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# CONTENTS

# Seremban Diabetes (SeDia) Cohort Study – A Study Proposal

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Diabetes is a major public health problem and involves a complex interplay of multiple factors. Being a non-communicable disease that has been described as "a pandemic of unprecedented magnitude spiralling out of control",[1] diabetes has been recognised as one of the fastest growing global health emergencies of the 21st century. In 2021, it was estimated that 537 million people have diabetes. Should there be no sufficient actions be taken to address the situation, this number is projected to reach 643 million by 2030, and 783 million by 2045.[1]

Diabetes has the highest rate of prevalence in Asia and one of the highest in the world. The prevalence of diabetes is steadily increasing everywhere. Worryingly, the prevalence of type-2 diabetes mellitus (T2DM) in Malaysia have almost doubled over the past 10 years and now includes rapidly rising numbers of children and adolescents.[2] At present, 1 in 5 adults (about 3.9 million people) aged 18 and above in Malaysia have diabetes,[3] the highest rate of incidence in Asia and gaining the title of "Sweetest Nation in Asia". It is projected that seven million Malaysian adults are to have diabetes by 2025, a worrying trend that will see diabetes prevalence of 31.3% for adults aged 18 years and above (1 in 3 adults).[4]

Diabetes imposes a substantial economic burden on countries, health systems, and patients with diabetes as well as their family members.[5-7] There has been considerable increase in global health expenditure due to diabetes, increasing from USD 232 billion in 2007 to USD 966 billion in 2021 for adults aged 20-79 years, representing a drastic 316% increase over a span of 15 years.[1] Nevertheless, the direct costs of diabetes are still anticipated to grow. It was estimated by the International Diabetes Federation (IDF) that total diabetes-related health expenditure will reach USD 1.03 trillion by 2030 and USD 1.05 trillion by 2045.[1] In Malaysia, the estimated total annual cost of diabetes was approximately USD 600 million in 2010 alone.[8, 9]

Among the Malaysian diabetes patients, almost 80% seek treatment at Ministry of Health (MOH) healthcare facilities.[10] Majority of the patients sought treatment at MOH health clinics (68.2%), followed by MOH hospitals (15.0%), private clinics (12.1%) and private hospitals (2.8%).[3] It was reported in 2017 that the annual direct healthcare costs from diabetes in Malaysia totalled about RM4.4 billion, 227 per cent higher than cancer (RM1.3 billion) and 11 per cent higher than cardiovascular disease (RM3.9 billion).[11] In addition, the proportion of Malaysians with risk factors for diabetes is still high.[3] This will indeed result in a substantial economic burden to the healthcare system and national economy. Certainly, this deserves attention and actions from all parties before the Malaysian healthcare system collapses.

Despite its name as being a disease of over sweetness, diabetes also entails with many disabling and life-threatening health complications which devastate the life of the sufferers. Diabetes causes vascular damage in multiple organ systems, leading to increased risk of cardiovascular diseases (CVD), nerve damage (neuropathy), chronic kidney disease (nephropathy), lower limb amputations, eye disease mainly affecting the retina (retinopathy) resulting in visual loss and even blindness.[1] The National Diabetes Registry 2019[12] audited 181,634 type 2 diabetes patients from 830 health clinics. The comorbidities reported for these patients were:

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(i) 80.4% hypertension;
(ii) 74.3% dyslipidemia;
(iii) 14.6% nephropathy;
(iv) 10.6% retinopathy; and
(v) 5.9% ischemic heart disease.

Moreover, incidence rates of serious diabetes-related complications like end-stage renal disease and lower extremity amputations are much higher in Malaysia as compared to other high-income countries.[13] Also based on the National Diabetes Registry 2019, there is a significant gap in the management of diabetes with more than 54.9-87.8% of the diabetes patients not achieving treatment targets.[12] Clearly, the global burden of such complications is huge, with diabetes now a leading cause for end stage renal disease, blindness and disability.[12, 14, 15] Rates of T2DM and related complications vary significantly across countries and regions. In particular, Asians are not only at higher risk for T2DM at lower levels of obesity and younger ages but also at increased risk of adverse outcomes.[16] Therefore, diabetes and diabetes-related complications contribute substantially to the global burden of disease, in terms of morbidity,[17] mortality,[18] reduced quality of life,[19, 20] and economic cost.[21]

Studies had reported that the risk of developing diabetes increased with the number of family members with diabetes, with the strongest risks being associated with children, where both parents had diabetes, as well as twins with a diabetic sibling.[22] It was remarked that offspring who have one parent with T2DM have an absolute risk of 20–40% of developing the condition.[23] Similarly, the risk also increased for individuals with a genetically unrelated family member with diabetes, such as a second-degree relatives and spouses.[22] Subgroup analysis of males versus females, and diabetic parents age below or above 60 years odds also portrayed similar results.[22] These findings are in line with a few studies conducted abroad[24-26] which found familial aggregation patterns of diabetes including half-siblings, first-degree relatives with type 1 and type 2 diabetes, as well as non-related family members. These findings strongly suggest that not only genetic dispositions, but also environmental factors would increase the risk of diabetes substantially.

The exponential increase in diabetes cases is significant as it does not only cause profound psychological and physical distress to both patients and carers, but also is becoming a major economic burden on the healthcare system and national economy. Nevertheless precision health promises a personalized intervention aimed at helping individuals achieve well-being and optimal health based on individual lifestyle, genetics, behaviours, and environment context. Unfortunately, the lack of longitudinal real-world data on T2DM management patterns and associated outcomes in a large number of Malaysian T2DM patients has hindered us to address this disease as a system problem, as opposed to a simple problem with a linear cause-and-effect relationship.

Besides, there is evidence for effective interventions to improve management of diabetes and to reduce its modifiable risk factors, but there are significant gaps in the knowledge base to translate these findings into action plans for the prevention, care and cure of diabetes in Malaysia. We hypothesize that genetics, individual lifestyle, environment and the socio-economy network dynamics, acting at different scales are contributing to T2DM. In addition to these, tertiary prevention of diabetes is also critical. Complications like end-stage renal failure (ESRF),

strokes and other major complications are common where diabetes hurts most, both financially and health wise (DALYs, QALYs, economic burden of disease). Therefore, it is important to aim, not only for glycaemic level targets but for A1C, blood pressure, and cholesterol (ABC) goals and manage therapeutic inertia (physician-, patient-, and system-related factors). From the big picture (especially in terms of policy) perspective, system factors must not be neglected. Health economic perspective is important. In addition, the Wagner Chronic Care Model includes six essential elements of a health care system that when integrated encourage high-quality chronic disease care:

(i) Community resources;
(ii) Health system;
(iii) Self-management support;
(iv) Delivery system design;
(v) Decision support;
(vi) Clinical information systems.

What may be needed is a system approach to understand and address T2DM.

Factors contributing to diabetes risk such as diet quality and quantity, little physical activity, short or disturbed sleep, smoking, and stress and depression have been identified by many studies.[27] These have led to the development of various T2DM risk stratification models to identify high-risk individual based on known risk factors and have been integrated into clinical guidelines to help guide decision making.[28] Although numerous cohort studies have included diabetes as part of the analyses, most of these studies suffer from major limitations. First, majority of the studies focus on western population with minimal involvement of Asian. Furthermore, the socio demographics and culture might be completely different to Malaysia and may not be directly interpretable into the Malaysian context. Second, most of these studies are considered "opportunistic" and focused on understanding limited factors in isolation and oversimplify complex relationships. Third, most studies used conventional methods and did not capitalize on the growing importance of capturing multi-dimensional data using state-of-the-art digital health technology and big data at community level to enhance diabetes prevention and its long-term effects on morbidity and mortality, which will be critical. Fourth, most studies did not include primary care-led health intervention to prevent diabetes, nor study the long-term effects of such interventions.

Therefore, the Seremban Diabetes (SeDia) Cohort was set up with an aim to use a combination of approach at population and individual levels to study the determinants of complications in individuals with T2DM and examine the role of genetic, physiological, environmental, lifestyle and psycho-social factors in the development of T2DM and its complications. The study will contribute tremendously to the understanding of complex interplay between lifestyle, environment, genetics and socioeconomic development in contributing to the increased prevalence of T2DM and how to address it.

As a disease cohort in multiethnic Malaysia, the SeDia cohort includes the following unique features:

1. Focusing on T2DM (n = 5000) and their family members (n = 5000) in Seremban with a minimal 12-year follow-up. Of note, Negeri Sembilan (Figure I) has the highest diabetes incidence

in the country (33.2%)[3] and the population demographic is closely resembling the Malaysian population (in terms of racial distribution, socio-economic status and etc).

2. Addressing the needs of the country in understanding the causal-effects relationship of T2DM in Malaysia.

3. Addressing the non-linear interactions among genetics/ physiology, lifestyle, environment, psycho-social, and healthcare delivery in the prevention, management and cure for diabetes.

4. Utilizing state-of-the-art mobile health, electronic health records and genomics technology to capture multidimensional data from the same individual in the most cost-effective manner, creating opportunities for innovations in achieving better diabetes outcomes.

5. Incorporating both observational and interventional elements in the same cohort for comparative effectiveness analyses.


*Figure 1: Map of Peninsular Malaysia showing the study site (in red circle)*

Through the SeDia Cohort, it is anticipated to provide a more complete understanding of the etiopathogenesis of T2DM and its related complications in Malaysia, with the long-term objective of improving care and outcomes of the patients. The data collected from this cohort will ideate new concepts in creating, enabling and sustaining better supportive policy, social and physical environments for healthy lifestyles with the ultimate long-term goal to prevent, care and create cure for diabetes.

With the collective rationales, the objectives for SeDia Cohort are:

1. To determine the incidence rate and the risk factors (sociodemographic, dietary, psychosocial, biological such as genomics/genetics, glycoproteomics, metabolomics, proteomics, lipidomics, cytokines and adipokines, hormonal, biochemical) and their interaction for:
   i) the development and progression of renal impairment and chronic renal failure
   ii) the development and progression of diabetic retinopathy
   iii) the development of angina pectoris and myocardial infarction
   iv) the development of transient ischaemic attack and stroke
   v) the development of limb gangrene
   vi) the development of diabetic neuropathy
   vii) hospitalisation and mortality
2. To determine the incidence rates and risk factors (sociodemographic, dietary, psychosocial, biological such as genomics/genetics, glycoproteomics, metabolomics, proteomics, lipidomics, cytokines and adipokines, hormonal, biochemical) and their interaction for:
   i) the development and progression of insulin resistance
   ii) the development and progression of impaired glucose tolerance
   iii) the development and progression of diabetes among patients with T2DM and their family members.
3. To develop:
   i) predictive biomarkers
   ii) statistical models and algorithms
   iii) diabetes complications risk score for patients with T2DM and their household family members

The establishment, maintenance and governance of SeDia Cohort is a collaborative public-private partnership between International Medical University (IMU), Kuala Lumpur and the Ministry of Health (MOH), Malaysia, represented by Negeri Sembilan Health Department and Seremban District Health Office. A Memorandum of Understanding was signed on 17th May 2022 between MOH and IMU. A Joint Steering Committee between Jabatan Kesihatan Negeri Negeri Sembilan (JKNNS) and IMU has been set up which is responsible for making all decisions related to policies and activities, supervising and monitoring the implementation of this MOU.

Aside from that, a Scientific Advisory Panel (SAP) has also been established with the aim to provide expert review, appraisal and guidance on the study protocol, implementation, analysis and evaluation of the progress of this SeDia cohort. SAP is anticipated to meet on an annual. The members of the SAP are:

1. Prof Dato' Dr Mafauzy Mohamed, Honorary Professor of Medicine and Senior Consultant Endocrinologist, Universiti Sains Malaysia.
2. Datuk Dr Zanariah Hussein, Consultant Endocrinologist Hospital Putrajaya and Head of Endocrinology Subspecialty Service, MOH.
3. Prof Datuk Dr Rahman Jamal, Founding Director of UKM Medical Molecular Biology Institute

(UMBI) and The Malaysian Cohort (TMC), Universiti Kebangsaan Malaysia.

4. Prof Edward Gregg, Professor and Chair in Diabetes and Cardiovascular Epidemiology, Royal Society Wolfson Fellow, School of Public Health, Imperial College London.

SeDia is a long-term observational cohort study on patients with diabetes and their household members. Seremban Health Clinic is chosen as study site as it is the main primary care health clinic which provides population-based prevention, management, and control of diabetes in Negeri Sembilan state. Patients with diabetes will be followed up for risk factors related to poor glycaemic control and the development of diabetic complications. The household family members will be followed up for risk factors for the development of diabetes.

It will be an open cohort with recruitment open to all patients with diabetes registered under the National Diabetes Registry (NDR) who are being followed up at Seremban Health Clinic. Household family members of these index patients with diabetes are to be invited to participate in the cohort. Each subject will be followed-up for at least 12 years after enrolment as the diabetes complications usually progress over the next 10 to 20 years from onset.[29] Recruitment will be started in 2023 and continued throughout the study.

Data will be collected from the subjects via face-to-face interviews through a series of questionnaires including socio-demographic information, 24-Hours Diet Recall, Global Physical Activity Questionnaire (GPAQ v2.0), Brief COPE Scale, Finnish Diabetes Risk Score, Summary of Diabetes Self-Care Activities (SDSCA), as well as Malaysia Medication Adherence Assessment Tool (MyMAAT). Clinical data of all patients will be retrieved from the medical records in the clinic. Besides that, blood samples will also be collected from the study subjects.

