population,  
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3 340 geographic locations, age groups, ethnicity and clinical diagnosis can be obtained.  
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5 341 Furthermore, information on blood transfusions and chelation therapy outcomes  
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7 342 obtained from the MTR can be studied to evaluate the efficacy of treatment received.  
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10 343 The interpretation of treatment outcome data can be used to help improve patient  
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12 344 management.

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14  
15 345 Before and during the early development of MTR in year 2007, local researchers  
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17 346 could only estimate the prevalence of thalassaemia and other figures related to the  
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19 347 disorder based on small, single-centered population or previous reports. The  
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21 348 previous reports were mainly focused on molecular characterisation of thalassaemia  
22  
23 349 or evaluation of quality of life outcome according to state, centre or ethnicity and did  
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25 350 not include the actual figure of reported cases in the respective region where the  
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27 351 study was conducted.[8, 9] Reports on estimated thalassaemia carrier rate in  
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29 352 Malaysia only referred to old data[10-12] and the previous works describing the  
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31 353 thalassaemia scenario in Malaysia had utilised data from the MOH annual report.[13]

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33  
34 354 The current estimate of the population of Malaysia is 32.6 million with Bumiputera  
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36 355 (including Malay and indigenous people of Sabah and Sarawak, such as Kadazan-  
37  
38 356 Dusun) comprising 69.1% of the entire population. This is followed by Chinese  
39  
40 357 (23.0%), Indian (6.9%) and 'Others' (1.0%).[14] In this study, patients of Indian  
41  
42 358 ethnicity are small in number as the Malaysian Indians' ancestors, who were mostly  
43  
44 359 from South India, rarely presented with  $\alpha$ - or  $\beta$ -thalassaemia.[11, 15-17]

45  
46 360 Malay ethnicity has a higher prevalence of HbE/ $\beta$ -thalassaemia. A point mutation at  
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48 361 CD26, the  $\beta$ -globin gene mutation causing HbE disease, is commonly detected in  
49  
50 362 Malaysian Malay patients during molecular characterisation.[11, 18] The highest

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3 363 proportion of HbE/ $\beta$ -thalassaemia patients in the current study were found in  
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5 364 Selangor, Kuala Lumpur, Kelantan and Kedah. The plausible factors are due to  
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7  
8 365 centralisation of thalassaemia referral centre (in the case of hospitals in Selangor  
9  
10 366 and Kuala Lumpur), being close to the capital or centre of migration (Selangor in  
11  
12 367 relation to Kuala Lumpur as capital of Malaysia) and being the border states (Kedah  
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14 368 and Kelantan, which promotes interaction between the populations of Thailand and  
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16  
17 369 Peninsular Malaysia).

18  
19  
20 370 TM is more common in the Kadazan-Dusuns ethnicity in Sabah due to a higher  
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22 371 prevalence of Filipino  $\beta$ -thalassaemia deletion in the ethnicity.[15, 19] Comprising  
23  
24 372 24.5% out of the Bumiputera population,[20] the registered cases in the MTR  
25  
26  
27 373 signifies that a large proportion of Kadazan-Dusuns are affected by TM.

28  
29  
30 374 HbH disease, which is commonly caused by the deletion of three  $\alpha$ -globin genes ( $--/\alpha$ )  
31  
32 375  $\alpha$ ), is predominant in the Malaysian Chinese.[16, 17] Although a single  $\alpha$ -globin gene  
33  
34 376 deletion like the  $-\alpha^{3.7}$  rightward single  $\alpha$ -globin gene deletion ( $-\alpha^{3.7}/\alpha\alpha$ ) are also  
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36  
37 377 present in the Malays and Indians, the Southeast Asian double  $\alpha$ -globin gene  
38  
39 378 deletion ( $--^{SEA}/\alpha\alpha$ ) that is common in the Malaysian Chinese is responsible for the  
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41  
42 379 clinical manifestation of the disease.[16]

