A multicentre, retrospective study of epidemiology and outcome of aplastic anaemia among adult population in Sabah and Sarawak from year 2006 to 2017

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ABSTRACT

Introduction: Aplastic anaemia (AA) is a rare disorder of bone marrow failure, characterized by bone marrow hypocellularity with pancytopenia. The annual incidence rates of AA in Asia are observed to be two to three times higher than Europe and North America. Since the introduction of immunosuppressive therapy (IST) and of allogenic stem cell transplant (SCT), the outcome of severe AA has significantly improved. We conducted a 12-year multi-centre retrospective study among the adult AA population in Sabah and Sarawak.

Materials and methods: A total of 119 AA patients had been identified from hospital records of the involved sites, namely Queen Elizabeth Hospital in Sabah, Sarawak General Hospital, Sibu Hospital, Miri Hospital and Bintulu Hospital in Sarawak from Jan 2006 to Dec 2017.

Results: The median age at diagnosis was 46 years, and native ethnic group from Sabah, Kadazan-Dusun, recorded the highest percentage of 41.2%, which could be explained by higher frequency of HLA-DRB1*15:01, an alelle linked to increased risk of AA, among this ethnic group. The majority of patients (59.7%) received cyclosporine (CsA) as monotherapy or in combination with other non-IST agents such as danazol, which was instituted in 48.7% of the patients, while a third of them (33.7%) received anti-thymocyte globulin (ATG) therapy with or without CsA, and 12.4% underwent allogenic SCT. The five-year overall survival (OS) for all AA patients was 76.1%. Elderly patients >60 years old and those with severe disease had more inferior 5-year survival.

Conclusion: A prospective study is warranted to determine the true incidence rate, epidemiological distributions, treatment outcome and overall survival of AA patients in Malaysia. Establishment of allogenic SCT in East Malaysia is imperative to make this curative therapy more accessible to patients with severe disease and improve the outcome.

KEYWORDS:
Aplastic anaemia, epidemiology, outcome, Sabah and Sarawak

INTRODUCTION

Aplastic anaemia (AA) is a rare disorder of bone marrow failure, characterized by bone marrow hypocellularity with peripheral blood pancytopenia. The annual incidence rates of AA in Asia, including countries like China, Korea, Japan and Thailand, are observed to be two to three times higher than Europe and North America, where the annual incidence is approximately 2.0 per million population per year.[1] In Malaysia, a retrospective epidemiological study of AA had been conducted in Sabah in the nineties, which revealed significantly higher incidence of AA at 4.8 per million population per year among the South East Asia regions with significant preponderance of the Kadazan-Dusun ethnic group.[2] Although AA has been known to be associated with several aetiologies, including environmental exposure to chemical, medical drugs and viral infections, it has also been linked to genetic susceptibility of certain population to AA.[3] Aplastic anaemia can be life-threatening in its severe form, with early mortality rate at three months as high as 22.6% in the very severe group of a Swedish cohort.[4] However, the outcome has significantly improved with 5-year survival of 70-80% in selected patient cohorts since the introduction of immunosuppresive therapy (IST) and of allogenic stem cell transplant (SCT).[4] In view of the lack of local epidemiological data in AA for the last two decades, this 12-year multi-centre retrospective study was performed to gain a better understanding of the demographic characteristics of AA and to look into real-world treatment outcome among the adult AA population in Sabah and Sarawak.

MATERIALS AND METHODS

A total of 259 adult AA patients had been identified from hospital records and new case registration of the involved sites, including Queen Elizabeth Hospital (QEH) in Sabah, Sarawak General Hospital, Sibu Hospital, Miri Hospital and Bintulu Hospital in Sarawak from January 2006 to December 2017. All AA patients diagnosed in other hospitals in Sabah were referred to QEH for further management as there was only one haematologist in the whole state of Sabah during the study period, hence captured in the AA registration list at QEH. Ethical approval was obtained from Medical Research

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and Ethics Committee (MREC), Ministry of Health Malaysia with registered ID NMRR-18-2160-42948 prior to the start of any study-related activities. Informed consent was not applicable as this was a retrospective study involving data collection which did not involve any investigational product or procedure on the subjects.

