Demographics and outcome of patients with congenital haemophilia in Sarawak, Malaysia

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ABSTRACT

Introduction: Sarawak has a population that is geographically and characteristically widely varied. This study aimed to determine the demographic profile of patients in Sarawak, Malaysia.

Materials and Methods – A cross-sectional study was conducted in 2019 at four major haemophilia treatment centres in Kuching, Sibu, Bintulu and Miri Hospitals, Sarawak. Demographic and clinical data were collected with consents from patients.

Results and Discussion: Ninety-six haemophilia patients were identified - 79(82.3%) haemophilia A(HA) and 17(17.7%) haemophilia B(HB). Severe haemophilia patients were noted in 45.6% (36/79) of HA and 64.7% (11/17) of HB. In all 44.3% of the HA and 52.9% of the HB population had no identifiable family history of haemophilia. Two-thirds of the patients with severe HA were on prophylaxis [24/36 (66.7%)] and only one-third [4/11 (36.4%)] in severe HB. Inhibitors developed in 9/79 (11.4%) of the HA population [3/79 (3.8%) high responders]. The median inhibitor titre was not significantly different between the different treatment groups – on demand versus prophylaxis (1.0BU versus 2.0BU; z statistic -1.043, p-value 0.297, Mann-Whitney test). None of the patients developed inhibitory alloantibodies to factor IX. Four HA patients (5.1%) underwent immune tolerance induction where one case had a successful outcome. Three severe HA patients received emicizumab prophylaxis and showed remarkable reduction in bleeding events with no thromboembolic events being reported. One female moderate HA patient received PEGylated recombinant anti-haemophilic factor. Eleven patients underwent radiosynovectomy. One mild HB patient succumbed to traumatic intracranial bleeding. Our data reported a prevalence (per 100,000 males) of 5.40 cases for all severities of HA, 2.46 cases for severe HA; 1.16 cases for all severities of HB, and 0.75 cases for severe HB. The overall incidence of HA and HB was 1 in 11,500 and 1 in 46,000, respectively.

Conclusion: This study outlines the Sarawakian haemophilia landscape and offers objective standards for forward planning. Shared responsibilities among all parties are of utmost importance to improve the care of our haemophilia population.

KEYWORDS:
Demographics; Haemophilia; Sarawak

INTRODUCTION

Haemophilia, an X-linked congenital bleeding disorder, may be inherited or arise from spontaneous mutation. Haemophilia A (HA) and haemophilia B (HB) are caused by deficiencies of factor VIII (FVIII) and factor IX (FIX), respectively. Overall, the global prevalence (per 100,000 males) reported by a recent meta-analysis was 17.1 cases for all severities of HA, 6.0 cases for severe HA; 3.8 cases for all severities of HB, and 1.1 cases for severe HB.[1] A total of 173,711 and 34,289 patients with HA and HB were identified by the World Federation of Haemophilia annual survey in 2018.[2] The expected number of males with haemophilia worldwide was 1,125,000, the majority of whom were undiagnosed, including an estimated 418,000 males with severe haemophilia.[1] A national study in Singapore conducted in 2015 reported that the local prevalence of HA to be 10.31 per 100,000 males and HB to be 2.11 per 100,000 males.[3] The only study on congenital haemophilia in Malaysia was reported by Duraisamy in 1998, where HA made up 72% and HB 12% of all congenital bleeding disorders.[4]

Sarawak, the largest state in Malaysia, has a very diverse population where 2.8 million people from 26 ethnic groups living on the island of Borneo, with the Dayaks making up 40%, Malays 24%, Chinese 24% and the others by the other minority groups.[5,6] There is currently no published study reporting the epidemiological data and outcome of haemophilia in Sarawak. We hope this study will help to show the demographic profile of patients in Sarawak and study their outcome in order to gauge the performance of our management model and allow forward planning.

MATERIALS AND METHODS

This cross-sectional study was conducted in 2019 at four haemophilia treatment centres in Sarawak: Sarawak General Hospital (SGH), Sibu Hospital, Bintulu Hospital and Miri Hospital. SGH houses a Comprehensive Haemophilia Treatment Centre (CHTC) and maintains the State Haemophilia Registry with data collected from the 4 regional

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hospitals stated above. The registry provides the baseline demographic information on our haemophiliacs as well as their clinical status. Consents were obtained from patients prior to any data entry into the registry.