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44  
45 380 In all registered patients, serum ferritin levels have been traditionally used for  
46  
47 381 monitoring iron overload. In general, we observed a remarkable improvement in the  
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50 382 trend of ferritin levels during the 12 years. The percentage of patients with ferritin  
51  
52 383 levels of  $\leq 2499$   $\mu\text{g/L}$  has increased and was pronounced in the 1000-2499  $\mu\text{g/L}$   
53  
54 384 group (from 406/1522 (26.68%) in 2007 to 1087/3091 (35.17%) in 2018) and the  
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56  
57 385 percentage of those with ferritin levels of  $\geq 5000$   $\mu\text{g/L}$  has declined, which was most  
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3 386 remarkable in the 5000-9999 µg/L group (339/1522 (22.27%) in 2007 to 511/3091  
4  
5 387 (16.53%) in 2018) (Figure 4). The single measurement of ferritin levels reported here  
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7  
8 388 has limitation in overall interpretation of iron overload in the patients as the readings  
9  
10 389 could be affected by inflammatory conditions. However, we believe that the overall  
11  
12 390 report helps us to understand the status of management of iron overload in our  
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14  
15 391 patients over the years to enable planning for better monitoring.  
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18 392 In our report, 62% of TDT patients were on iron chelation therapy. Importantly,  
19  
20 393 61.7% of our patients had an iron overload of between 1000 and 4999 µg/L.  
21  
22 394 Approximately 3.6% of our patients had very high levels of ferritin of ≥ 10000 µg/L  
23  
24  
25 395 and about 16% of the patients had ferritin levels of 5000-9999 µg/L, which underlines  
26  
27 396 the need for optimisation of chelation therapy.  
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30 397 Early initiation of chelation therapy and close monitoring is paramount to prevent  
31  
32 398 complications from iron overload. Here, clinicians are encouraged to prescribe iron  
33  
34 399 chelator monotherapy whenever possible unless the chelation regime is inadequate  
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36  
37 400 to control the iron overload or patients are not compliant including intolerance  
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40 401 towards subcutaneous infusion DFO of 8-12 hours.[21]. In such situations this could  
41  
42 402 lead to a change from subcutaneous DFO to oral chelator DFX or DFP or a  
43  
44 403 combination therapy. Oral chelator DFX, a dispersible tablet taken once daily is the  
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47 404 preferred option observed in the current study as it is more feasible in younger  
48  
49 405 patients as young as 2 years old compared to oral DFP, a tablet or capsule, taken 3  
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51 406 times daily.[21, 22]. In the analysis, the older patients were more likely have been  
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54 407 started on DFP before the approval of DFX use in Malaysia in year 2005,[21] and  
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56 408 then continue with the same medication. A combination therapy is usually initiated  
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58 409 when intensive therapy is needed to overcome severe iron overload. Improvement in  
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3 410 management of iron overload and improved compliance to iron chelators especially  
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5 411 the oral preparations could likely explain for the declined levels of serum ferritin  
6  
7 412 observed in the past few years. The oral DFX monotherapy was mainly prescribed to  
8  
9 413 the young patients and oral DFP was given to the adult patients. Overall, the above  
10  
11 414 findings of ferritin levels trend should be interpreted with caution as cardiac  
12  
13 415 complications due to iron overload is still the leading cause of death among the  
14  
15 416 thalassaemia patients. Furthermore, the age groups with high mortality are rather  
16  
17 417 young compared to other registry reports.[23] Other complications like endocrine  
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19 418 dysfunction were not specifically recorded in the MTR. However, hypogonadism was  
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21 419 found to occur in 22%[24] of young adults and adults with TDT and short stature has  
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23 420 also been reported.[25, 26] Thus, intensification of chelation therapy, improvement  
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25 421 on monitoring of iron overload, and compliance to chelation therapy is needed in all  
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27 422 patients.  
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34 423 In recent years, the government started investing in magnetic resonance imaging  
35  
36 424 (MRI) T2\* sequence, to evaluate and monitor myocardial iron concentration  
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38 425 specifically. Radiologists were trained and the service can be accessed in a few  
39  
40 426 regions in the country. Clinicians managing TDT are now able to access MRI T2\* for  
41  
42 427 active surveillance of iron overload and this will help them to optimise chelation  
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44 428 therapy for their patients.[27, 28] However, the MRI T2\* data collection for the MTR  
45  
46 429 has not started and the feasibility of entering the findings into the registry is  
47  
48 430 underway.  
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53 431 Prevention of affected births is a challenge in Malaysia. To date, prenatal screening  
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55 432 of thalassaemia is still very low although it can be conducted upon request and the  
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57 433 cost is covered by the national health system if conducted in the government  
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3 434 hospitals. Despite multiple meetings and forums with medical and religious experts,  
4  
5 435 which have been conducted since 2004, a policy on prenatal screening and  
6  
7 436 diagnosis is yet to be developed. The multiethnic cultures and religions practised in  
8  
9 437 the country play a huge role in prenatal diagnosis and therapeutic abortion. In a local  
10  
11 438 study, majority of the study respondents were open to prenatal diagnosis, but less  
12  
13 439 than one-third agreed to performing both prenatal diagnosis followed by termination  
14  
15 440 of affected foetuses. More than 75% of those declining claimed that religious  
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17 441 restriction is the main reason.[29] Accessibility to prenatal diagnosis in some regions  
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19 442 and family planning consideration are also among the contributing factors.  
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25 443 In Malaysia, therapeutic abortion is permitted based on The Penal Code  
26  
27 444 (Amendment) Act 1989 (Act A727), which allows abortion within 120 days of  
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29 445 conception only if the continued pregnancy poses a greater threat to the mother's life  
30  
31 446 or to her physical or mental health than would the termination of the pregnancy.  
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33 447 Although this can affect the incidence of new TM cases, the current overall trend of  
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35 448 affected births and newly diagnosed TDT cases suggests that the public awareness  
36  
37 449 initiatives by MOH have given positive outcomes. Initiatives such as offering free  
38  
39 450 early population screening, periodical health education and public awareness have  
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41 451 helped to identify carriers and increased awareness on the risk of giving birth to a  
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43 452 thalassaemic child. However, there were public concerns related to creating anxiety  
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45 453 and stigmatising youth who are affected.  
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51 454 Overall, when we look at the trend of declining numbers of yearly new cases  
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53 455 especially from 2015 onwards, we believe that continuous health education, public  
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55 456 awareness programme and improved management of the thalassaemic in Malaysia  
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57 457 over the last 10 years have provided positive return on the investment.  
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3 458 Although the MTR is able to identify and collect most of the important information on  
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5 459 thalassaemia patients nationwide, certain records are still incomplete. A limitation of  
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7 460 the MTR report may pertain to the missing data in several variables of the total  
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9 461 number of registered patients; serum ferritin levels, MRI T2\* findings, end organs  
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11 462 complication, causes of death and birth summary, as some details were not  
12  
13 463 accessible or not recorded in the patients' notes. Furthermore, as the MTR is a  
14  
15 464 dynamic, real-time web system, the numbers of reported cases change through time  
16  
17 465 hence the figures might differ following periodical update of the report. For instance,  
18  
19 466 the total number of affected births in year 2017 or 2018, may only be captured when  
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21 467 the patients present with symptoms related to thalassaemia later than the year of  
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23 468 birth. Therefore, a definite cut-off point is needed each time a report is generated to  
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25 469 ensure the most updated data is presented.