Attempts had been made to trace the case notes and clinic folders from Haematology clinic and medical record unit of respective hospitals, and only 119 case notes were retrievable. There were 140 patients (diagnosed in earlier years) from the AA registry of QEH whose case notes were not traceable since QEH was not equipped with central computerised system for clinical notes documentation, hence they were not included in the study. The retrieved case notes were reviewed, and all the relevant information, including patient's demographic details, environmental and occupational exposure to chemicals and toxin, full blood count on presentation, diagnostic bone marrow results, treatment details and outcome, were tabulated into a predesigned case report form. Assessment of exposure to chemicals and toxins, such as solvents and pesticides, was done by history taking from patients or family members. Diagnostic bone marrow aspirate and trephine biopsy reports were traced from the central pathology laboratory of Queen Elizabeth Hospital and Sarawak General Hospital, which handle all the bone marrow trephine specimens from the whole state of Sabah and Sarawak respectively, and reviewed to confirm the diagnosis of AA. Aplastic anaemia is defined as pancytopenia with a hypocellular bone marrow in the absence of an abnormal infiltrate or marrow fibrosis with at least two of the following: haemoglobin concentration (Hb) <10 g/dL, platelet count <50 x $10^3/\mu$L, neutrophil count <1.5 x 10/μL. Disease severity was classified according to modified Camitta criteria as followed:[5]

1. Severe AA (SAA): Marrow cellularity <25% (or 25-30% with <30% residual haematopoietic cells), plus at least two of: (i) neutrophils <0.5 x$10^3/\mu$L, (ii) platelets <20 x$10^3/\mu$L (iii) reticulocyte count <20 x$10^3/\mu$L (<60 x$10^3/\mu$L for automated reticulocyte counting)
2. Very severe AA (VSAA): As for SAA but neutrophils <0.2 x$10^3/\mu$L
3. Non-severe (NSAA): AA not fulfilling the criteria for SAA or VSAA

Outcome assessment was done at one year, three years and five years from the date of diagnosis, which was based on response criteria from 'Guidelines for the diagnosis and management of adult aplastic anaemia' of British Society for Haematology 2016:[5]

(a) Response criteria in severe/very severe AA

- None (NR)
  Still fulfil severe disease criteria
- Partial (PR)
  Transfusion independent
  No longer meet criteria for severe disease
- Complete (CR)
  Haemoglobin concentration normal for age and gender
  Neutrophil count >1.5 x$10^3/\mu$L
  Platelet count >150 x$10^3/\mu$L

(b) Response criteria for non-severe AA

- None (NR)
  Blood counts are worse, or do not meet criteria below
- Partial (PR)
  Transfusion independence (if previously dependent) or doubling or normalization of at least one cell line or increase of baseline:
  - Haemoglobin concentration of >3 g/dL (if initially <6)
  - Neutrophils of >0.5 x$10^3/\mu$L (if initially <0.5)
  - Platelets of >20 x$10^3/\mu$L (if initially <20)
- Complete (CR)
  Same criteria as for severe disease

Patients with congenital or secondary bone marrow failure due to chemotherapy or radiotherapy, hypoplastic MDS and patients of age 12 years and below at the time of data collection were excluded from the study.

Demographic characteristics of patients were summarised using descriptive statistics, such as median for numerical variables, frequency and proportion for categorical variables, which were presented in tables. Association of different treatment modalities to disease outcomes was assessed using Pearson's Chi-square test at 0.05 significance level. Overall survival (OS) was defined as the time taken from confirmation of diagnosis to death from any cause or last follow-up. Mortality was confirmed through hospital certification of death or National Registration Department (JPN). Patients who were alive or lost to follow-up were censored. The OS rates were calculated using Kaplan-Meier (KM) method for three months, one year, three years and five years. Differences in OS between groups were compared and tested using the Log-rank test at 0.05 significance level.

RESULTS

Epidemiological characteristics

A total of 119 adult patients with confirmed diagnosis of AA had been identified over the 12-year study period, with 82 patients from Sabah and the remaining 37 from Sarawak. The number of AA cases retrieved in each year from 2006 to 2017 for Sabah and Sarawak is represented in Figure 1. Female preponderance was observed among the AA patients in this cohort, with a male-to-female ratio of 1:1.64. The median age at diagnosis was 46 years, and the majority of patients were from the late middle age group 40-59 years (37.8%, n=45), followed by young adult group 19-39 years (31.9%, n=38) (Table I). Native ethnic group from Sabah, Kadazan-Dusun, recorded the highest percentage 41.2% (n=49), followed by Malay and Bajau, who both recorded 10.9% (n=13) respectively, while Iban had the highest percentage 7.6% (n=9) among the other Sarawak indigenous groups.