Data were collected in English using a standardised form (available online and on paper), quality checked and reviewed. Demographic data collected included age at study, gender, ethnicity and which part of the state they came from. Clinical data pertaining to haemophilia comprised the types and severity of haemophilia, treatment options and outcome. Disease severity was defined by: (a) Severe – clotting factor level less than 1% of normal or below 1IU/dL; (b) Moderate – clotting factors 1-5% of normal or 1-5 IU/dL; and (c) Mild – clotting factor 5 to 40% of normal or 5-40 IU/dL. The most recent inhibitor titre in Bethesda Unit (BU) was recorded and used in statistical analysis.

Ordinal or categorical data was expressed as frequency and percentage. The relationship between inhibitor titres and treatment groups was analysed using Mann-Whitney test. The prevalence of inhibitor between on-demand (OD) and prophylaxis groups was analyzed using Fisher's Exact test. Statistical significance was determined as *p*-value less than 0.05.

RESULTS

In the population of 2.8 million in Sarawak, a total of 107 patients with congenital bleeding disorders were identified – 79 (73.8%) HA and 17 (15.9%) HB. The others being non-haemophilia bleeding disorders, totaling 11 patients were Von Willebrand disease (4), Factor VII (3), FX (3) and FXI (1). Demographic and clinical characteristics of these individuals are shown in Table I and II. Their ages ranged from 6-month-old to 66-year-old. All except one were males. Severe haemophilia patients were noted in 45.6% (36/79) of HA and 64.7% (11/17) of HB. Almost half (44.3%) of our HA and 52.9% of our HB population had no identifiable family history of haemophilia. All patients included in our registry were Malaysians. The incidence of HA and HB in Sarawak was shown in Table III.

Two-thirds of our patients with severe HA were on prophylaxis [24/36 (66.7%)] and only one-third [4/11 (36.4%)] in severe HB. Out of all moderate HA patients, four (15.4%) were on prophylaxis due to bleeding events and target joints. The clinical profile of the latter subset is shown in Table IV. The one female with moderate HA presented with scalp and multiple intramuscular haematoma. She required 144 vials of Factor VIII concentrate (each vial 250IU) the year before she was switched to prophylaxis and subsequently enrolled into a clinical trial in 2015. Post study, she was provided free access to PEGylated recombinant anti-haemophilic factor (ADYNOVI). None of the moderate HB patients received prophylaxis.

Inhibitors developed in 9/79 (11.4%) of our HA population [3/79 (3.8%) high responders]. The median inhibitor titre was not significantly different between different treatment groups – OD versus prophylaxis (1.0BU versus 2.0BU; z statistic -1.043, p-value 0.297, Mann-Whitney test). The prevalence of HA patients with inhibitors in OD and prophylaxis treatment groups were 5.9% (3/51) and 21.4% (6/28), respectively. This was statistically not significant (*p*-value 0.061, Fisher's Exact test). None of our patients had inhibitory alloantibodies to FIX.

Immune tolerance induction (ITI) was initiated in three Sarawakian HA paediatric patients with inhibitors using a dose regimen of 100 IU/kg/day at Ampang Hospital – national haematology centre in Malaysia. The pre-ITI inhibitor titre levels were 6.2, 9.0 and 54.5 BU, respectively. Inhibitors were successfully removed in one patient who had pre-ITI inhibitor level of 9.0BU after 2.5 years of ITI treatment with absence of inhibitors to date. However, ITI treatment failed in two others and was stopped as they continued to have frequent bleeds (about 2 bleeds per month) and required OD bypassing agents. ITI treatment was tried in one adult HA patient but was unsuccessful in eradication of the inhibitor hence ITI never took off in Sarawak due to the high cost of treatment and reluctance of patients to comply with the protocol. The other five non-ITI patients with inhibitors were non-bleeders with pre-ITI inhibitor titre levels being 0.55BU, 0.6BU, 2.0BU, 2.2BU and 48.0BU, respectively.