## 470 **CONCLUSION**

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

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

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For peer review only

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498 Abu Bakar.

## 499 **STATEMENT OF AUTHORS' CONTRIBUTION**

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



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11  
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14

15 510 The authors have no competing interests  
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18 511 **PATIENT CONSENT**  
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21  
22 512 The study utilises secondary data from a database, thus no informed consent was  
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24 513 required.  
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27 514 **ETHICAL APPROVAL**  
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30  
31 515 This study has been approved by Medical Research and Ethics Committee, Ministry  
32  
33 516 of Health Malaysia (National Medical Research Register ID: NMRR-17-2410-37653).  
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36 517 **DATA AVAILABILITY STATEMENT**  
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40 518 The data in this report were collected from the Malaysian Thalassaemia Registry.  
41  
42 519 Data are available upon reasonable request. Any request to access the data must be  
43  
44 520 made to the Ministry of Health, Malaysia.  
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47 521 **WORD COUNT**  
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51 522 4383 words  
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3 617 **FIGURE LEGEND(S)**  
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6 618 **Figure 1 Cumulative numbers of registered thalassaemia patients in each state**  
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8 **of Malaysia.**  
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12 620 **Figure 2 Distribution of cumulative number of registered cases in year 2018 in**  
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14 621 **the Malaysian Thalassaemia Registry (MTR) according to age groups.**