Clinical characteristics

Analysis of the clinical characteristics of AA patients revealed that the lowest median pre-transfusion haemoglobin upon presentation was 5.95 g/dL, white blood count (WBC) 2.3x10^3/uL, absolute neutrophil count (ANC) 0.6x10^3/uL and platelet 7x10^3/uL for all severity groups. About half of the patients (n=61) were classified as having severe AA upon presentation, while 23.5% (n=28) had very severe AA. In the

Table I: Demographics of Aplastic Anaemia patients (n=119)

Variables	N	(%)	Age at diagnosis Median
All	119		46 years
Age groups at diagnosis			
13 – 18 years	12	(10.1)	
19 – 39 years	38	(31.9)	
40 – 59 years	45	(37.8)	
60 and above	24	(20.2)	
Gender			
Male	45	(37.8)	31 years
Female	74	(62.2)	51 years
Ethnic groups			
Kadazan-Dusun	49	(41.2)	47.0 years
Malay	13	(10.9)	42.0 years
Bajau	13	(10.9)	28.0 years
Chinese	12	(10.1)	57.0 years
Iban	9	(7.6)	42.0 years
Bidayuh	4	(3.4)	48.5 years
Rungus	3	(2.5)	29.0 years
Others	15	(12.6)	

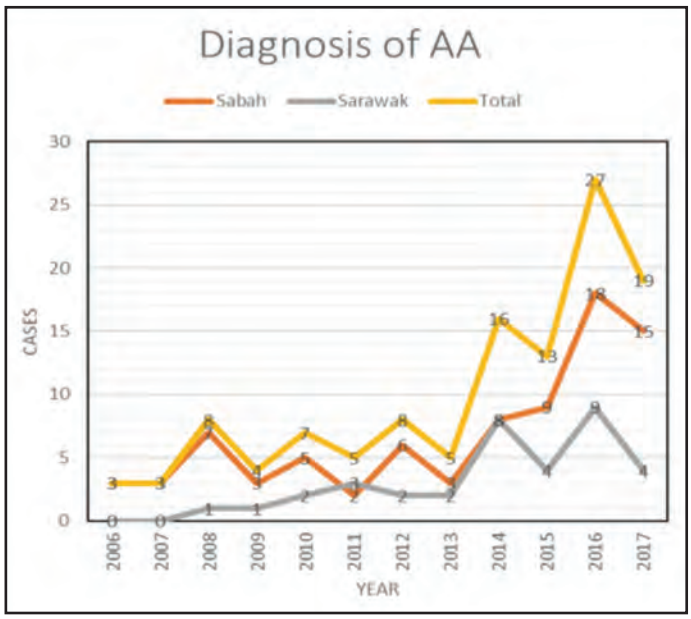

Fig. 1: Number of aplastic anaemia cases retrievable in Sabah and Sarawak from year 2006 to 2017 (n=119)

SAA category, patients aged between 40 and 59 years recorded the highest number of 23/61 (37.7%), followed closely by 22/61 (36.1%) patients from the young adult age group 19-39 years (Figure 2). It was also observed that a total of 39 patients (43.8%) from SAA and VSAA groups were from the transplant-eligible age group of below 40 years old. 19.3% of this cohort (n=23) were elderly patients aged 60 years and above, and 17 of them had severe and very severe disease.

Treatment

Among the SAA and VSAA patients (n=89), only 11 of them (12.4%) underwent allogenic SCT as curative treatment, while those who were not transplant-eligible (33.7%, n=30/89) received anti-thymocyte globulin (ATG), mostly in combination with CsA, as immunosuppressive therapy. Patients who underwent allogenic SCT and received ATG therapy were from the younger age group, with the median age at diagnosis 26 years and 32 years respectively. More than half of the patients from all severity groups (59.7%, n=71) had received cyclosporine (CsA), either as single-agent IST or in combination with other non-IST agents. 24 patients (20.2%) who were unable to tolerate or failed to respond to CsA had also received other IST agents, including mycophenolate mofetil (MMF) and tacrolimus, as the second-line treatment. Two non-IST agents, namely danazol and eltrombopag, were also used across all severity groups, with danazol being instituted in almost half of the patients (48.7%, n=58) patients, and eltrombopag in only 4 patients.