As part of this study, a questionnaire data entry tool will be designed as a means for data input of each participant. Having to ensure accuracy of data collection in mind, the tool will be designed by the scientific expertise in the study team and subsequently developed by a professional vendor with experience in mobile application and web development. The developed tool will also serve as a sophisticated, stable platform for data storage while allowing data to be entered with ease. The system will be able to create reports and queries to compile necessary output files for managing the day-to-day activities of the study (for example data files to allow linkage to external data sources and summary participation statistics).

In addition, another MOU has also been inked with the Pantai Medical Centre Sdn Bhd of IHH Healthcare on 2nd August 2022. As part of this agreement, the IHH Healthcare had agreed to sponsor a total of RM2million for the SeDia Cohort Study.

Being the first large-scale cohort study on diabetes of its kind to be conducted in Malaysia, SeDia cohort study marks the first important step towards obtaining data that is socio-culturally relevant to the local community. By understanding the complex connections between various factors encompassing genetics and family history of diabetes to lifestyle and environmental factors, SeDia Cohort Study will ultimately uncover optimal strategies for diabetes prevention and treatment. Subsequently,

this knowledge can be translated into implementing evidence-based public healthcare policies and programmes that are relevant to the local community, ensuring the efficacy of developed treatment and prevention initiatives in addressing the escalating burden of diabetes in Malaysia. On top of that, the SeDia Cohort study also provides an opportunity for researchers to gain a deeper understanding of the role of genetics and the environment within the local community which will help further improve diabetes management guidelines and public health policies towards better health outcomes.

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# Awareness and acceptance of Pre-exposure Prophylaxis (PrEP) for HIV among undergraduate students in a private medical university in Malaysia

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**Background:**

Pre-exposure prophylaxis (PrEP) is an evidence-based strategy recommended for at-risk-populations for prevention of HIV transmission. However, the level of PrEP awareness and acceptance among Malaysian undergraduate students is currently unknown.

**Objectives:**

To assess the sexual activities, sexual behaviors, risk perception, awareness, and acceptance of PrEP of medical compared to non-medical students in a private medical university.

**Method:**

Demographic data, sexuality, sexual activity and behaviors, source of HIV knowledge, self- perceived risk of HIV, awareness and acceptance of PrEP were collected using an online anonymous survey among medical and non-medical students at a private medical university. Descriptive, comparative and regression analyses were performed where applicable. A *p*-value $< 0.05$ was considered statistically significant.

**Results:**

A total of 369 (187 medical, 182 non-medical) students responded. The median age was 22 with female:male ratio of 2:1. Eighty-one (22%) were sexually active of which 54% used condoms inconsistently, 58% had condomless sex in the preceding six months and 35% had casual or transactional sex. Despite this, 33 perceived themselves to be at low risk of HIV. Most learned about HIV from their coursework. PrEP awareness was 40% versus 20% while PrEP acceptance was 69% versus 67%, between medical and non-medical students, respectively.

**Conclusion:**

Awareness of PrEP among medical students was low and even lower among non-medical students. PrEP acceptance was fair after viewing an introductory video on PrEP. PrEP must be included in the course curriculum. Studies to identify reasons for PrEP-hesitancy should be conducted to help guide policies and initiatives toward promoting PrEP as an additional tool in HIV prevention.

***Keywords:*** *Preexposure prophylaxis, Malaysia, HIV, acceptance, awareness*

## Introduction

Pre-exposure prophylaxis (PrEP) against Human Immunodeficiency Virus (HIV) is the use of anti-HIV medication to keep HIV-negative people from being infected. PrEP is approved as an addition to the armament of effective tools for the prevention of HIV transmission by the U.S. Food and Drug Administration (FDA). PrEP has been shown to be safe and highly effective when taken as prescribed.[1]

Annually, there are up to two million new HIV infections worldwide. In the absence of an effective vaccine to prevent HIV transmission, behavioral and biomedical HIV prevention strategies to reduce HIV acquisition are the main strategies against HIV transmission. PrEP has been shown to reduce the risk of sexual transmission of HIV by between 75% to 99% in various at-risk populations.[2-6]

Many countries in the West have approved PrEP for HIV prevention while other countries, particularly in the Asia Pacific region, have embarked on several PrEP implementation projects.[7] In Malaysia, PrEP is

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part of the Ministry of Health's "National Strategic Plan to end AIDS by 2030". Until recently, the access and availability of PrEP is restricted to a small number of private clinics or hospitals in major cities. Awareness of PrEP in at-risk communities and the general public is low.

The age of sexual debut among university undergraduates in Malaysia aged between 17 to 30 years was 18.2 years with a prevalence of sexual intercourse of 20%. More than half of them reported engaging in sexual activities and behaviors that placed them at significant risk of acquiring sexually transmitted infections (STI) including HIV.[8] Another Malaysian study among adolescents aged between 15 – 21 years reported a prevalence of sexual intercourse of 9% with low level of contraceptive prevalence.[9] Clearly some adolescents and young adults in Malaysia are at greater risk of exposure to HIV and other STIs.

There are very few studies on awareness and acceptance of PrEP among university students in the Asia Pacific region. A Thai study among 641 university students in a public university reported that 67% were willing to accept PrEP.[10] The level of PrEP awareness and acceptance among Malaysian undergraduate students is currently unknown. This study was conducted among medical and non-medical undergraduate students from a private medical university in Malaysia to explore their sexual activities, sexual behaviors, risk perception, and the awareness and acceptance of PrEP of medical students compared to non-medical students.

## Methods

### *Study site and sample size calculation*

An online survey was conducted among medical and non-medical undergraduate students at the International Medical University (IMU), a private medical university in Malaysia. The study period was between November 2017 and June 2018. The total number of undergraduate students in the university at the time of the survey was 3111. The sample size required for statistical significance was calculated to be 342 with a 95% confidence interval, assuming a 20% non-participation rate.

### *Survey tool and recruitment of students*

The online questionnaire had five sections. The first section contained questions to collect demographic data such as gender, age, and course of study. The second section explored the relationship status, sexuality, sexual activities, and behaviors of the students in the preceding six months. The third section explored the sources from where the students had acquired their knowledge of HIV, prior HIV testing, self-perceived risk of HIV acquisition, and awareness of PrEP. In the fourth section, the participants were asked to watch a short introductory online video on PrEP.[11] In the last section, the participants were asked about their willingness to accept PrEP as an HIV-prevention tool. The average time to complete the questionnaire online was between 10 to 15 minutes. Recruitment of participants was done via invitation emails to the students' university email accounts and publicity via closed student groups on social media. Participation was voluntary and pre-participation consent was obtained online.

***Ethical approval***

This research project was approved by the Joint Research and Ethics Committee of the IMU (CSc/Sem6(04)2018).

***Statistical analysis***

Descriptive analysis methods were used to describe the demographic characteristics, including sexual activities and behaviors. Comparison between medical and non-medical students was made using chi-square analysis. A *p* value of <0.05 with a 95% confidence interval was considered statistically significant. All statistical analyses were conducted using the SPSS Version 20.0 (SPSS Inc., Chicago, IL)

**Results**

***Participants' characteristics and risk factors for HIV transmission of respondents.***

Out of 3111 students, 369 students (187 medical versus 182 non-medical) participated. The median age was 22 (range 18 – 36) years. The female to male ratio was 2:1. Most were not in a relationship (229, 62.1%), one-third were in monogamous relationship (130, 35.2%) and 10 (2.7%) students were in non-monogamous relationship. Most identified as heterosexuals (302, 81.8%) while 27 (7.3%) and 19 (5.1%) identified as homosexuals and bisexuals, respectively. Eighty-one (22.2%) students were sexually active. (Table I)

**Table I: Demographic characteristics of study respondents (n = 369)**

| | FREQUENCY | PERCENTAGE |
|---|---|---|
| **GENDER** | | |
| Female | 241 | 65.3 |
| Male | 128 | 34.7 |
| **COURSE OF STUDY** | | |
| Medical | 187 | 50.7 |
| Non-medical | 182 | 49.3 |
| **RELATIONSHIP STATUS** | | |
| Not in a relationship | 229 | 62.1 |
| In a monogamous relationship | 130 | 35.2 |
| In a non-monogamous relationship | 10 | 2.7 |
| **SEXUALITY** | | |
| Heterosexual | 302 | 81.8 |
| Homosexual | 27 | 7.3 |
| Bisexual | 19 | 5.2 |
| Prefer not to say | 21 | 5.7 |
| **SEXUALLY ACTIVE** | | |
| Yes | 81 | 22.2 |
| No | 288 | 77.8 |

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***Sexual activities and behaviors, HIV testing and self-perceived risk of HIV acquisition.***

Fifty-eight (15.8%) of 81 sexually active students had at least one sexual intercourse in the preceding month. Thirty-seven (10%) students reported condoms use all the time during sexual intercourse while 44 (12.0%) used condoms some of the time or not at all. Thirty-five students (9.5%) had condomless sex in the preceding month. Seventy-six students (20.5%) had between 1 – 10 sex partners while 5 (1.5%) students had more than 10 sex partners in the preceding month. (Table II)

Seventy students had regular sex partners while 21 students had casual sex partners. Four and three students either paid or were paid for sex, respectively. Seventy-one students had engaged in oral sex, 59 in vaginal sex and 22 in anal sex. One-hundred-thirty-nine (37.7%) students had tested for HIV in the preceding 6 months. Thirty-three (14.4%) students perceived themselves to be at low risk of HIV acquisition while 20 (37.8%) students perceived themselves to be at moderate to high risk of HIV acquisition. (Table II)

**Table II: Sexual behavior, sexual activities, HIV testing and perceived risk of HIV acquisition**

| | FREQUENCY | PERCENTAGE |
|---|---|---|
| **Last sexual activity (n = 81)** | | |
| < 1 month | 58 | 71.6 |
| 1 – 2 months | 13 | 16.0 |
| 3 – 4 months | 6 | 7.4 |
| 5 – 6 months | 2 | 2.5 |
| > 6 months | 2 | 2.5 |
| **Used condoms during sex in the preceding month (n = 81)** | | |
| All the time | 37 | 45.7 |
| Some of the time | 25 | 30.9 |
| Not at all | 19 | 23.4 |
| **Last condomless sex (n = 81)** | | |
| < 1 month | 35 | 43.2 |
| 1 – 2 months | 9 | 11.1 |
| 3 – 4 months | 2 | 2.5 |
| 5 – 6 months | 1 | 1.2 |
| > 6 months | 4 | 5.0 |
| Prefer not to say | 30 | 37.0 |
| **Types of sexual partners (n = 81)** | | |
| Regular partner | 70 | 86.4 |
| Casual partners | 21 | 25.9 |
| Paid for sex | 4 | 4.9 |
| Was paid for sex | 3 | 3.7 |

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**Table II: Sexual behavior, sexual activities, HIV testing and perceived risk of HIV acquisition**

| | | |
|---|---|---|
| **Types of sexual activities (n = 81)** | | |
| Vaginal | 59 | 72.8 |
| Anal | 22 | 27.2 |
| Oral | 71 | 87.7 |
| **HIV testing in the preceding 6 months (n = 369)** | | |
| Yes | 139 | 37.7 |
| No | 230 | 62.3 |
| **Perceived risk of HIV acquisition via sex (n = 53)** | | |
| Low | 33 | 62.2 |
| Moderate | 17 | 32.1 |
| High | 3 | 5.7 |

***Source of HIV knowledge.***

The majority of the students reported their course of study provided them with knowledge about HIV. Plenaries and self-reading were the major sources of HIV knowledge for these students. (Table III)

**Table III: Source of knowledge of HIV (n = 369)**

| | Medical (%) n = 187 | Non-medical (%) n = 182 |
|---|---|---|
| **Does your course of study provide you the knowledge about HIV?** | | |
| Yes | 183 (97.8) | 141 (77.5) |
| **Source of HIV knowledge** | | |
| Plenaries | 153 (81.8) | 63 (34.6) |
| PBL/TBL | 111 (59.4) | 54 (29.7) |
| Elective posting | 44 (23.9) | 11 (6.0) |
| Self-reading | 161 (86.1) | 106 (58.2) |
| Hospital/Clinic visit | 109 (58.3) | 40 (22.0) |

** Med: medical ; Non-med: non-medical.*

***Awareness and acceptance of PrEP***

More medical students (75, 40.1%) were aware of PrEP compared to non-medical students (36, 19.8%), ($p < 0.001$). After viewing a short video on PrEP, 69% of medical versus 67.8% of non-medical students were willing to accept PrEP as an HIV-prevention tool ($p = 0.772$). Eighty-six percent of medical versus 87.8% of non-medical students who were willing to accept PrEP would also use a condom during sexual intercourse ($p=0.676$). (Table IV)

**Table IV: Awareness and acceptance of PrEP**

| | Medical (%) n = 187 | Non-medical (%) n = 182 | p-value* |
|---|---|---|---|
| **Awareness of PrEP** | | | |
| Yes | 75 (40.1) | 36 (19.8) | < 0.001 |
| **Willingness to take PrEP after viewing PrEP video** | | | |
| Yes | 129 (69.0) | 123 (67.6) | 0.772 |
| No | 58 (31.0) | 59 (32.4) | |
| **Will you use a condom while on PrEP?** | | | |
| Yes | 111 (86.0%) | 108 (87.8%) | 0.676 |

** Chi-square test for medical versus non-medical students, $p < 0.05$ considered significant.*

**Discussion**

The prevalence of sexual activity among teenagers in Malaysia was reported to be 5.4% among school-going teenagers aged 12 – 19 years, and 12.6% among urban teenagers aged 15 – 20 years, respectively.[12] The prevalence of sexual activity among the student population aged 18 – 36 in this study was 22.2% (81/369). Eighty-six percent of them had sexual intercourse in the preceding 1-2 months. A quarter of them had casual sex partners while a small number had engaged in transactional sexual intercourse. Only 45% reported consistent condom use while 58% had at least one condomless sexual intercourse in the preceding six months. Sexual activities included oral, vaginal, and anal sex. About 38% (20/53) of sexually active students perceived their risk of HIV acquisition to be moderate to high. Overall, 37.7% (139/369) had tested themselves for HIV at least once in the preceding six months.