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18 622 **Figure 3 Percentage of thalassaemia patients according to ethnicities and**  
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20 623 **geographical region.** The percentage was calculated against the total number of  
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22 624 patients in each respective geographical region. 'Other Sabah's Indigenous' includes  
23  
24 625 Pribumi Sabah, Bajau, Murut, Rungus and Sino Kadazan; 'Sarawak's Indigenous'  
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26 626 includes Pribumi Sarawak, Iban, Bidayuh and Melanau; and 'Others' includes Orang  
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28 627 Asli, Thais, mixed ethnicities, foreigners and other ethnicities.  
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32 628 **Figure 4 Serum ferritin levels of regularly transfused thalassaemia patients**  
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34 **between 2007 and 2018.** The number of patients with ferritin level of  $\leq 2499$   $\mu\text{g/L}$   
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36 629 have increased over time.  
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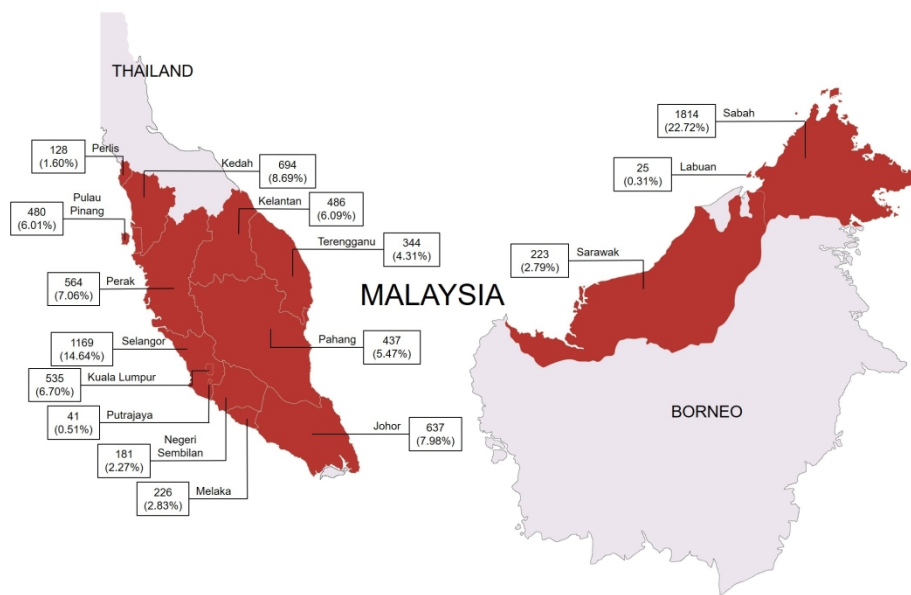


Figure 1 Cumulative numbers of registered thalassaemia patients in each state of Malaysia.

192x121mm (300 x 300 DPI)

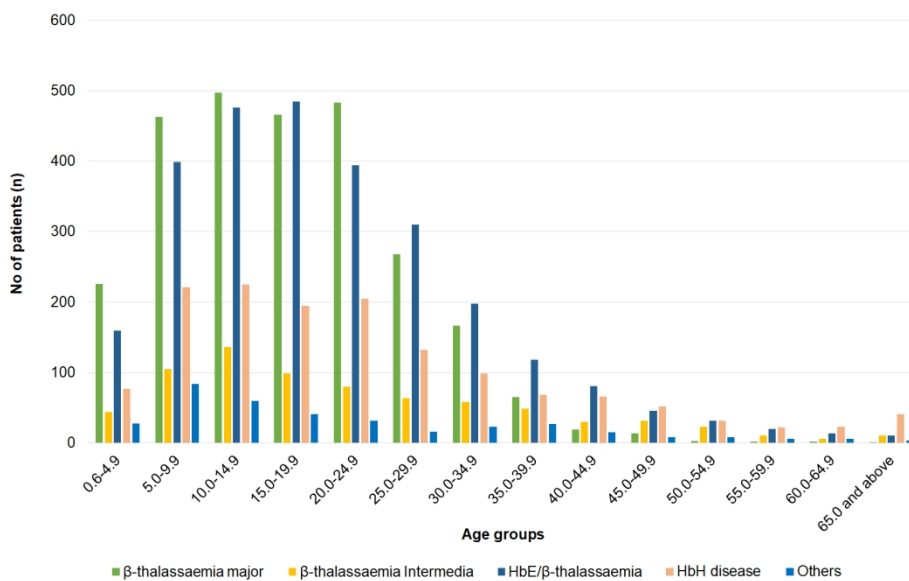


Figure 2 Distribution of cumulative number of registered cases in year 2018 in the Malaysian Thalassaemia Registry (MTR) according to age groups.