Outcome

Patients with NSAA, who all received non-ATG oral therapy,

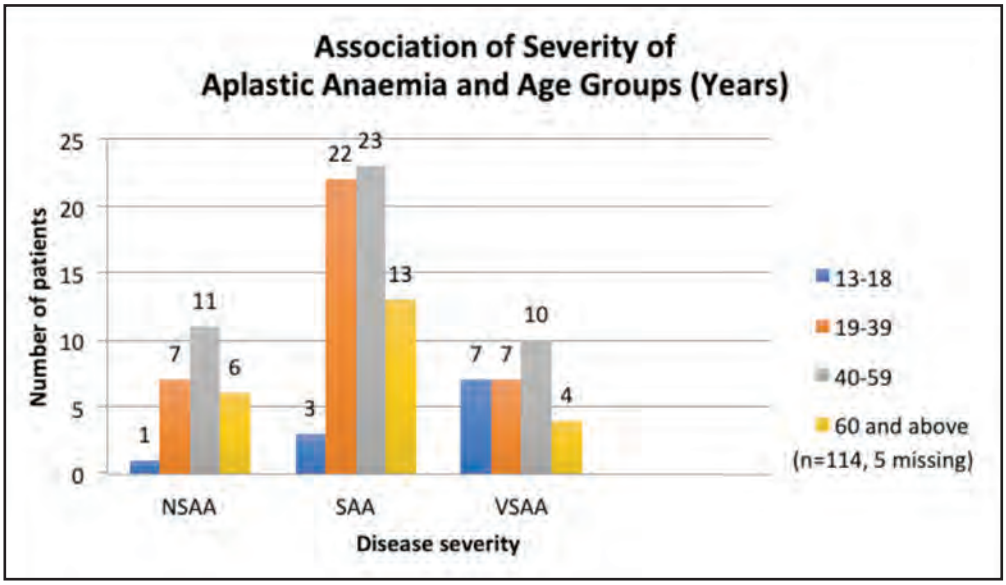

Fig. 2: Number of aplastic anaemia cases in different age groups according to disease severity (n=114, 5 with missing severity data)