Out of the nine patients who developed inhibitory alloantibodies to FVIII, three (including two patients who failed ITI earlier) fulfilled the criteria for compassionate use of emicizumab prophylaxis (3mg/kg every 2 weeks). All three had severe HA with a median latest inhibitor titre of 3.0BU, ranging from 1.6 to 20.0BU. Two had achieved 100% reduction in bleeding events after receiving emicizumab. One, who failed ITI earlier, had an episode of minor spontaneous bleed one day prior to the scheduled dose, which fully resolved after emicizumab administration without any bypassing agents. Two patients who required walking aids prior to commencement of emicizumab were able to ambulate independently post treatment. One of them failed ITI earlier. None had any adverse events. No thromboembolic events were identified.

Four and three HA patients were hepatitis B and C carriers, respectively. One patient with severe HB was a hepatitis B carrier. There was one case of human immunodeficiency virus (HIV) infection in a patient with HA. All except one received plasma-derived factor concentrate. Eleven patients (11.6%) who had recurrent target joint pain underwent radiosynovectomy. One mild HB patient, who was diagnosed at 5-month-old succumbed to traumatic intracranial bleeding at the age of 27 months.

DISCUSSION/ CONCLUSION

CHTC registry which was started in January 2019 reported a prevalence (per 100,000 males) of 5.40 cases for all severities of HA, 2.46 cases for severe HA; 1.16 cases for all severities of HB, and 0.75 cases for severe HB. This data was based on the latest 2020 male population estimates reported by the Department of Statistics, Malaysia.[5] This figure was likely under-reported in contrast to the prevalence reported by a recent meta-analysis and Singapore data.[1,3] According to the Annual Global Survey 2016, a total of 1360 HA and 235 HB patients were reported in Malaysia, respectively.[8] This gives

Table I: Demographic data and inhibitor status of haemophilia A patients in Sarawak, Malaysia

	Mild (%)	Moderate (%)	Severe (%)	Total (%)		
Severity	17 (21.5)	26 (32.9)	36 (45.6)	79 (100)		
Age distribution						
< 10	3	3	8	14 (17.7)		
10-19	3	14	9	26 (32.9)		
20-29	7	3	9	19 (24.1)		
30-39	1	4	7	12 (15.2)		
40-49	0	2	2	4 (5.1)		
50-59	1	0	1	2 (2.5)		
≥ 60	2	0	0	2 (2.5)		
Ethnicity						
Chinese	4	7	6	17 (21.5)		
Malay	6	5	11	22 (27.9)		
Sarawak native	7	14	19	40 (50.6)		
Division					**Male population 2019 ('000)**	**Prevalence (100,000males)**
Kuching (HTC)	9	17	10	36 (45.6)	409.8	8.8
- Kuching	9	14(1female)	10	33 (41.8)	357.5	9.0
- Lundu	0	2	0	2 (2.5)	20.4	9.8
- Bau	0	1	0	1 (1.3)	31.9	3.1
Serian	0	0	3	3 (3.8)	53.5	5.6
Samarahan	1	3	1	5 (6.3)	50.5	9.9
Sri Aman	0	0	0	0 (0.0)	39.4	0.0
Betong	1	1	0	2 (2.5)	63.5	3.1
Sarikei	0	0	0	0 (0.0)	33.8	0.0
Mukah	0	0	0	0 (0.0)	28.8	0.0
Sibu (HTC)	0	3	9	12 (15.2)	164.5	7.3
Kapit	0	0	0	0 (0.0)	32.2	0.0
Bintulu (HTC)	2	0	9	11 (13.9)	145.1	7.6
Miri (HTC)	4	2	4	10 (12.7)	230.7	4.3
- Miri	4	2	1	7 (8.9)	190.6	3.7
- Marudi	0	0	3	3 (3.8)	40.1	7.5
Limbang	0	0	0	0 (0.0)	52.7	0.0
- Limbang	0	0	0	0 (0.0)	28.7	0.0
- Lawas	0	0	0	0 (0.0)	24.0	0.0
Inhibitors^						
High responders	0	0	3*	3 (3.8)		
Low responders	0	1	5	6 (7.6)		

^ High responders - inhibitor above 5BU; low responders – inhibitor levels less than 5BU which did not increase with exposure to additional factor
* Pre-ITI inhibitor titre was used
HTC: Haemophilia treatment centre

rise to a prevalence (per 100,000 males) of 8.34 cases for all severities of HA and 1.44 cases for all severities of HB in Malaysia. The proportions of our HA and HB in Sarawak were consistent with the finding reported by Duraisamy.[4]