154x96mm (300 x 300 DPI)



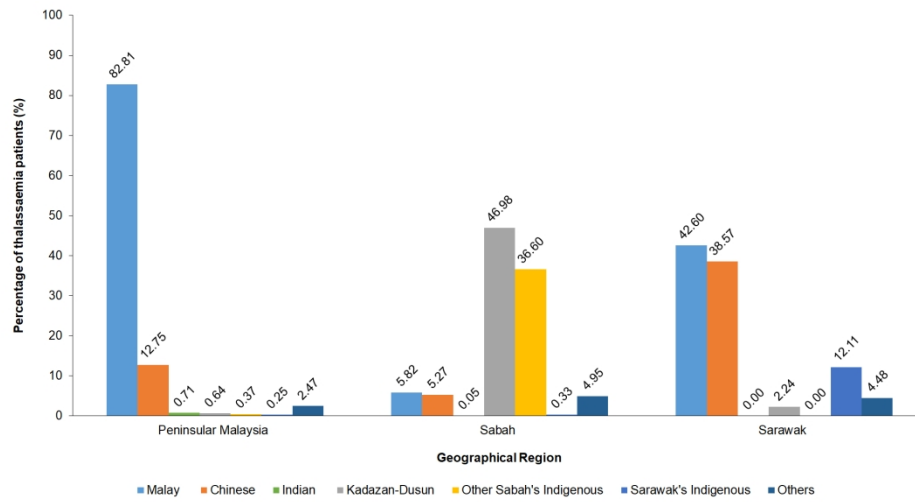


Figure 3 Percentage of thalassaemia patients according to ethnicities and geographical region. The percentage was calculated against the total number of patients in each respective geographical region. 'Other Sabah's Indigenous' includes Pribumi Sabah, Bajau, Murut, Rungus and Sino Kadazan; 'Sarawak's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

183x105mm (300 x 300 DPI)

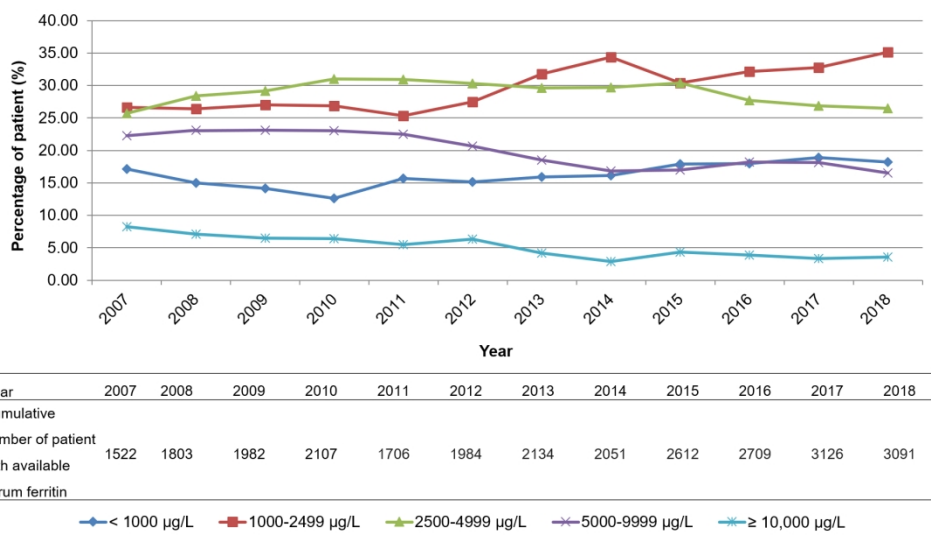


Figure 4 Serum ferritin levels of regularly transfused thalassaemia patients between 2007 and 2018. The number of patients with ferritin level of  $\leq 2499 \mu\text{g/L}$  have increased over time.

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 <sup>a</sup>    | N/A <sup>b</sup> | 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   |

<sup>a</sup> 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.

<sup>b</sup> 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.