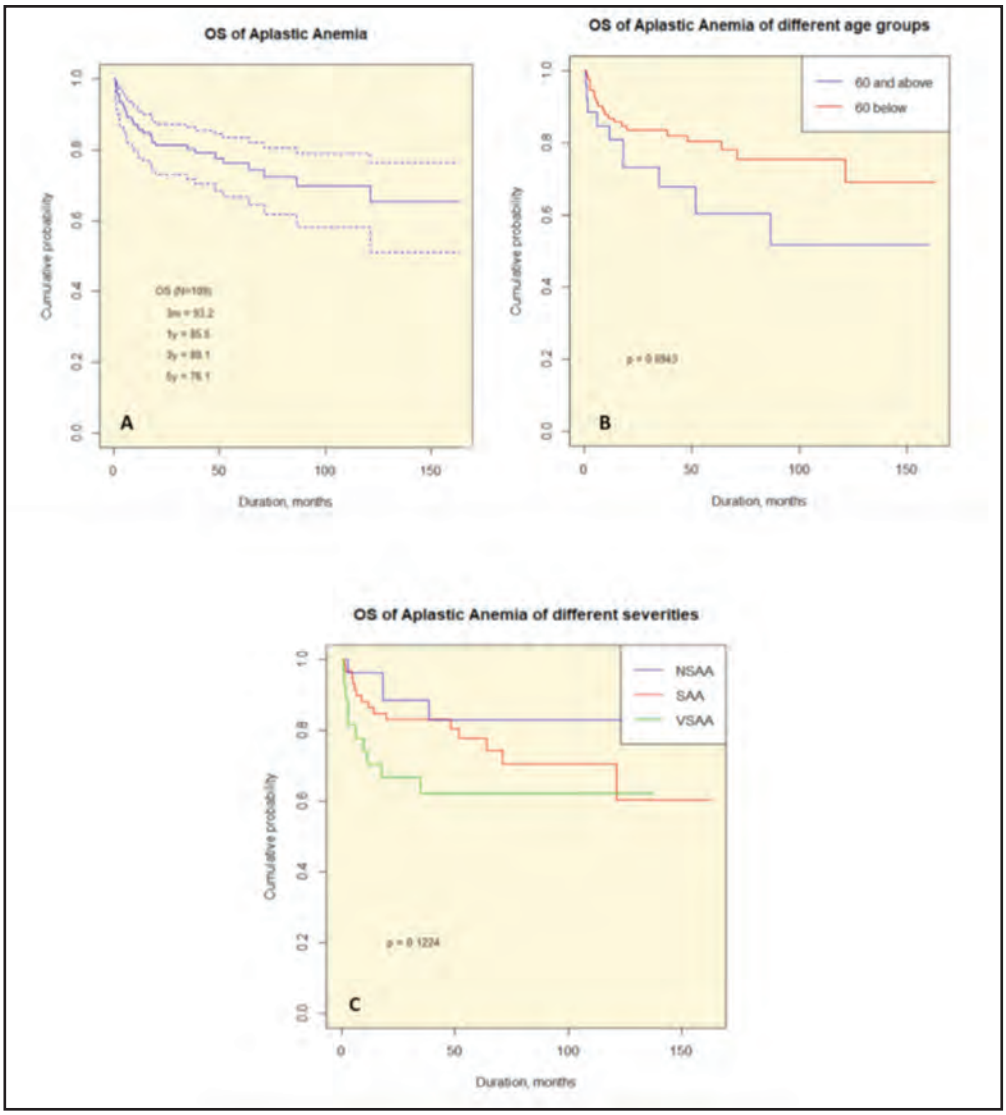

Fig. 3: A) Overall survival at 3 months, 1 year, 3 years and 5 years; B) overall survival by age group below and above 60 years; C) overall survival by disease severity