The prevalence of sexual activity among the students in this study may be considered high with a significant risk of HIV acquisition through unsafe sexual practices including inconsistent condom use, multiple sexual partners, and a relatively low rate of HIV testing.

Almost 88% of all students acknowledged their course curriculum covered HIV as a topic. Medical students appeared to have more exposure to education about HIV through the various teaching-learning modalities compared to their non-medical counterparts ($p< 0.001$) who, by nature of their course, may have less clinical exposure and hence less exposure to patients

with HIV infections. Nevertheless, the awareness of PrEP was low for both groups of students: 40.1% among medical students versus 19.8% among non-medical students ($p < 0.001$). This may be because PrEP was not covered as a topic in their curriculum.

However, after viewing a short video regarding PrEP during the survey, almost 70% (129/187) of medical students and 68% (123/182) of non-medical students indicated they were willing to accept PrEP. This suggests that once awareness of PrEP is attained, acceptance of PrEP was fairly good. At the same time, 86% (111/129) of medical students and 88% (108/123) of non-medical students indicated they will continue to use the condom during sexual intercourse while on PrEP, suggesting they had a "more-is-safer" approach to keeping themselves safe from HIV. These students may not be aware of the high efficacy of PrEP as an HIV prevention tool. PrEP has been shown to reduce HIV transmission from sexual intercourse by 99% when taken daily in men who have sex with men (MSM) and by 75% in heterosexual partners.[2-4,6]

Prior to 2023, access to PrEP was restricted to very few private health clinics or hospitals, and community-based centers managed by non-government organizations that were concentrated in major cities in Malaysia. In January 2023, the Ministry of Health, Malaysia launched a pilot project to provide complimentary PrEP in the form of oral tenofovir-emtricitabine in adults at high risk of sexually acquired HIV infection in 18 health clinics throughout the country.[13] This nationwide initiative has enabled easier access to PrEP for people at risk of acquiring HIV sexually. However, easier access means nothing if awareness of the benefits of PrEP is lacking. If the result of our study is any indication, awareness of PrEP is evidently lacking among tertiary students including medical students. Efforts to raise awareness of the benefits and availability of PrEP need to be stepped up especially among the at-risk communities and sexually active youths and adults. PrEP should be included as a topic in HIV education in all formal and non-formal sex education programmes or activities at all levels of engagement in the community and at every educational level.

### *Study limitations*

The survey was conducted online anonymously. There were too few students who identified as non-heterosexuals, and those who had multiple sexual partners to allow for meaningful statistical analyses. The study was conducted in a private medical university which would naturally have HIV-related topics in the curriculum of various medical and non-medical programmes. This may not be the case in non-medical tertiary centers of higher learning in the country. The latter are likely to have significantly fewer HIV-related topics in their curricula and even lower awareness of PrEP. Acceptance of PrEP before the viewing of an educational video on PrEP was not assessed, as with the reasons for PrEP-hesitancy.

## Conclusions

Awareness of PrEP among medical students was low and even lower among non-medical students. After viewing a short video on PrEP, acceptance of PrEP by both groups of students was fair. Efforts to raise awareness of PrEP including education about PrEP must be included in the course curriculum and may even be at pre-university levels. Studies to identify reasons for PrEP-hesitancy should be conducted which can then help guide policies and initiatives toward promoting PrEP as an additional tool in HIV prevention.

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# Prevalence of cyberbullying and its effects on studies, personal life and mental health of medical students in a private medical university in Malaysia

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**Introduction:** Cyberbullying is the use of information and communication technologies to support deliberate, repeated, and hostile behaviour by an individual or group to harm others. Cyberbullying may negatively affect the studies, personal lives and mental health of victims who are students. We report on the prevalence of cyberbullying and its effects on personal lives, studies, and mental health among medical students.

**Methods:** A self-administered online questionnaire was used to collect demographic data, determine the prevalence of cyberbullying, and its effects on personal lives, studies and mental health of medical students. Student-t test was used for comparison of means, and logistic analysis was used to identify predictors of being cyberbullied.

**Results:** 40 out of 261 study participants reported being cyberbullied in the preceding 6 months (prevalence: 15.3%). Cyberbullying did not negatively affect the studies and personal lives of victims. Most victims reported none or minimal-to-mild depression. Malay ethnicity was a predictor of being cyberbullied. Female students were 5-times more likely to be cyberbullied because of their lifestyle compared to males.

**Conclusion:** The prevalence of cyberbullying among medical students in this study was relatively low compared to reports from other universities. Cyberbullying had little to no effect on the studies, personal life, and mental health of medical students in our study. Malay ethnicity was a significant predictor to being cyberbullied. Females were more likely to be cyberbullied for their lifestyle. Support systems, awareness of good internet etiquette, and promotion of early help-seeking behaviour, especially targeted at identified vulnerable groups, should be put in place to check the practice of cyberbullying.

***Keywords:*** *cyberbullying, Malaysia, medical students, personal life, mental health*

## INTRODUCTION

Cyberbullying is defined as wilful and repeated harm inflicted through the medium of electronic text.[1]

Victims of cyberbullying may suffer from depression, anxiety, stress, and poor social skills.[2] The medical curriculum, with its heavy workload, frequent assessments, and competitive environment, predisposes medical students to high levels of stress and requires good mental health to perform well. The negative psychological effects of being cyberbullied may negatively impact the ability of medical students to cope with their studies, and as a result, they may perform poorly in the studies and have reduced concentration in classes.[2]

A study among 464 undergraduate students from six universities in Greece reported a low prevalence of cyberbullying of 3.2%. The male gender was identified as a predisposing factor. The negative effects of being cyberbullied included loneliness and low self-esteem.[3] In contrast, a Malaysian study among 712 private and public university students reported a much higher prevalence of cyberbullying of 66% with wide-ranging negative effects including feelings of insecurity, over-sensitivity to surroundings, avoidance of internet use and electronic devices, and in severe cases, suicidal thoughts and suicidal attempts among cyberbullied victims. Male gender and Malay ethnicity were identified as predictors of being cyberbullied.[4]

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To date, there has been limited data on cyberbullying among Malaysian medical students, with only one such study in a public medical university of Malaysia showing a high prevalence of 24.4% cyberbullying over the past six months.[5] The prevalence of mild depression among cyberbullied victims was 34.0%.[5] We researched the prevalence of cyberbullying, possible predisposing factors, and its effects on the studies and personal lives of medical students at a private medical university in Malaysia.

## METHODS

### *Study design, setting and sample size*

A cross-sectional convenience sampling study was conducted among the medical students at a private medical university in Malaysia, from January to June 2020, using an online questionnaire. There were 1361 medical students at various stages of medical studies at the time of this study. The calculated sample size required for statistical significance was 300 with 95% confidence level (CI) with 5% margin of error. The formula used to derive the sample size was as follows:

$$Sample\ size = \frac{\frac{z^2 \times p(1-p)}{e^2}}{1+\left(\frac{z^2 \times p(1-p)}{e^2 N}\right)}$$

N = population size, e = margin of error (percentage in decimal form), *z* = *z*-score, where *z*-score is taken to be 1.96 to achieve a confidence interval of 95%.

### *Inclusion and exclusion criteria*

All medical students were eligible. Non-medical students and those who declined to participate were excluded.

### *Study tool*

The study tool was a 10-minute online questionnaire created with Google Forms. The link to the questionnaire was distributed to all students through their respective student representatives. Participation was voluntary, with consent obtained online. The questionnaire consisted of 5 parts, from A to E. Part A contained questions to capture social demographic data, including types of social media used, and time spent on social media. This part was intended to see if there is any relationship between certain social demographic factors and being cyberbullied. In Part B, participants were required to view a short Youtube video on what cyberbullying was, to ensure they understood if they had been cyberbullied before providing their response. Participants were then asked if they had been cyberbullied in the last six months, which will give the prevalence of cyberbullying.[6] Participants were questioned if they had been cyberbullied only for the past six months to ensure that their recall of the cyberbullying and the negative effects was more current, and therefore, more reliable. As we had limited the timeframe of the question, we did not include a question to explore if the participants had ever been victims of cyberbullying for those who answered 'No' to the initial question. Part C was adapted from a similar study which was done on the non-medical students in the University of London.[7] This part contained questions which explored personality, physical appearance, personal beliefs, lifestyle, ethnicity, political opinion, sexual orientation, and disability as possible aspects on which the victims were cyberbullied. Questions in Part D explored the possible negative effects of cyberbullying on the studies and social lives of

the students using a 5-point Likert scale where 1 represented "strongly disagree", 2 "disagree", 3 "unsure or neutral", 4 "agree", and 5 "strongly agree". In Part E, we had used the Patient Health Questionnaire-9 (PHQ-9), a multipurpose screening instrument and freely available in the public domain, to assess the severity of depression among cyberbullied victims. Participants were scored from 0-27. The severity of depression was determined by the total score, with 0-4 suggesting minimal or no depression, 5-9 as mild, 10-14 as moderate, 15-19 as moderately severe, and 20-27 as severe depression. The PHQ-9 recorded 88% sensitivity and specificity.[8] As Part C was adapted from another source, the questionnaire was piloted and validated locally with randomly selected medical students at the university. Minor post-piloting adjustments were made to the questionnaire, mainly to facilitate better comprehension before distribution.

### *Statistical analyses*

Descriptive analysis was used to delineate the demographic data from Part A and the prevalence of cyberbullying in Part B. One-sample Student t-test was used to determine the effect of cyberbullying on students' studies and social lives using data from Part C. Binary regression analysis was used to identify if gender, ethnicity, types of social media, and time spent on social media were predictors of being cyberbullied. A $p$-value <0.05 with a 95% confidence interval was considered statistically significant. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 26 for Windows 10. This research was approved by the university's Joint-Committee on Research and Ethics on April 16, 2020 and assigned the project number CSc/Sem6(02)2020.

## RESULTS

### *Demography*

Two-hundred-sixty-one students participated. The male: female ratio was 3:5. The majority were Chinese (177, 67.8%), followed by Indians (39, 14.9%), Malays (17, 6.5%) and others (28, 10.7%). The mean age was 22. The sample population in this study was reflective of the student composition of the university at the time. Majority were 3rd year students (106, 40.5%). The top 3 most popular social media applications used were WhatsApp (258, 98.9%), Instagram (190, 72.8%) and Facebook (111, 42.5%). A total of 96 (36%) participants spent 3-4 hours on social media daily, 81 (31%) spent 1-2 hours, 65 (24.9%) spent more than 4 hours, and only 21 (8%) spent less than 1 hour. The demographic data are summarised in Table I.

**Table I: Demographic data of participants**

| DEMOGRAPHIC PARAMETER | NUMBER (N) | % |
|---|---|---|
| **GENDER** | | |
| Female | 102 | 39.1 |
| Male | 159 | 60.9 |
| **ETHNICITY** | | |
| Malay | 17 | 6.5 |
| Chinese | 177 | 67.8 |
| Indian | 39 | 14.9 |
| Others | 28 | 10.7 |

Table I: Demographic data of participants

| | | |
|---|---|---|
| **AGE** | | |
| <20 | 23 | 8.8 |
| 20-25 | 231 | 88.5 |
| >25 | 7 | 2.7 |
| **SOCIAL MEDIA APPS USED** | | |
| Whatsapp | 258 | 98.9 |
| Facebook | 111 | 42.5 |
| Instagram | 190 | 72.8 |
| Facebook messenger | 102 | 39.1 |
| Snapchat | 86 | 33.0 |
| WeChat | 35 | 13.4 |
| Twitter | 34 | 13.0 |
| Skype | 22 | 8.4 |
| Facetime | 18 | 6.9 |
| Dating apps | 6 | 2.3 |
| **TIME SPENT ON SOCIAL MEDIA** | | |
| < 1 hour | 21 | 8.0 |
| Between 1-2 hours | 81 | 31.0 |
| Between 3-4 hours | 94 | 36.0 |
| > 4 hours | 65 | 24.9 |

***Prevalence of cyberbullying***

Forty students reported being cyberbullied in the preceding 6 months, with a prevalence of 15.3%. Seventeen (42.5%) were males and 23 (57.5%) were females with no statistically significant difference between the genders ($p$ = 0.725).

***Effects of being cyberbullied on personal life and studies***

Being cyberbullied had no significant negative effect on the studies and personal lives of the students, including class attendance ($p$ = 0.001), meeting deadlines ($p$ = 0.013) and personal hygiene ($p$ = 0.001). However, feelings of 'poor self-image' and affected 'relationship with friends' were reported, although they were not statistically significant ($p$ = 0.917 and 0.514, respectively). The results are summarized in Table II.