From our data, the overall incidence of HA and HB was 1 in 11,500 and 1 in 46,000, respectively. This is considerably lower than the data reported by a study in which the incidence of HA and HB was reported to be approximately 1 in 5,000 and 1 in 30,000, respectively.[9] This might be attributed to the fact that patients with mild haemophilia who were non-bleeders and those who refused to come forward for medical diagnosis are not captured in this study. This is the first study representative of the whole Sarawak looking at the demographics of haemophilia. Having the knowledge of the prevalence of haemophilia patients in each population is important for us to deliver haemophilia care closer to the community. Based on this study, we think that haemophilia may be undiagnosed in isolated parts of Sarawak; hence more effort needs to be done to increase awareness and improve the diagnosis of haemophilia among the health care workers.

Several studies reported that about one-third of cases arise from a spontaneous mutation with no family history of haemophilia.[3,10,11] However, our data found 45.8% with absence of family history. We are uncertain whether it is because parents and patients are not forthcoming with a good 3-generation family history and testing or we have a higher frequency of spontaneous mutation which necessitates genetic mutation studies which are not readily available in Malaysia.

Our study shows that haemophilia A gene is present among the Sarawak indigenous groups which constitute almost half of the state population.[5,6] Haemophilia B gene although present in all the ethnic groups, seems to be disproportionately higher amongst the Malays. This might be due to the fact that about half [5/9 (55.6%)] of the Malay HB patients are blood-related. The issues confronting our haemophilia population and their caregivers are varied and complex. The key factors resulting in no treatment in two-fifth of the severe haemophilia patients include: (a) from patients or resistance of parents to intravenous injection; (b) cost and accessibility to factor replacement; and (c) logistic

Table II: Demographic data and inhibitor status of haemophilia B patients in Sarawak, Malaysia

	Mild (%)	Moderate (%)	Severe (%)	Total (%)		
Severity	3 (17.6)	3 (17.6)	11 (64.7)	17 (100)		
Age distribution						
< 10	1	1	4	6 (35.3)		
10-19	0	0	3	3 (17.6)		
20-29	1	0	1	2 (11.8)		
30-39	1	1	3	5 (29.4)		
40-49	0	1	0	1 (5.9)		
50-59	0	0	0	0 (0.0)		
≥ 60	0	0	0	0 (0.0)		
Ethnicity						
Chinese	0	0	1	1 (5.9)		
Malay	1	1	7	9 (52.9)		
Sarawak native	2	2	3	7 (41.2)		
Division					**Male population 2019 ('000)**	**Prevalence (100,000males)**
Kuching (HTC)	2	0	3	5 (29.4)	409.8	1.2
- Kuching	1	0	3	4 (23.5)	357.5	1.1
- Lundu	1	0	0	1 (5.9)	20.4	4.9
- Bau	0	0	0	0 (0.0)	31.9	0.0
Serian	0	0	1	1 (5.9)	53.5	1.9
Samarahan	0	1	2	3 (17.6)	50.5	5.9
Sri Aman	0	0	0	0 (0.0)	39.4	0.0
Betong	0	0	1	1 (5.9)	63.5	1.6
Sarikei	0	1	1	2 (11.8)	33.8	5.9
Mukah	0	0	0	0 (0.0)	28.8	0.0
Sibu (HTC)	1	1	3	5 (29.4)	164.5	3.0
Kapit	0	0	0	0 (0.0)	32.2	0.0
Bintulu (HTC)	0	0	0	0 (0.0)	145.1	0.0
Miri (HTC)	0	0	0	0 (0.0)	230.7	0.0
- Miri	0	0	0	0 (0.0)	190.6	0.0
- Marudi	0	0	0	0 (0.0)	40.1	0.0
Limbang	0	0	0	0 (0.0)	52.7	0.0
- Limbang	0	0	0	0 (0.0)	28.7	0.0
- Lawas	0	0	0	0 (0.0)	24.0	0.0
Inhibitors	0	0	0	0 (0.0)		

HTC: Haemophilia treatment centre

Table III: Incidence of haemophilia A and B in Sarawak, Malaysia from 2011 to 2019