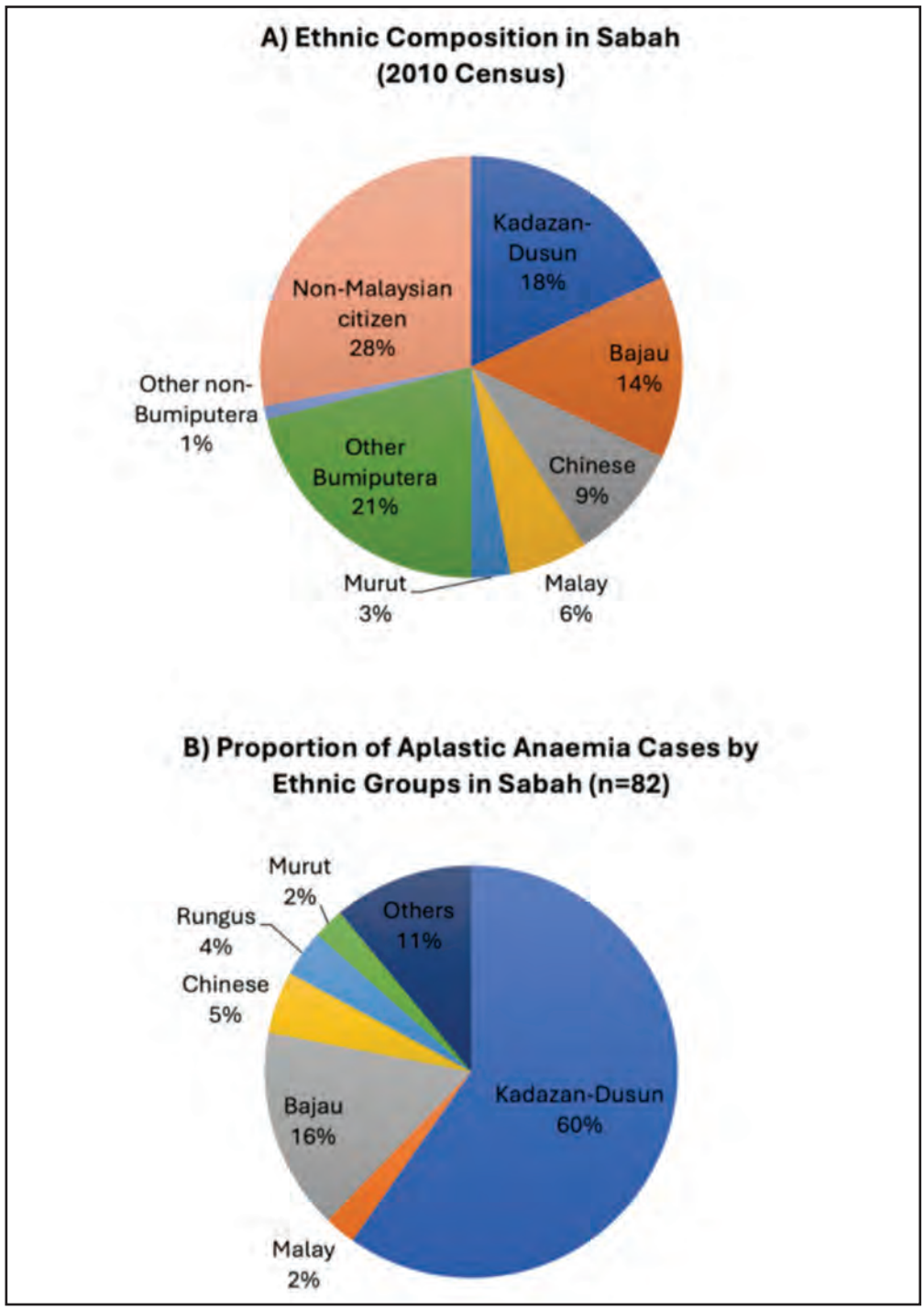

Fig. 4: A) Ethnic composition in Sabah according to Malaysian population census 2010; B) Proportion of aplastic anaemia cases by ethnic groups in Sabah (n=82)

demonstrated an overall response rate of 75% (complete response, CR 16.7% and partial response, PR 58.3%) with a lower mortality rate of 16.7% compared to those with severe disease. In the SAA and VSAA groups, the CR rates were 24.6% and 25% respectively, and the mortality rates were observed to be higher at 24.6% for SAA and 39.3% for VSAA patients in our cohort. Of the 11/89 patients (12.4%) with SAA and VSAA who had undergone allogenic stem cell transplant, 9 of them achieved complete response (CR), while 2 deaths were observed due to upper gastrointestinal haemorrhage and undetermined cause. The remaining non-transplanted patients in these both severity groups had poorer outcome, with 40.3% (n=31) of them demonstrating no response or death. Patients who were not transplant-eligible were analysed according to ATG and non-ATG treatment group, and it was found that there was no significant difference in the treatment outcome in terms of CR rate (20% and 24.6%) and PR rate (40% and 38.6%) (p=0.887). In the non-ATG treatment group, outcome was not assessed according to individual IST and non-IST groups due to treatment heterogeneity.

Survival

The median follow-up duration was 45.8 months, with a total of 31 deaths during follow up. The three-month, one-year, three-year and five-year overall survival (OS) for all AA patients was 93.2%, 85.5%, 80.1% and 76.1% respectively (Figure 3A). Patients in the elderly age group >60 years were observed to have a dismal outcome, with five-year OS of only 60.3% compared to patients <60 years (80.3%) (p=0.0943) (Figure 3B). Further analysis of patients aged below 60 years showed an overall trend of a better outcome in the younger age groups although not achieving statistical significance (p=0.2). There was no significant difference in OS between male and female genders (p=0.40). Patients with VSAA were observed to have the lowest 5-year OS of 62.2%, compared to those with SAA (77.6%) and NSAA (82.9%) (p=0.12) (Figure 3C). Among the patients who had severe disease and were not transplant-eligible, the 5-year OS rate of SAA patients who received ATG treatment was observed to be higher (93.3%) compared to the non-ATG treatment group (79.4%), although this was not statistically significant (p=1.0). The 3-year OS rate of VSAA in the ATG treatment group (64.3%) also appeared to be superior compared to the non-ATG treatment group (42.9%) despite lacking statistical significance (p=0.40).