**Table II: Effects of being cyberbullied on medical students' personal life and studies**

| VARIABLES | MEAN* | SD | *p* ** |
|---|---|---|---|
| Academic performance adversely affected | 2.78 | 1.493 | 0.347 |
| Declining class attendance | 2.28 | 1.261 | 0.001 |
| Difficulty in meeting deadlines | 2.45 | 1.339 | 0.013 |
| Hard to focus in class | 2.98 | 1.609 | 0.922 |
| Trouble falling asleep | 3.00 | 1.485 | 1.000 |
| Trouble staying asleep | 2.63 | 1.444 | 0.109 |
| Sleeping more than usual | 2.73 | 1.450 | 0.238 |
| Struggling to maintain personal hygiene | 2.20 | 1.344 | 0.001 |
| Poor self-image | 3.03 | 1.510 | 0.917 |
| Change in appetite | 2.83 | 1.375 | 0.426 |
| Relationship with family affected | 2.78 | 1.493 | 0.347 |
| Relationship with friends affected | 3.15 | 1.442 | 0.514 |

* *One-sample t-test using "3" as test value. Mean values above 3 indicates agreement with the statements and values below 3 indicates disagreement with the statements.*
*SD: Standard deviation.*
** *p-value with 95% confidence interval.*

***Effects of being cyberbullied on depression***

Among the 40 students who were cyberbullied, 15 (37.5%) reported feeling minimal or no depression, and 13 (32.5%) reported feeling mildly depressed. However, 5 (12.5%) students reported feeling moderately depressed, 5 (12.5%) reported feeling moderate-to-severely depressed, and 2 (5%) feeling severely depressed.

Using "minimal/none" as a comparator, there was no statistically significant difference in each of the depression category. Only 8 (20%) respondents attributed their depression to being cyberbullied, while 12 (30%) reported they were depressed even before being cyberbullied. Twenty (50%) were unsure if their depression was due to being cyberbullied.

Twelve respondents (6 males and 6 females) had suicidal thoughts in the preceding month, while 8 (4 males and 4 females) had attempted suicide in the past.

***Predictors of being cyberbullied***

Ethnicity was a statistically significant predictor of being cyberbullied ($p$ = 0.017) with Malay ethnicity

being the significant predictor ($p$=0.030). Gender, types of social media used, and time spent on social media were not significant predictors.

***Aspects of being cyberbullied***

Lifestyle was the only statistically significant aspect of being cyberbullied ($p$ = 0.027) where female students were 5-times more likely to be cyberbullied compared to male students. Personality, physical appearance, beliefs, ethnicity, political opinion, sexual orientation, and disability were not significant aspects, as shown in Table III.

**Table III: Aspects of being cyberbullied**

| Aspect | Total (%) | Male (%) | Female (%) | *p* value* | Odds ratio (female/male) |
|---|---|---|---|---|---|
| Personality | 22 (55%) | 9 (52.9%) | 13 (56.5%) | 0.538 | 1.16 |
| Physical appearance | 16 (40%) | 6 (35.3%) | 10 (43.5%) | 0.424 | 1.41 |
| Personal beliefs | 11 (27.5%) | 6 (35.3%) | 5 (21.7%) | 0.276 | 0.51 |
| Lifestyle | 15 (37.5%) | 3 (17.6%) | 12 (52.3%) | 0.027 | 5.10 |
| Ethnicity | 11 (27.5%) | 5 (29.4%) | 6 (26.1%) | 0.546 | 0.85 |
| Political opinion | 2 (5%) | 1 (5.9%) | 1 (4.3%) | 0.676 | 0.73 |
| Sexual orientation | 2 (5%) | 2 (11.8%) | 0 (0%) | 0.174 | - |
| Disability | 1 (2.5%) | 0 (0%) | 1 (4.3%) | 0.575 | - |
| Others | 7 (17.5%) | 3 (17.6%) | 4 (17.4%) | 0.649 | 0.98 |

* *p-value with 95% confidence interval*

## DISCUSSION

This study on cyberbullying was done at a private medical university and the participants were medical students. The prevalence of cyberbullying in our study was 15.3% (40/261). Their personal lives and studies were not adversely affected as a result of being cyberbullied. Although they reported varying degrees of depression, with the majority having experienced minimal or no depression, more worrying were the few who had suicidal thoughts or had attempted suicide.

Malay ethnicity was the only significant predictor of being cyberbullied. Lifestyle was the only identified aspect of being cyberbullied with females being 5-times more likely than males to be cyberbullied in this aspect.

***Prevalence of cyberbullying***

Local studies have reported that a significant percentage of Malaysian young adults have been cyberbullied, ranging from 18.6% to 66%.[4,5,9] In comparison, the prevalence of being cyberbullied in our study was relatively low (15.3%) for this age group. In the three studies mentioned, the majority of the students were Malays making up 52.5%, 49.6% and 65.8% respectively, whereas in our study,

the majority were Chinese (67.8%) and the Malay students were few in number (6.5%). This may explain the difference in the prevalence between our study and the aforementioned studies. Nevertheless, it is noteworthy that Malay ethnicity had the highest prevalence of being cyberbullied and was a significant predictor of being cyberbullied in both studies. The reasons for this will be discussed in a later section.

Interestingly, a study conducted among Malaysian medical students in a public university showed a prevalence of cyberbullying of 24.4%, which was higher compared to our study (15.3%).[5] The difference in results may be due to our research being carried out at a private medical university with well-established guidelines and policies for the proper use of social media.

***Effect on studies and personal life***

Being cyberbullied did not adversely affect the studies or personal life, although some reported varying degrees of depression. This is in sharp contrast to another study in Israel among undergraduate students, which reported significant academic, interpersonal, and family problems.[10] Other studies have reported negative effects on mental health, completion of assignments, and relationships outside of the university.[11,12]

The difference in our results may be due to increased awareness of the negative consequences of cyberbullying and early help-seeking behaviours due to the easy accessibility of various support services offered by the university, including counselling services, psychiatrists and clinical psychologists, as well as mentoring programmes.

***Depression severity as a result of cyberbullying***

Most of the students reported having only minimal to mild depression from being cyberbullied. This differed from the other studies, which showed the majority of cyberbullied victims had experienced negative emotions including depression, low self-esteem resulting in avoidance of socialising, use of computers and anxiety upon receiving emails or messages.[3-5] The difference may be due to early help-seeking behaviours among the participants in our study, although we did not explore this aspect in our study. Similarly, a low prevalence of depression was reported among students who were cyberbullied may be because they had good coping strategies, including early formal, and informal help-seeking behaviour, presence of friends with similar academic stressors and a good mentoring system.[13] The private medical university, which was the study site, had heavily invested on counselling facilities and helplines, which may have helped students to cope with negative emotions after experiencing cyberbullying.

***Malay ethnicity was a significant predictor of being cyberbullied***

Malay ethnicity was the single significant predictor of being cyberbullied in our study ($p$ = 0.017) although there were only 17 (6.5%) Malays among the 261 students surveyed. The Research Institute for Malaysian Youth Development reported the highest prevalence of cyberbullying (67.5%) among Malay youths compared to other races.[14] In contrast, a study conducted among undergraduate engineering, computing, and management students in a Malaysian public university, where the majority of the respondents were Malays, reported no significant relationship

between ethnicity and cyberbullying behaviours.[15] A literature review of 14 studies conducted among college and university students found that students of minority races often faced bias and aggression from non-minority students.[16] Although Malay students were the minority in our study, we could not ascertain if they were bullied by other Malay students or students from other ethnic groups.

***Females were more likely to be cyberbullied for their lifestyle***

Our study found that female students were 5-times more likely to be cyberbullied because of their lifestyle compared with males. These lifestyle choices include the way in which one chooses to live or behave. More females than males were cyberbullied for their lifestyle through the spreading of rumours, online stalking and threats.[17] This was attributed to females spending more time on social media and other communication platforms.[16] Similarly, in our study, 23.4% of females spent an average of 3-4 hours on social media compared to 12.6% of males, which may account for the higher chances of females being cyberbullied.

## STUDY LIMITATIONS

The total number of respondents in our study was slightly lower than the targeted sample size of 300 students due to time constraints in the collection of data. This may have resulted in lower reported prevalence of cyberbullying in this study. There was a possible occurrence of self-selection bias in our study as the participants were recruited through convenience sampling, which may falsely over-represent or under-represent individuals who have experienced cyberbullying. Although the Malay race was a significant predictor for being cyberbullied, we were unable to ascertain if they were bullied by fellow Malays or other races as it was not part of our study objective. Follow-up studies should be done to identify the characteristics of cyberbullies and the help-seeking behaviours of cyberbullying victims. We note that more senior clinical students responded to our survey on cyberbullying. This may be due to their higher use of the internet and social media in the course of their studies. These two factors have been associated with an increased risk of cyberbullying. In addition, senior students have been reported to be more impulsive and less sympathetic to fellow students.[18]

## CONCLUSION

The prevalence of cyberbullying among medical students in our study was low compared to reports from other universities. Although Malays were the minority ethnicity in our study, being a Malay was a significant predictor of being cyberbullied. Females were 5-times more likely to be cyberbullied for their lifestyle compared to males. Being cyberbullied did not negatively affect the studies and personal life of the students, and most reported only minimal or mild depression.

Although the prevalence is relatively low, anti-cyberbullying programmes, including a strong student support service and a suicide prevention hotline, must be put in place by the university. Awareness of the ethical use of internet resources and appropriate measures should be emphasised to the students from the very early phase of their studies. Faculty members should be trained to recognize red flags in students who exhibit signs of being cyberbullied.[19-21]

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# Quality evaluation of child feeding related websites on complementary feeding in Malaysia

Zi Jie Lim, Kanimolli Arasu, Seong Ting Chen

**Introduction:** The internet is widely used by parents to access child feeding related information. The accuracy and reliability of information available online remain uncertain. The objective of this study was to evaluate the quality of child feeding related websites on complementary feeding for children aged 6-24 months in Malaysia.

**Methods:** A cross-sectional study was conducted between December 2021 to April 2022 to evaluate complementary feeding-related websites in the Bahasa Malaysia (BM) language. The key terms were entered into Google Chrome and the first 30 websites were screened. Websites that could not be accessed due to broken links, duplicated websites and not freely accessible websites were excluded from the study. The quality was evaluated using Health-Related Websites Evaluation Form to appraise content, accuracy, author, currency, audience, navigation, external links, and structure of the web-based information. The website was rated as excellent (at least 90% of the total possible score), adequate (75-90%) and poor content (<75%).

**Results:** Twenty-one websites out of 1006 websites screened were selected for evaluation. 81% of the websites were rated as excellent while 19% were with adequate quality. Websites with excellent quality ratings had higher scores for currency ($p$=0.039) and navigation ($p$=0.039) as compared to adequate quality websites.

**Conclusions:** This study highlighted that complementary feeding practices websites in the BM language were generally of good quality. The accuracy, currency and content of these websites can be further improved by including the resources developed by dietitians to optimise child feeding practices for optimal growth and development of children between 6–24 months.

***Keywords:*** *Child feeding information, evaluation, internet, quality, websites*

## Introduction

The internet has become a vital mass medium for consumers to seek health-related information online.[1] There are growing numbers of internet users in Malaysia. The Department of Statistics Malaysia (DOSM) showed that in 2020, 91.7% of Malaysian households were using the internet.[2] In addition, the percentage of the Malaysian population that uses the internet to search for health-related information and services increased from 45.2% in 2019 to 61.9% in 2020.[3] Among all internet search engines, Google Chrome is the most used browser by Malaysians.[4]

Parents are increasingly accessing the internet to seek information on supporting the growth and development of their children in different life stages.[5] Child feeding information obtained from multiple resources leads to confusion,[6] especially since the websites chosen are not evidence-based.[7] This leads to difficulties in distinguishing between trusted and untrusted websites or reliable and unreliable information. Unusually, parents rated unreliable information as helpful[8] which leads to detrimental feeding practices.

Inappropriate complementary feeding practices such as solids not introduced after six months of age cause long-term feeding problems.[9] In the local setting, a study of 300 children between 6–24 months of age

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showed only 68.8% of breastfed infants and 34.6% of non-breast-fed infants had a minimally acceptable diet.[10] Children's first foods and feeding experience can impact their immediate survival as well as over their lifetime.[11] Thus, it is crucial to ensure that parents obtain reliable and trusted information on child feeding practices to prevent any potential risks.[12] However, the wide access to multiple information online with no known credibility can be detrimental.[13] There is limited information on the quality of the websites providing information regarding child feeding practices. Hence, this study was conducted to evaluate the quality of child feeding related websites on complementary feeding for children aged 6–24 months in Malaysia.

## Methods

### *Study design*

This study was a cross-sectional study conducted from December 2021 to April 2022. Ethical approval was obtained from the IMU Joint Committee on Research and Ethics [BDN I-2021 (07)].

### *Inclusion and exclusion criteria*

The inclusion criteria included websites that provide child feeding information in the Bahasa Malaysia (BM) language and with the latest updated content from 2014 onwards. Websites with advertising content and related to industries were also included. The exclusion criteria were duplicate websites, websites that require payment for access, websites that involve research output (journals) and websites that provide child feeding information in other languages.

### Data collection

### *Stage 1: Website Selection*

Google Chrome was used to search for child feeding related websites. The relevant key search terms in the Bahasa Malaysia language used were "*memperkenalkan makanan pelengkap* (introducing complementary food), *makanan pelengkap* (complementary food), *kanak-kanak berusia 6–24 bulan* (children between 6-24 months), *alahan pemakanan* (food allergies), *rumusan bayi* (milk formula), *makanan jejari* (finger food), *jadual makanan bayi 6–24 bulan* (meal plan for 6–24 months), and *makanan separa pepejal* (semi solid food)". The first 30 websites in the Google Chrome search engine were screened. This was based on the consideration that most users usually clicked and looked through the search output within the first three pages.[14] Websites that met the inclusion criteria were selected for evaluation. The searching of websites was done by one researcher while the selection of the websites for evaluation was done by all the researchers.