Year	Live birth (male) in Sarawak[5,7]	Haemophilia A birth	Incidence	Haemophilia B birth	Incidence
2011	22,318	4	1 in 5578	0	0
2012	22,517	1	1 in 22,517	0	0
2013	20,415	3	1 in 6,805	0	0
2014	21,243	1	1 in 21,243	1	1 in 21,243
2015	20,551	2	1 in 10,276	0	0
2016	19,652	1	1 in 19,652	1	1 in 19,652
2017	19,547	1	1 in 19,547	1	1 in 19,547
2018	18,876	1	1 in 18,876	1	1 in 18,876
2019	18,876*	2	1 in 9,438	0	0
Total	183,995	16	1 in 11,500	4	1 in 46,000

*Data on total number of male live birth in Sarawak in 2019 was unpublished at the time of manuscript writing, thus the data in 2018 was used.

Table IV: Clinical profile of moderate haemophilia A patients receiving prophylaxis in Sarawak, Malaysia

No.	Gender	Ethnicity	Age of first bleed	Type of bleed	Type of FVIII concentrate	Target joint(s)	Inhibitor status and level
1	Male	Native	At birth	Sub-aponeurotic haemorrhage	Plasma	Absent	Absent
2	Female	Malay	11 months old	Left parietal, scalp and intramuscular haematoma	Recombinant, PEGylated (ADYNOVI)	Absent	Absent
3^	Male	Native	3 years old	Left ankle haemarthrosis and iliopsoas haematoma	Plasma	Left elbow, left knee	Absent
4	Male	Native	10 years old	Iliopsoas haematoma	Plasma	Absent	Absent

^ This patient underwent left knee radiosynovectomy

difficulties owing to widely varied geographical characteristics. Therefore, treatment regimens in Sarawak is tailored to the Sarawakian haemophilia population where we try to provide haemophilia care accessibility to all district hospitals. Patient and family-centered haemophilia courses are organized to promote a holistic care, which may be facilitated through shared decision making (SDM), an intervention in which the patient and healthcare professionals collaborate in making healthcare decisions based on the best interest of patients. As Sarawak has limited transportation accessibility and this poses significant challenges to many patients, we try to encourage, engage and train parents and patients to self-administer the factor concentrates at home.

The inhibitor development rate for our HA population (11.4%) is slightly higher than the reported norms of 5 to 7%.[12] Due to the considerable cost, prophylaxis therapy with bypassing agents or bispecific antibody is not widely practised in Sarawak. Therefore, only three HA patients with inhibitors and significant bleeding events/ restricted mobility were treated with emicizumab. The relationship between inhibitor titres and treatment groups in our study was found to be statistically not significant, which might be attributable to the small sample size of our population who developed alloantibodies.

Genetic testing for HA and HB is available in Malaysia, adopting long range polymerase chain reaction (PCR) and DNA sequencing methods to detect genetic mutations in haemophilia. However, the take-up rate is not high due to cultural reasons by the local community. Awareness of haemophilia disease in Sarawak community needs to be ramped up in the future.

Limitations of this study include a small sample size and the results were generally descriptive. The data of haemophilia patients who deceased prior to the registry commencement date might be incomplete. Additional studies focusing on the quality-of-life of patients, socio-economic status, bleeding manifestations, complications and genetic mutations are warranted. It is also of utmost importance to study per capita usage of factor concentrate in addition to the related cost-utility and cost-effectiveness analysis.

In conclusion, this study outlines haemophilia landscape in Sarawak and thus can offer objective standards for planning ahead. Shared responsibility among haemophiliacs, families, care providers, public agencies, non-government organizations (NGOs) and insurance policy makers should be heightened so as to improve the care of our haemophilia population. An economic evaluation should be conducted to determine the best model of treatment for haemophilia patients in Sarawak.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval for this study was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia with registered ID NMRR-19-2722-50668.

COMPETING INTERESTS

The authors declare that they have no competing interest.

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The authors declare no financial disclosure.

AUTHORS' CONTRIBUTIONS

ASOT was responsible for the study design, data collection, data analysis and manuscript writing. QYW, YYT, CHC and CTK participated in data collection and contributed to data analysis. GBO and LPC were involved in the study design and manuscript editing. All authors read and approved the final manuscript.

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