DISCUSSION

The frequency of newly-diagnosed aplastic anaemia cases has been observed to be significantly higher in the state of Sabah than any other parts of Malaysia. An epidemiological study of AA in Sabah by Yong et al (2) in the nineties revealed an annual incidence rate of 4.8 per million population, which was higher than that of other South East Asian countries.[2] Since then, there is lack of epidemiological or outcome data on AA in Malaysia, which prompted us to embark on this retrospective study to gain more understanding in the epidemiology and outcome of AA in Sabah. We also included the state of Sarawak as Sarawak is situated on the Island of Borneo which may share similar ethnicities and cultural behaviour as its neighbour Sabah. Hence it would be interesting to explore if there was any difference in the AA epidemiological and outcome data of both states.

From the data collected, it was observed that the number of new cases diagnosed in Sabah each year had been consistently higher than that in Sarawak, and the total number of cases recorded in Sabah over the 12-year period of this study (n=82) was more than twice higher than that recorded in Sarawak (n=37). The population of Sabah from Malaysian Census 2010 was reported as 3.21 million, ranking the third among other states and was slightly more populous than Sarawak, which reported a population of 2.47 million in the fourth place.[6] However, the incidence rate was not analysed as slightly over half of the case notes of the patients from the Sabah AA registration list were not retrievable, hence rendering the incidence rate to be under-reported if it were to be analysed. This is a major limitation of this retrospective study, as most of the hospitals in the state of Sabah and Sarawak still rely on manual documentation of clinical notes, except for Bintulu Hospital in Sarawak, and many of the initial volumes of case notes containing diagnostic clinical and laboratory information were not retrievable, especially for patients who were diagnosed in the earlier years of this study period.

Another interesting demographic finding is that the native ethnic group of Kadazan-Dusun from Sabah was observed to be of the largest proportion (41.2%) of the total AA cases (Figure 4B). In comparison to the percentage of the Kadazan-Dusun in Sabah population, which was only 18% according to the 2010 Malaysian census (Figure 4A),[6,7] the percentage of AA cases diagnosed among the Kadazan-Dusun in Sabah was disproportionately higher at 59.8%. This striking finding is better depicted when the calculated incidence of AA among the Kadazan-Dusun revealed an incidence rate of 113.1 per million population compared to only 16.7 per million population among the non-Kadazan-Dusun AA patients in Sabah. Similar observation had been reported by Yong et al, who also found the Kadazan-Dusun to represent a large proportion of 77% of their AA study cohort in Sabah.[2] A genetic study performed by Institute for Medical Research, Malaysia in 2010 among the Kadazan-Dusun AA patients and genetically-matched controls in Sabah had demonstrated that there was increased frequency of HLA-DRB1*15:01 among the Kadazan-Dusun, and this allele was significantly associated with AA.[8] In another meta-analysis by Liu et al in 2016, it was concluded that HLA-DRB1*15 and HLA-DRB1*15:01 polymorphism were potential risk factors for AA in the majority of the studies,[9] which could probably explain the increased incidence of AA among the Kadazan-Dusun ethnic group.

In recent years, a few population-based studies have demonstrated that age is one of the prognostic factors which determines the survival rate in AA patients. In a Sweden AA study in 2000-2011, the five-year OS of AA patients aged above 60 years was significantly lower (38.1%, p=0.001) compared to those aged between 40-59 years (70.7%, p=0.029), and Taiwan nationwide population AA study (2001-2010) demonstrated similar inferior five-year OS in patients above 60 years old (38%, p=<0.001) compared to patients aged between 40-59 years (60.9%).[4,10] Patients aged above 60 years from our study cohort were also observed to have more inferior five-year OS (60.3%) compared to those below 60 years (80.3%), although not statistically significant (p=0.094). Among all the severity groups, patients with severe disease were also observed to have poorer outcome (Figure 3C), with VSAA group doing the worst. Other population studies in Sweden, Taiwan and China have also demonstrated similar trend of OS according to disease severity.[4,10,11]