### *Stage 2: Website Evaluation*

The selected websites were evaluated using the Health-Related Website Evaluation Form (HRWEF)[15] to assess the quality of selected websites. The evaluation components of this form included website information, content, accuracy, author, currency, audience, navigation, external links, and structure. Two (2) points were given if the website met the criteria of the subcomponent, 1 point if it did not meet the criteria and 0 point if the criteria did not apply to the respective website. The rating

of websites was based upon the Malaysian Dietary Guidelines for Children and Adolescents 2013 and the Recommended Nutrient Intake 2017. A total possible point was computed to determine the overall rating of the website. If the website scored at least 90%, it was rated as "Excellent", indicating this website is an excellent source of information that can be recommended to the readers. Readers can easily access and understand the information contained on this site. The website that scored at least 75% was rated as "Adequate", indicating the website provides relevant information and can be navigated without much trouble. However, it might not be the best website possible. Care should be taken to discuss what information was found on this website and what information is still needed. The website that was rated "Poor" was those with score < 75%, indicating the website should not be recommended. The validity and reliability of the information that appeared on these websites cannot be confirmed.[15]

### *Statistical Analysis*

The data collected was analysed using SPSS version 28.0. Descriptive statistics were used to describe the evaluation components' scores and quality categories of the websites. Independent student t-test and Mann-Whitney test were used to assess the difference in total percentage score of the evaluation components between website quality categories. The Spearman Correlation was used to examine the correlation between each evaluation component of the HRWEF. The correlation coefficient (r-value) greater than 0.3 represented a positive correlation. The significance level was set at $p < 0.05$ with a 95% of the confidence interval.

## Results

By inserting the key search terms into the Google Chrome, the first 30 websites were reviewed and a total of 1006 websites were selected for screening. Only 69 websites met the inclusion criteria, and these websites were further screened. Forty-eight websites were eliminated due to insufficient information for evaluation criteria to evaluate the quality of the complementary feeding practices. Twenty-one websites were eligible for evaluation (Figure I).

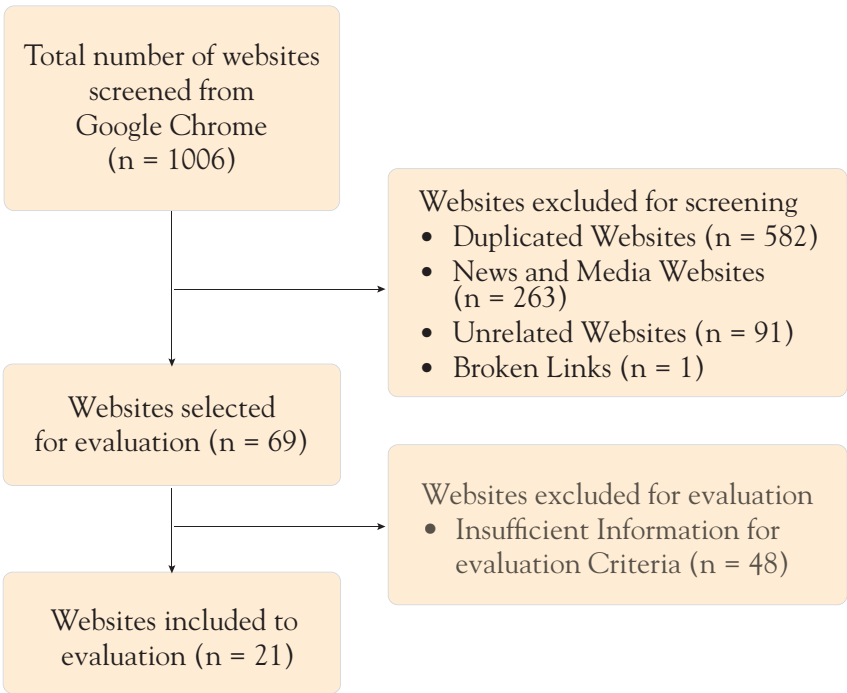


*Figure I: Flow chart of website selection for evaluation*

***Website Quality***

The 21 websites evaluated had an average score of 92.38 ± 3.65. The majority of the websites (81%) were categorised as excellent (mean score: 93.65 ± 0.61). There were four websites which were categorised in the adequate category (mean score: 87.00 ± 1.41). There was no website with poor quality.

***Percentage Score for Evaluation Components***

Table I presents the mean percentage score for evaluation components of websites. The component of whether the information was suitable for the intended audience (100.0 ± 0.00) and the ease of navigation (99.52 ± 2.18) scored the top two highest percentage scores. The audience can understand the website's information as limited jargon was used and the reading level was suitable for the target audience. Besides, the majority of the websites could be easily found and navigated by using search mechanisms. On the other hand, the websites that had lower scoring on external links (31.05 ± 41.42) as a majority of these websites did not provide the reliable external links that connect to reliable information or sources.

**Table I. Percentage Score for Evaluation Components of the 21 selected websites**

| EVALUATION COMPONENTS | TOTAL PERCENTAGE SCORE (MEAN ± SD) |
|---|---|
| Content | 88.10 ± 6.80 |
| Accuracy | 95.24 ± 10.06 |
| Author | 88.33 ± 26.14 |
| Currency | 95.24 ± 21.82 |
| Audience | 100.00 ± 0.00 |
| Navigation | 99.52 ± 2.18 |
| External Links | 31.05 ± 41.42 |
| Structure | 85.24 ± 5.12 |

*The data is presented in mean ± SD*

***The difference in the websites categorised as "excellent" and "adequate"***

As shown in Table II, there was a significant difference ($p$ = 0.039) between the excellent and adequate quality websites in terms of the latest updated information (currency) and ease of navigation. The other evaluation components did not differ between the excellent and adequate quality websites ($p > 0.05$). A higher number of websites in the excellent category had the latest updated information (currency) and were easier to navigate compared to the adequate quality websites ($p$=0.039).

**Table II. Difference of Total Percentage Score of the Evaluation Components between Website Quality Categories**

| EVALUATION COMPONENT | EXCELLENT (n=17) | | ADEQUATE (n=4) | | P-VALUE |
|---|---|---|---|---|---|
| | MEAN±SD | MEDIAN (IQR) | MEAN±SD | MEDIAN(IQR) | |
| Content | 89.41±6.59 | | 82.50±5.00 | | 0.065 |
| Accuracy | 97.06±8.30 | | 87.50±14.43 | | 0.087 |
| Author | 91.47±25.36 | | 75.00±28.87 | | 0.267 |
| Currency [a] | | 100.00 (0.00) | | 100.00 (75.00) | 0.039* |
| Audience [a] | | 100.00 (0.00) | | 100.00 (0.00) | 1.000 |
| Navigation [a] | | 100.00 (0.00) | | 100.00 (8.00) | 0.039* |
| External Links | 30.82±43.40 | | 32.00±37.27 | | 0.961 |
| Structure | 85.29±5.15 | | 85.00±5.77 | | 0.921 |

*SD: Standard deviation; IQR: Interquartile Range.*
*Data expressed as mean ± SD unless otherwise stated. Independent sample t-test was used for normally distributed data.*
[a] *Presented as median (IQR). Mann-Whitney test was used for statistical analysis of skewed data.*
* *P < 0.05 was considered statistically significant.*

**Discussion**

This study found that child feeding related websites in the BM language were mostly of excellent quality. This is a contrasting finding to the results of the systemic review which states that the majority of infant feeding websites were scored poor quality.[13] However, the systemic review evaluated 600 English websites while our study only evaluated 21 BM websites. It is pertinent that the child feeding related websites need to be of good quality as in recent years mobile health technologies and digital nutrition promotion through websites are considered as promising strategy to improve child feeding practices.[16,17]

Besides being of good quality, the websites evaluated in this study scored highly in the "accuracy" component. Comparatively, a local study done by Mohd Shukri N *et al* (2022) showed that almost half of the data on the Facebook posts on breastfeeding information was deemed to be misleading and inaccurate.[18] However, these were based on Facebook posts which can be posted by any individuals compared to the websites we evaluated which were managed by non-governmental organisations and industries. The accuracy of data on websites related to feeding practices is important as inaccurate information can adversely influence and mislead parents on their understanding of children's nutritional needs.[19]

Additionally, the evaluated websites in this study provided current and relevant information as this was evident through high scores obtained for the evaluation component of "currency". The websites posted the publication date and updated the information according to any changes in the field. This is important as outdated information is a noteworthy obstacle towards education and could be easily misled by the information obtained from internet resources.[20]

Even though most of the websites had a good quality rating, we found that the website could be further improved in several evaluation components. For example, a moderate percentage score was obtained in the evaluation component of "author". Most websites did not have information of the name, educational background, the author's credibility, and the institution associated with the authors. This is crucial as identification of authorship is important as readers would trust a particular website if they recognised the authorship to be trustworthy.[21]

Majority of the readers (83%) would rate trusted websites based on their "content" instead of the "design" of the websites.[22] Similarly in our study we found that the percentage score in "content" was higher than the "structure" component. The moderate scoring was due to most of the websites evaluated did not clearly state or infer the purpose and the external links were not fully provided. This can be further supported by the observation on the lowest score for the evaluation component of "external links". External links are important as they help to increase visibility and relevance of website, add value to user experience and increase back linking opportunities which in return optimises ranking in various search engine resource page.[23]

Another important finding was the differences in the excellent quality and adequate quality website in terms of "currency" and "navigation" evaluation components. The total percentage score of both "currency" and "navigation" were higher for the "excellent" quality of websites as compared to "adequate" quality. Not all websites in the adequate quality group managed to revise their information in line with the latest guidelines such as the Malaysian Dietary Guidelines for Children and Adolescent (2013).[24] For instance, the website did not follow the accurate information according to the guideline on the recommended daily food intake according to different age groups that can influence the nutritional needs of the children. Additionally, for the "navigation" component, the internal links provided by the "adequate" quality websites did not really add to the usefulness of the websites, as compared to "excellent" websites.

There were a few limitations in our study. Firstly, the websites were limited to Bahasa Malaysia-based websites which were not representative of all websites accessed by Malaysian parents. Next, the selection of the websites was based upon the specific keywords in the official BM language. This study did not include other ethnic language and non-proper or slang terms in BM language. Hence, the websites chosen may not reflect the whole child feeding related information available. Additionally, the researchers did not evaluate the readability of the information on the selected websites which may limit the accessibility especially for individuals with a lower educational background.[5,11]

## Conclusion

In short, the quality of child feeding websites in the BM language for children aged 6–24 months in Malaysia is generally of good quality. The study findings also identified the areas for improvement to increase the quality and usability of the information on child feeding related websites. Organisations and website creators should include healthcare professionals to ensure the content in the websites is evidence-based and accurate to prevent child feeding malpractices among the parents.

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# Non-Hodgkin lymphoma research (excluding all B cell lymphoma) in Malaysia: A review

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**Introduction:** Lymphoma is a diverse group of malignant proliferations that arise as discrete tissue masses. The 5th edition of the World Health Organization classification of Tumours of Haematopoietic and Lymphoid Tissues was released on 22nd June 2022. The WHO-HAEM5 classification of Mature T and NK neoplasms is further subclassified into various categories which are detailed in this review.

**Methods:** A search was conducted using bibliographic databases, various repositories, and the Clinical Research Centre website retrieving journal articles, conference proceedings, book Chapters, guidelines, and thesis. The search terms used were Malaysia AND lymphoma.

**Results:** The search earmarked a total of 561 papers. There were nine case series retrieved from 1967 to 2022. The site, age distribution, prognostic markers, and the various subclassification of NK/T cell lymphomas were studied. The gastrointestinal tract was the commonest site for extranodal lymphomas. Prognostic markers associated were EBV, C-MYC protein and staining for CD2, CD3, CD20, CD56, and CD57 antigens.

For anaplastic large cell lymphoma (ALCL), CD30 (Ki-1) and ALK antigens were noted as important. The use of 18F-Fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) has emerged as an important investigation. Various chemotherapeutic regimens, surgical interventions where necessary and autologous peripheral blood stem cell transplantation when indicated are the mainstay of treatment.

**Conclusion:** Research on NK/T cell lymphoma, including ALCL, has been ongoing in recent years. This review adds on to the existing literature on lymphoma in Malaysia that can lead to further research, into the diagnosis and treatment of lymphoma in Malaysia and around the world.

***Keywords:*** *Lymphoma, NK/T cell, anaplastic large cell lymphoma (ALCL), Malaysia*

## INTRODUCTION

The haematopoietic system develops from stem cells that divide into myeloid and lymphoid progenitor cells. The myeloid cells form erythrocytes, platelets and myelocytes which in malignant states are leukaemias. Lymphoid progenitor cells give rise to B-cells, T-cells and natural killer cells and their subsequent derivatives. In malignancy, lymphoid cells give rise to lymphomas. Lymphoma is a diverse group of malignant proliferations that arise as discrete tissue masses. There are geographic variations in the incidence of subtypes of lymphoma that have been studied.[1,2] For example, follicular lymphoma is prevalent in Western countries, while T-cell lymphomas are more common in Asia.[1,3] Virchow is credited with naming the disease in 1858 and the history of classification of the disease and notable geographical variations has been discussed by Peh and Poppema.[4]

The malignant lymphomas were historically broadly categorised as Hodgkin lymphoma/disease (HL) and non-Hodgkin lymphoma (NHL), with a worldwide prevalence of 5% to 6% of all malignancies.[5] Malignant lymphomas are the fourth most common

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cancer encountered in Malaysia, according to the Malaysian National Cancer Registry Report 2012-2016. The lifetime risk for males is 1 in 176; 1 in 167 for Malays, 1 in 189 for Chinese and 1 in 283 for Indians. The lifetime risk for females is 1 in 252; 1 in 245 for Malays, 1 in 280 for Chinese and 1 in 324 for Indians. These rates have all increased from the previous report covering the period 2007-2011. Staging was reported for 1,394 (40.9%) and 1,027 (42.5%) cases respectively for males and females. Of these 62% in males and 59% in females were detected at late stage (III & IV).[6]

The 5th edition of World Health Organization classification of Tumours of Haematopoietic and Lymphoid Tissues was released on 22nd June 2022.[7] A relatively conservative approach was taken in making changes to the nomenclature to allow for continuity in daily practice and ongoing clinical trials. The WHO-HAEM5, like all 5th Edition WHO tumour volumes, applies a hierarchical system for classification. That is, it organises diseases in order of increasing levels of specification: category (e.g, mature B-cell), family/class (e.g, large B-cell lymphomas), entity/type (e.g, diffuse large B-cell lymphoma, not otherwise specified) and subtype (e.g, diffuse large B cell lymphoma, not otherwise specified, germinal center B-cell-like). Entities and subtypes have been formulated such that the implementation of the WHO-HAEM5 classification system is possible globally, in all settings.[7]

The aim of this study is to provide clinicians who manage lymphoma in Malaysia and investigators a resource of background information about lymphoma in Malaysia. It is also to facilitate future research by collecting what is known so that the gaps can be identified.

## METHODOLOGY

The objectives of this study are to look at the prevalence and reports of non-Hodgkins lymphoma in Malaysian literature and also review some aspects of the disease including treatment and outcomes where available.

A search was conducted on the following: (1) bibliographic databases (PubMed and Scopus); (2) Individual journal search of Malaysian health-related journals; (3) A targeted search of Google and Google Scholar; (4) Searching of Malaysian institutional repositories; (5) Searching of Ministry of Health and Clinical Research Centre websites including the National Cancer Registry. The citations were manually entered or imported into the bibliographic software Zotero.

The search terms used were Malaysia AND lymphoma, and information in this report was extracted from a more comprehensive library of published data that covered all lymphomas till July 2022. The search was performed on 18th May 2021 and repeated on 3rd July 2022 and shown in the PRISMA flowchart in the results section (Figure I). The review of Diffuse Large B Cell Lymphoma (DLBCL) has been published separately.[8]

Inclusion criteria included the following: All published reports (case reports and case series) in Malaysia of lymphoma in general, NK/T cell and ALCL, articles published in English and published between 1967 until 2022. Exclusion criteria for our review included

articles which were reported from countries other than Malaysia, articles published in languages other than English, articles which included only other lymphomas other than NK/T cell lymphoma and ALCL and those published prior to 1967.

## RESULTS

The search earmarked a total of 451 publications. An additional 65 publications were noted on 3rd July 2022. Six authors (LKG, SPV, AFS, PTK, IAS and NIJ) carefully examined all 516 publications and deleted unrelated publications. The final number of publications used in this study was 83. Our review on DLBCL has recently been published.[8]

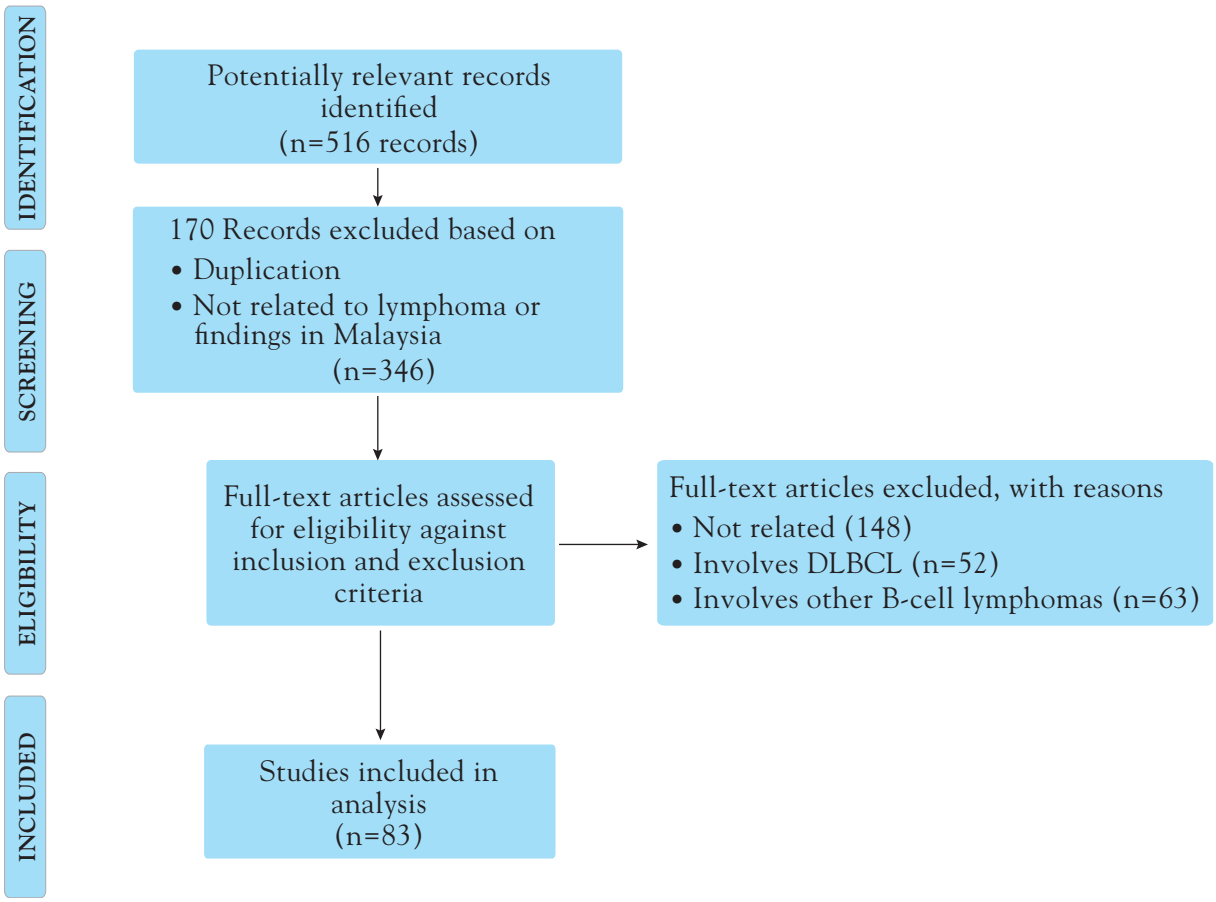


*Figure 1: PRISMA diagram of workflow*

## OVERVIEW

Table I is a summary of hospital-based collections of case series from various institutions, many from the Klang valley but some focusing on East Malaysia. The classification of lymphoma in the early years was of Hodgkins and non-Hodgkins lymphoma but it has changed over the years. Later series use the WHO classification and its subsequent revisions.

**Table I: Summary of case series showing the demographic distribution and types of lymphoma**

| AUTHOR | YEAR | NUMBER OF CASES | LOCATION | M:F RATIO | AGE | ETHNICITY CHINESE MALAY INDIANS | B-CELL | T-CELL | HL | NOT SPECIFIED |
|---|---|---|---|---|---|---|---|---|---|---|
| Sinniah, Tan, Lin [9] | 1967-1980 | 24 | University Hospital (UH) | 19:5 | 1-12 | Chinese 16<br>Malay 3<br>Indian 5 | 10 | | 14 | |
| Bosco and Cherian [10] | 1980- 1984 | 149 | University Hospital (UH) | | | Chinese 92<br>Malay 36<br>Indian 17 | 100 | | 49 | |
| Chai, *et al* [11] | 1981- 1983 | 61 Sarawak<br><br>46 Sabah | | 66:41 | 2-78 yrs<br>Mean 41 yrs | Chinese 11<br>Malay 15<br>Ind Sarawak 35<br><br>Chinese 2<br>Malay 2<br>Indian 1<br>Ind Sabah 41 | 80 | 16 | 11 | |
| Mancer [12] | 1983-1987 | 57 | Universiti Kebangsaan Malaysia (UKM) | 34:23 | 4-72 yrs<br>Mean 50 yrs | Chinese 19<br>Malay 31<br>Indian 7 | | | 8 | Low grade 1<br>Intermediate 29<br>High 19 |
| Peh, *et al* [13] | 1993- 1999 | 80 | Klang | 52:28 | 3-86 yrs<br><br>51-60 (27.5%) | Chinese 4 (5%)<br>Malay 64 (80%)<br>Indian 12 (15%) | 57 | 9 | 14 | |
| Peh, *et al* [14] | 1996-1998 | 70 | Sarawak | 46:23 | 4-85 yrs<br>Mean 49.9 yrs | Iban 27<br>Malay 22<br>Chinese 9<br>Bidayuh 8<br>Unknown 4 | 58 | 1 | 9 | Null cell 1<br><br>Unclassified 1 |
| Peh, *et al* [15] | 1997-1999 | 91 | Sabah | 56:32 | 51-60 (22%) | Chinese 8<br>Malay 7<br>Kadazan 27<br>Bajau 8<br>Dusun 6<br>Other Ind Sabah 30 | 68 | 14 | 8 | 1 |
| Menon, *et al* [16] | 2005-2006 | 77 | Paediatrics Hospital Kuala Lumpur (HKL) | | | | 27 | 37 | 13 | |
| Salam [17] | 2010-2015 | 210 | Pantai Premier Pathology | 116:94 | | Chinese 111<br>Malay 58<br>Indian 16<br>Others 21 | 175 | 10 | 25 | |

Lymphoma was diagnosed in 7% of 350 childhood malignancies seen in the University Hospital from 1967-1980 (Table I). Sinniah *et al*, noted that of 24 cases of paediatric lymphoma, 13 refused treatment and they presented late. Eight of the 14 cases with HL were in Stage IV. Nevertheless, four of their HL patients and one with NHL were alive at the time of reporting.[9] Reporting about 40 years later, Menon *et al*. found that lymphomas formed 11% of 730 childhood malignancies over an 18-month period seen at the clinic of the Paediatric Institute of Hospital Kuala Lumpur.[16]

**Distribution of sites**

In cases from Sabah, Peh SC *et al*.[15] found that 43 (47.2%) presented with the disease in the lymph nodes and 42 (46.1%) were extranodal. The sites for six (6.7%) cases could not be determined. The common extranodal sites were the gastrointestinal tract (4), tonsil (4), oral cavity (4), testis (2), spine (2), nose (2), and the remainder 4 were in other sites.

In a series of gastrointestinal lymphomas seen from 1967 to 1973 in the University Hospital, Ti *et al*. reported that of 17 cases (5% of gastrointestinal malignancies), the small intestine was the commonest site involved although many had multiple sites of disease. All were adults with ages ranging from 21 to 76, averaging 49 years.[18]

Among 210 cases in Kuala Lumpur, Salam *et al*.[17] noted 96 (46%) with lymph node disease versus 114 (54%) with extranodal disease (Figure II). The common extranodal sites were the gastrointestinal tract (31, 27%), Waldeyer ring (15, 13%) thyroid and mediastinal (10 each, 9%) and other sites (48, 41%).

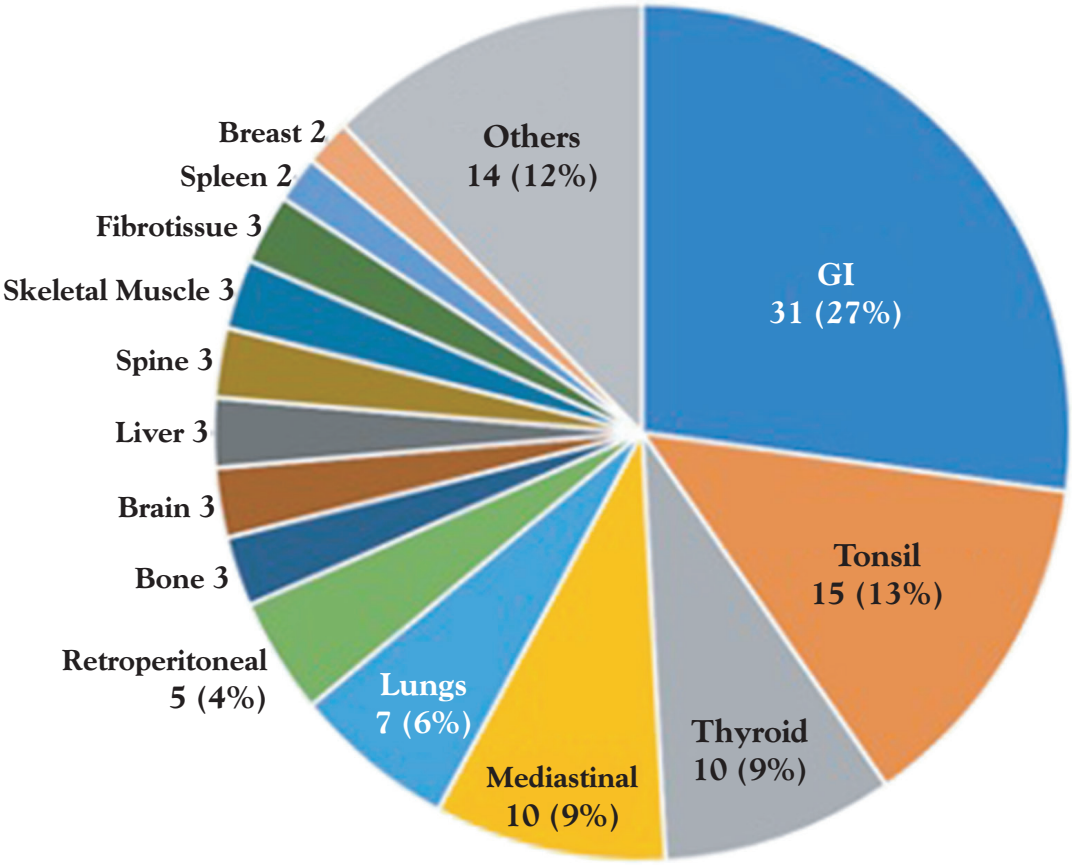


*Figure II: Distribution of extranodal lymphomas among 114 patients in Malaysia. (Salam)*[17]

**Age groups**

Salam *et al.*[17] noted that among the series of 210 cases, the elderly (>70 years) Chinese formed the majority (18/29, 62%). However, in the 20–30-year age group, Malays were 59% (13/22). The types of lymphoma could account for this difference, as well as a change of incidence in age cohorts.