Despite the dismal outcome in patients with severe aplastic anaemia, long-term survival can be achieved in a major proportion of the patients with the advent of allogenic stem cell transplantation and immunosuppresive therapy as the definitive treatment.[12] In patients younger than 40 years with HLA-matched sibling donor, stem cell transplant should be the first-line therapy.[13] In this study cohort, there were 39 patients with SAA and VSAA younger than 40 years old, but only 11 patients underwent allogenic SCT. Inavailability of HLA-matched sibling donor was likely one of the reasons that some of the remaining 28 patients were not transplanted. In

addition, logistic and financial issues were also among the compounding factors that hindered patients from the East Malaysian states to travel all the way to Ampang Hospital in West Malaysia, which is the referral centre for Sabah and Sarawak for allogenic stem cell transplant. Since the survival outcome of SAA and VSAA had been shown to be more inferior compared to NSAA, and a significant proportion (43.8%) of patients with severe and very severe disease in this cohort were aged younger than 40 years, more patients should be aimed for allogenic stem cell transplant as the first-line treatment if HLA-matched sibling donor is available. The establishment of allogenic stem cell transplant service in Sabah and Sarawak will likely be able to overcome the logistic issues as mentioned earlier and increase the opportunities of patients being cured of this potentially fatal disease. In the absence of matched sibling donor, matched unrelated donor transplantation, which is offered in Ampang Hospital, can also be considered in younger patients who fail first-line immunosuppresive therapy.[13] First-line immunosuppresive therapy (IST) usually consists of horse or rabbit anti-thymocyte globulin (ATG) in combination with cyclosporine for patients with severe disease, with a response rate of 60-80%.[14] Of 89 patients with SAA and VSAA in this study, only 30 patients (33.7%) received ATG and cyclosporine as the first-line IST. More than half of the patients with severe disease (53.9%) did not receive ATG and were treated with cyclosporine with or without danazol. Due to vast geographical factor, many AA patients in Sabah and Sarawak presented late to the nearest healthcare facilities in critically ill condition with neutropenic sepsis, hence rendering them unfit for ATG as the initial IST. In addition, elderly patients above 60 years old, who constituted 19% of the SAA and VSAA groups, were generally the frailer group and at higher risk of acute and delayed toxicities of ATG-based treatment, resulting in lower ATG uptake as IST among patients with severe disease.

Several limitations had been identified in our study, and one of them was the retrospective study design, in which data collection process was hindered by lack of central or computerised data storage and effective data tracing system in the involved sites. From the total 259 AA patients identified, 222 patients were obtained from QEH AA registration list from year 2006 to 2017, but only 82 case notes were retrievable and the remaining 140 were unaccounted for. The majority of the unretrievable case notes belonged to patients diagnosed in earlier years and those who were deceased or no longer under active clinic follow up. 37 AA patients were identified from the hospital sites in Sarawak via manual tracing of case note filing and clinic registration book. However, there is still a possibility that some deceased AA patients diagnosed in the earlier years were not captured due to manual tracing method. Failure to trace the case notes of slightly more than half of the total patients identified (54%) is a major limitation to the study, resulting in our inability to accurately report the incidence rate of AA among adult population in Sabah and Sarawak. Nevertheless, the number of AA cases in Sarawak had been observed to be lower compared to Sabah over the years of study period. Other epidemiological data, including occupation and exposure to chemical toxins, were largely missing for many patients due to the retrospective nature of the study, and hence not analysed and reported. Although AA can be part of the disease spectrum of paroxysmal nocturnal haemoglobinuria (PNH), there was lack of PNH data for analysis as PNH screening test was not readily available in Sabah and Sarawak during the study period. Other limitations include small sample sizes for treatment subsets and number of deaths, which might have resulted in lack of sufficient statistical power to detect significant differences. There was also likely selection bias in view of the heterogeneity of our patients and long treatment period with a variety of treatment and supportive care modalities. In patients with severe disease who were not transplant eligible, a selection bias would be expected to occur in those who were younger and fitter for ATG treatment, and a proportion of those who were elderly or unfit would have either succumbed to the complications of severe AA or excluded from ATG treatment.

CONCLUSION

Although Sabah and Sarawak are located on the same Borneo Island, a significantly higher frequency of aplastic anaemia cases among the adults is observed in Sabah compared to Sarawak, particularly among the native Kadazan-Dusun ethnic group, who are likely to be genetically susceptible to the disease. Advanced age above 60 years and severe disease are likely associated with inferior outcome. Despite the dismal outcome in patients with severe aplastic anaemia, long-term survival can be achieved in a major proportion of the patients with the advent of allogenic stem cell transplantation and immunosuppresive therapy as the definitive treatment.[12] A nationwide prospective study is warranted to gain accurate information on incidence rate, epidemiological distributions, risk factors, treatment outcome and overall survival among AA patients in our country.

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