**Prognostic Markers**

Peh noted that all EBV associated lymphomas were of the type A virus and none were of type B nor were there mixed infections.[19] EBV was detected in 6/8 (72.5%) of HL and 8/83 (9.6%) of NHL cases. Peh *et al.*[13] who reviewed cases in Klang, 7/9 of T-NHL and 6/57 of B-NHL were associated with EBV. Most Epstein-Barr virus encoding region (EBER)-positive cases did not express the T- or B- cell antigen, shown by double staining T-NHL with CD20 and CD3 antigens. Yunos noted that 11% (2/18) NHL of the lower GI tract demonstrated positive signals for EBV/EBER.[20]

Dendritic cells are antigen presenting cells within the immune system responsible for initiating T-cell based responses. Hussin *et al.* examined lymph node tissue from 32 cases of various types of lymphoma compared with lymph nodes with inflammatory disease and found a reduction in dendritic cell counts in lymphoma tissue, and found immature dendritic cells located within tumour tissue while mature dendritic cells were more in the peri-tumoural areas.[21]

The International Working Formulation divided non-Hodgkin's lymphoma (NHL) into three grades: low, intermediate, and high. Wang and Peh reported that Ki-67 immunostaining is a useful adjunct to the histological grading of NHL.[22] Peh studied the frequency of NHL in different ethnicities in Malaysia and reported the highest frequency in Chinese (107/232), Malays (41/232) and Indians (21/232).[22]

Norizan *et al.* looked at the DNA ploidy status of 37 case of all lymphomas in HKL between 1990-1995 and noted that 12% were near diploid, 67% were hyperdiploid and 21% were hypodiploid. The majority of hyperdiploid lymphomas were B cell NHL.[23]

**C-MYC**

A review of 634 lymphomas in the department of Pathology, Hospital USM from 2001 to 2018 found that 55 (8.8%) were NK and T cell lymphomas. Thirty-two with adequate tissue samples were selected for C-MYC immunochemistry staining. Among them 21 (65.6%) were males and 11 (34.4%) females. The median age was 38 years (8 to 81). Malays accounted for 90.6% (29), with 2 Chinese and 1 Indian. Ten (31.3%) were lymph nodes and 22 (68.8%) extranodal biopsies. C-MYC protein expressions were detected in 25/32 (78.1%) cases, 5/6 were T lymphoblastic lymphoma, 7/8 T-cell lymphoma, not subtyped, 4/6 ALK-positive ALCL, 4/6 peripheral T-cell lymphoma, not otherwise specified, 3/3 extranodal NK/T-cell lymphoma, nasal type and 2/3 of others. There is no significant association between C-MYC protein expression and the patient's age, gender, Ann Arbor staging, LDH levels, B symptoms, extra-nodal involvement, and ECOG status. Only 17 (53.2%) patients received chemotherapy. Ten (31.3%) were treated with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) as the first line treatment. Eleven (34.4%) patients died in the follow-up period, eight of whom had C-MYC expression.[24]

**Types of lymphoma**

## NATURAL KILLER (NK) T-CELL LYMPHOMA

NK cells account for 5–10% of peripheral lymphocytes and have some T-cell markers but they do not have to pass through the thymus to mature. In the Asian populations in Hong Kong, Japan, Taiwan, China and Malaysia, approximately 90% of nasal lymphomas show natural killer (NK)/T-cell phenotype whereas the majority of lymphomas of the nasal region in Western populations are B-cell phenotypes. Nasal lymphoma accounts for 4-7% of all lymphomas. Over a period of 20 years, a total of 41 formalin-fixed and paraffin-embedded biopsy tissues from 31 patients (22 males, 9 females) with these nasal lymphomas were examined in the Department of Pathology, University of Malaya. Their ages ranged from 8 to 77 years. Eight were nasal T-NHL, 19 were nasal NK/T cell lymphomas and 4 nasal-type lymphomas of NK/T-cell phenotype. Among the 19 nasal NK/T cell lymphomas, there were 7 Malays, 11 Chinese, 1 Kadazan and in the nasal-type NK/T cell lymphomas, there were 1 Malay, 2 Chinese and 1 Indian. All nasal and nasal-type NK/T-cell lymphoma cases expressed CD3 and CD56. CD57 expression was observed only in one case. Of the nasal NK/T-cell lymphoma cases, 12/19 (63%) expressed CD2, but none in the three cases of nasal-type NK/T-cell lymphoma. TIA-1 is equally and strongly expressed by all the nasal, nasal-type and T-cell NHL cases. EBER was detected in 18/19 (95%) of the nasal NK/T cell lymphoma.[25]

A 31-year-old Malay man with nasal NK/T cell lymphoma presented with prolonged fever of unknown origin and had enlarged mesenteric nodes at laparotomy, died nine days after diagnosis.[26] These nasal lesions may be misdiagnosed as infection, and missed on biopsy and then treated as such before it is diagnosed correctly at an advanced stage.[27-30] Noradina *et al.* reported a 37-year-old man who presented with one week of diplopia with a large enhancing nasopharyngeal mass with intracranial extension to the cavernous sinuses and local infiltration together with intracranial abscesses. He died before treatment could be started.[31] Another 56-year-old Indonesian man presented with myiasis alongside his NK/T cell lymphoma in Sabah. Whether maggots were of any use or detrimental was not known as he went back to Indonesia and his outcome was not known.[32]

A 56-year-old man presented with right eye redness, reduced vision, and periorbital swelling for five weeks duration and had a two-month history of nasal obstruction. He was treated with antibiotics. When improvement was not seen after a week, biopsy of the nasal tissue was done and immunohistochemical staining of tissue was positive for CD3, TIA, EBER-ISH and negative for CD20, CD10, TdT, cyclin-D1, CD4, CD8, CD5, CD30 and ALK. The Ki-67 proliferative index was high (~60–70%). Sadly, he succumbed after one month of chemotherapy.[33] Another 39-year-old man presented with bilateral nasal obstruction for four months. A nasal endoscopy showed irregular mucosa of the nasal cavity and biopsy reported as extranodal NK/T cell lymphoma, nasal type. EBER-ISH was positive. He was treated with six cycles of gemcitabine, oxaliplatin and L-asparaginase and peripheral blood stem cell transplant. He was asymptomatic until nine months and developed a splenic abscess which required splenectomy. He was asymptomatic for a further two years.[34]

NK/T-cell lymphoma mimicked Crohn's disease in a 46-year-old Chinese man who presented with six months history of abdominal pain, weight loss and rectal bleeding. Colonoscopy revealed multiple aphthous ulcers within the ileo-caecal region and distal transverse colon, separated by normal mucosa, as in skip lesions of Crohn's colitis. Immunohistochemical studies on the resected bowel confirmed a T-cell monoclonality, presence of cytotoxic granules and Epstein-Barr virus (EBV) infection.[35] Tai *et al.* reported a high frequency of EBV association with NK/T-cell lymphomas.[36] Yap reported a case of a 73-year-old man with NL/T-cell lymphoma involving the left pectoral muscle with a rare, but possibly significant, peripheral eosinophilia. The patient did not have lymphadenopathy but had a 1cm liver lesion and a pathological fracture of the femur.[37]

## SUBCUTANEOUS PANNICULITIC T-CELL LYMPHOMA (SPTL)

SPTL is a rare variant of peripheral T-cell lymphoma characterized by infiltration of lymphoma cells within the subcutaneous tissue. Ng et al. reported five cases (1M, 4F), aged from 13 to 35 years, between 2001 to 2004 seen in Hospital Kuala Lumpur. CD3 was positive in four cases. CD 8, CD30, and TIA were noted in one case each. Two patients achieved remission, two died and one was lost to follow-up.[38] SPTL was also diagnosed in a 25-year-old man in Johor Bharu who presented initially with lymph node like swellings. Biopsy from the forearm and thigh later achieved the diagnosis. The SPTL cells expressed CD2, CD3, CD8, CD7, TIA, Perforin and TCR Alpha/Beta.[39]

Five cases of SPTL were seen during the period from 2001-2004 at the Department of Dermatology, Hospital Kuala Lumpur. All five presented with multiple subcutaneous nodules on the face, trunk and limbs of one week to six months duration with associated fever and weight loss. Skin biopsy of all patients showed infiltration with atypical lymphoid cells in the upper dermis and subcutaneous fat. These neoplastic cells showed CD3 and CD30 positivity in three patients with CD8, TIA-1 and LCA (Leucocyte common antigen) being positive in one patient. One patient was treated with prednisolone and subcutaneous Roferon and were in remission. Two patients who were planned for chemotherapy had deteriorated rapidly and succumbed to septicaemia from pancytopaenia.[40]

A 10-year-old Malay boy with stage IV T-cell NHL (pulmonary involvement), diagnosed through a biopsy of a forearm soft tissue swelling, developed pure red cell aplasia (PRCA) and autoimmune haemolytic anaemia (AIHA) after beginning therapy on the EORTC-VHR protocol.[41]

## PRIMARY CUTANEOUS LYMPHOMA

Guan and Gan in 2016 reported a rare case of primary cutaneous T-cell lymphoma gamma-delta subtype of cutaneous T-cell lymphomas in a 66-year-old Malay man who presented with a three-week history of rapidly growing skin nodules and skin rashes all over his body.[42]

Primary cutaneous anaplastic large cell lymphoma (PC-ALCL) is a rare subtype of primary cutaneous lymphoma. They usually present as nodules which

can ulcerate over the head and neck region. Heng *et al.* reported a 73-year-old man who presented with two painless, ulcerating nodules over the right pre-auricular and angle of the mandible. A hypodense lesion in the liver indicated metastasis. Biopsy revealed PC-ALCL. Tumour cells were positive for CD30, CD4, CD5, EMA, and CD25. They were CD3, CD8, CD20 and ALK- negative. He responded well to chemotherapy.[43] Lee has reviewed cutaneous T-cell lymphoma among Asians, including Malaysians.[44]

## ADULT T-CELL LEUKAEMIA/LYMPHOMA (ATLL)

ATLL is a rare T lymphoproliferative neoplasm commonly associated with Human T-cell lymphotropic virus type-1 (HTLV-1).[45] ATLL is most prevalent in Japan; however, some sporadic cases are reported worldwide. Cases of ATLL are rarely seen in Malaysia, and HTLV-1 is not endemic in Malaysia. One case of ATLL with positive HTLV-1 infection was found in a 51-year-old Indian woman with incidental lymphocytosis while being investigated for pallor and giddiness. On examination, there were bilateral enlarged cervical lymph nodes with no hepato-splenomegaly or skin lesions.[45]

## INTESTINAL T-CELL LYMPHOMA (ITL)

Intestinal T-cell lymphoma (ITL) is an aggressive neoplasm of intraepithelial T cells that affects the small bowel. One form, enteropathic-asssociated T-cell lymphoma (EATL) occurs as a complication of coeliac disease common in Western countries. Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) was previously known as EATL type 2 and is more common in Asia.

Liong *et al.* reported EATL type 2 in a 50-year-old Chinese man with chronic diarrhoea for six months and weight loss of 17 kg. Initial CT scan and endoscopy did not confirm the diagnosis. Repeat CT scan showed a well-defined large enhancing mass in the mesentery adjacent to an area of thickened jejunum and surgical resection proved the diagnosis. The tumour cells were strongly positive for CD3, CD8 and CD56, and negative for CD4, CD5, CD30 and EBER. The patient recovered from surgery and was given chemotherapy but died four months after diagnosis.[46]

Another 36-year-old man who presented with a five-week history of intractable diarrhoea was found on CT scan to have mural thickening at the duodenojejunal junction. Subsequent jejunofiberoscopy showed a circumferential ulceration at the jejunum. Histoimmunopathology confirmed the diagnosis of EATL type 2. His disease was refractory to standard front-line chemotherapy and was given second-line salvage therapy in view of CNS and intracranial involvement. He died nine months after the initial diagnosis.[47]

Kasinathan[48] reported a previously healthy 70-year-old woman of Chinese ethnicity who presented with a four-week history of abdominal pain, persistent vomiting, and jaundice. There were no palpable lymphadenopathies or organomegaly. A whole-body CT imaging was consistent with stage 1E disease (Ann Arbor staging) showing a mass at the 2$^{nd}$ part of the duodenum only. The histology was consistent with monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL). The tumour cells were positive for CD3, CD5, CD7, CD8, CD56, TCR gamma/delta,

TIA-1 and granzyme B. Ki67 proliferation index was 70%.[48] She was treated with two cycles of CHOP and then two cycles of gemcitabine and platinum-based chemotherapy before she succumbed to the disease.

## PERIPHERAL T-CELL LYMPHOMA (PTCL)

Peripheral T cell lymphoma comprises 10-15% of NHL and usually carries a poor prognosis. The expressions of NOTCH1, GATA3, and c-MYC have been linked to a poorer prognosis in PTCL.[49] Chang CY reported a rare case of PTCL presenting as a pleural effusion with no prior illness. He reported that lung involvement occurs in 8% of lymphoma cases. The patient declined treatment and succumbed in three months.[50]

## T-CELL LYMPHOMAS (not specified)

T-cells constitute 65-80% of the circulating pool of small lymphocytes. In lymph nodes, they are located in the inner subcortical region, and not the germinal centres.

An 11-month-old girl was admitted to the Paediatric Allergy Unit with severe allergic angioedema and no response to treatment with antihistamines and corticosteroid therapy at another hospital.[51] Investigations revealed a lymphoproliferative malignant pathology found in the supradiaphragmatic and infradiaphragmatic areas. A final diagnosis of T-cell NHL was made on lymph node biopsy.[51]

A high-grade T-cell NHL was diagnosed concurrently with AIDS in an 18-month-old boy with gross hepatosplenomegaly and generalized lymphadenopathy. His disease responded to chemotherapy, but he defaulted for three months returning with fever, bruises and cervical lymphadenopathy. Despite having opportunistic infections on return to chemotherapy, he responded to treatment again and survived disease free for 2 ½ years. He succumbed to febrile illness at four years and ten months with no evidence of recurrence of the lymphoma.[52]

## ANAPLASTIC LARGE CELL LYMPHOMA (ALCL)

ALCL which are considered a subset of T-cell lymphomas, are rare tumours, accounting for 2-3% of adult non-Hodgkin lymphomas and often involves both lymph nodes and extranodal sites. The most common mutation in ALCL is a translocation involving the anaplastic lymphoma kinase (ALK) gene that results in ectopic expression of ALK protein in lymphoid tissue. Using immunostaining targeting at the 2p23 region of the ALK protein and fluorescence in situ hybridisation (FISH), Tai *et al.* detected this in 24/34 (71%) of the cases in Kuala Lumpur, and it was significantly higher in childhood cases (100%) when compared to adult cases (47%).[53] The analyses by FISH were consistent with the results from immunostaining of ALK protein, but the analyses were only successful in 15/34 (44%) cases.

Jayaram and Abdul Rahman[54] reported three cases of lymphatic ALCL from University Malaya in 1997 that were positive for CD30 (or Ki-1 antigen), which was first described in 1985. They were in a 9-year-old girl, a 15-year-old boy and a 66-year-old man.[54]

In 2008, Siti-Aishah *et al.* reported a case of a 44-year-old woman who presented with a firm, mobile mass in the left iliac fossa region, bilateral axillary

lymph nodes and a mass encasing the right upper lobe bronchus.[55] Histopathological examination revealed that the mass was infiltrated by large lymphoid cells with marked nuclear atypia, including kidney-shaped nuclei which expressed ALK, CD30 and EMA but not for T-cell (CD45RO and CD3), and B-cell (CD20 & CD79α) markers. FISH analysis showed a t (2;5) (p23; q35) chromosomal translocation. She was staged at Stage IIA, received six cycles of CHOP chemotherapy, and remained disease-free two years after diagnosis, despite also having pulmonary tuberculosis after one year and completing treatment for that as well.

Yaakup *et al.* described a 34-year-old immunocompetent woman with a primary oesophageal ALCL, CD30 and $ALK^+$ of T-cell phenotype presenting with a two-year history of dysphagia.[56] She was treated with chemotherapy and endoscopic oesophageal dilations and stenting, resulting in complete remission of the lymphoma and resolution of the dysphagia. She underwent autologous peripheral blood haematopoietic stem cell transplantation and remained disease-free two years after the diagnosis.

The diagnosis of a small cell variant of ALCL in a 13-year-old boy with a huge mass on his right arm of six months duration was also reported in 2008.[57] Histopathology revealed sheets of malignant small round blue cells immunopositive for LCA, CD43, CD45Ro, CD30, EMA, ALK-1 and CD99, but negative for CD20, TdT, myogenin, myoD1, NSE, bcl-6, bcl-2 and CD10. FISH testing excluded the diagnosis of Ewing's sarcoma/PNET. The mass resolved with chemotherapy, but he died of septic shock.

A 29-year-old man presenting with backache and left thigh pain was found to have an inflammatory mass on CT scan and initially treated with antibiotics. At surgery, the left psoas muscle was found filled with unhealthy reddish looking inflammatory tissues. Histopathological examination revealed an anaplastic large T-cell lymphoma immunohistochemically positive for CD 30, EMA and ALK1.[58]

A 10-year-old Malaysian girl was seen for a seven-month history of multiple swellings over the left thigh, upper arm, and anterior chest which continued to increase in size and to ulcerate. There were shotty cervical and inguinal lymph nodes palpable. The chest and thigh masses were debulked at surgery and the specimens confirmed a diagnosis of ALK-1-positive ALCL involving the muscle.[59]

A 30-year-old Malay gymnasium instructor with a history of chronic intramuscular testosterone enanthate presented with six weeks of night fevers, weight loss, and bony pain. 18-FDG PET/CT imaging showed a hypermetabolic large anterior mediastinal mass with diffuse hypermetabolism in the liver, spleen and axial skeleton.[60] Bone marrow trephine and mediastinal tissue histology were consistent with leukaemic ALK-negative ALCL. He was treated with CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisolone) induction chemotherapy in which he required intensive antibiotic and blood support but succumbed to the disease.[60]

ALCL with a monomorphic small-cell pattern was found in a 34-year-old woman with intractable epigastric pain with multiple gastric erosions and

nodules that were first diagnosed as inflammatory lesions both endoscopically and histologically.[61] She developed severe back pain due to a pathologic T3 thoracic vertebral body fracture, and imaging studies confirmed disseminated systemic disease involving abdominopelvic lymph nodes and cervical and thoracic vertebral bodies. In addition, the needle biopsy of the pelvic lymph node disclosed diffuse proliferation of monomorphic small round cells that were diffusely positive for CD30 and ALK. ALCL was also diagnosed in a 26-year-old man who presented with a mass in the jaw. His lymphoma was also present in the T4 vertebra and skull.[62]

## LYMPHOMA IN EXTRA-NODAL SITES AND/OR NON-SPECIFIED TYPES

Although classification and understanding of lymphoma has advanced, there still remains a collection of cases that are hard to label correctly. In addition, historical reports from the period before the tools and systems of the latest WHO classification were applied, bear the mark of the times but are worth noting in this review, if not for anything but to appreciate the past, and remember the future too will be different. These are indicated site wise below.

### Waldeyer's Ring

Waldeyer's ring refers to a ring of lymphoid tissue found in the throat, the tonsils, adenoids and back of the tongue. In a series over 10 years of 30 patients (14 males, 16 females), aged 14 to 76 years, there were 20 patients (67%) with tonsillar involvement, 8 (27%) with nasopharyngeal involvement, 1 (3%) with tongue base lymphoma, and 1 with anterior tongue involvement. Most patients (77%) presented at an early stage. Histologically, 25 patients (83%) had high-grade diffuse large B-cell lymphoma, 4 (13%) had T-cell lymphoblastic lymphoma, and 1 (3%) had follicular lymphoma. Twenty-one patients (70%) were treated with chemotherapy, 4 (13%) received adjuvant chemotherapy with either radiotherapy or surgery, 3 (10%) resorted to other forms of treatment (primarily traditional remedies), and 2 (7%) declined treatment altogether.[63]

### Nose and paranasal sinuses including parapharyngeal spaces

Tan *et al.* detected seven cases of malignant non-Hodgkin's lymphoma of the nose and paranasal sinuses at HUKM over a three-year period from 1983 to 1986. Three patients had "histiocytic" (large cell) lymphomas and two had mixed lymphocytic "histiocytic" (small and large cell) lesions. One patient had a poorly differentiated lymphocytic lymphoma. All the patients received 4000-4500 rads of radiotherapy. In six patients, the response was dramatic with relief of local symptoms within two to three weeks of commencement of treatment.[64]

Sharudin *et al.* reported a rare case of Parapharyngeal space (PPS) B-cell non-Hodgkin lymphoma with superimposed tuberculosis (TB) and fungal infection that presented with several episodes of syncope and hemodynamic depression.[65] T-Cell type lymphoma has also been found as a mass eroding the nasal septum in a 48-year-old man.[66]

### Eyelid and Lacrimal sac

In a study of 136 patients with eyelid tumours in Alor Star, Kedah, Tan *et al.* found that 22 (16.2%) were malignant. Six of them were lymphoma, five MALT

and one FL.[67] Lymphoma has also been reported in the lacrimal sac.[68,69]

**Oral**

Reviewing 42 extranodal cases of oro-maxillofacial NHL at the University Hospital from 1980 to 2012, Ramanathan *et al.* recorded 9 mandible, 8 cheek, 7 maxilla, 7 palate, 4 salivary gland, 2 soft palate, 2 gingival cases and 1 each from the tongue, lip and floor of the mouth. Their mean age was 41.6 years. There were 24 males and 18 females. Nineteen were Malays, 18 Chinese, 3 Indian and 2 Indonesian. Twenty-six were B-cell type, of these six cases were Burkitt's lymphomas. Only ten cases were T-cell lymphoma, with three cases of NK/T-cell lymphoma.[70]

Abdelrahim *et al.* supported the view that at least a relatively smaller proportion of B-cell NHLs that occur in the oral cavity and maxillofacial region do not have a pathogenic association with EBV from their study.[71]

**Respiratory Tract**

Peh *et al.* studied archival material of 29 NHL cases from University Malaya and found a preponderance of T-cell lymphoma of the upper aerodigestive tract in the ethnic Chinese group of Malaysian patients, and EBV was strongly associated with T-NHL but not with B-NHL. Their results also suggested that type-A EBV is the prevalent sub-type in Asian NHL of the upper aerodigestive tract.[72]

Deng *et al.* noted a case of pulmonary lymphoma which initially presented like tuberculosis in a 11-year-old boy who presented with productive cough, left-sided chest pain, fever and night sweats and chest radiograph showed consolidation and cavitation in the lung.[73] He was treated with anti-tuberculosis drugs for 12 months without improvement. A left pneumonectomy was performed, and non-Hodgkin's lymphoma was diagnosed on histopathology. He was treated with chemotherapy but defaulted follow-up a few weeks after starting therapy.[73]

**Abdomen**

A 14-year-old girl with Stage III B-NHL presented with a hard suprapubic mass fixed to the anterior rectum with a four-week history of pain. At laparotomy, a large inoperable pelvic tumour was found. Examination of the bone marrow and CSF showed no abnormality. At seven years of age, she had been diagnosed and treated for acute lymphoblastic leukaemia and relapsed four years but was well for three years after re-treatment.[74]

Malignancies of the small bowel are rare, but lymphomas can occur there. A histiocytic NHL, not further defined, arising from the terminal ileum in a 50-year-old Malay man causing an entero-vesical fistula has been noted.[75]

**Bone**

Non-Hodgkin's lymphoma of the bone has been reported in the pelvis of a ten-year old child.[76] The patient absconded after one course of chemotherapy.

**Other organs**

Non-Hodgkin's lymphoma not further specified has also been reported in the male breast.[77] Ng *et al.* described a case of primary spinal lymphoma in a 15-year-old girl who first presented with chronic

low backache and acute urinary retention.[78] Spinal surgery was performed on her. Two years later she was readmitted with similar symptoms and the MRI showed a soft tissue mass at the previous surgical site with bony erosion of S1 to S3. Surgery was again performed, and a biopsy was taken. The histology and immunophenotype were suggestive of primary spinal cord lymphoma. Due to the localised nature of the tumour and the intractable pain, the patient was treated with radiotherapy to which she responded.[78]

## DISCUSSION

NK/T-cell lymphomas are rare EBV-related malignancies. They have a predilection for Asian and South American populations. Majority of these lymphomas are of NK-cell lineage, and a minority of T-cell lineage. They are predominantly of extranodal origin.[79]

Clinically, three subtypes can be distinguished: nasal, non-nasal, and disseminated. Nasal NK/T-cell lymphomas usually present as stage I/II disease and involve the nose, nasopharynx and the upper aerodigestive tract. Non-nasal NK/T-cell lymphomas often present as stage III/IV disease and involve the skin, gastrointestinal tract, testis and other soft tissues. Disseminated NK/T-cell lymphoma may present with a leukaemic phase, is rapidly fatal and involves multiple organs.[79]

### General management

Although lymphomas are a wide spectrum of diseases, several features in the investigations and supportive care can apply across the spectrum.

### Staging

In the 21st century, 18F-FDG-PET-CT has emerged as an important imaging modality in lymphoma management, improving the accuracy of staging, assessing treatment response and surveillance. A Malaysian consensus statement has been published based on the Deauville scoring system (2009) and the Lymphoma Response Assessment Criteria (2014), so that clinicians can share a common language in the reporting of FDG PET-CT imaging.[80] Initial evaluation of NK/T-cell lymphoma requires PET/CT and quantification of circulating EBV DNA.[79]

### Treatment

NK/T-cell lymphomas are radiosensitive tumours, but radiotherapy alone is inadequate with relapse rates that are unacceptable. Conventional regimens containing anthracycline are ineffective. Regimens that incorporate asparaginase are currently considered the standard of care. Combined chemotherapy and radiotherapy results in very high response rates and cure in a significant proportion of patients with stage I/II disease. Asparaginase-containing regimens are needed for stage III/IV disease. Interim and end-of-treatment PET/CT scan and circulating EBV DNA are prognostic and useful in the evaluation for additional therapy.[79]

### Autologous peripheral blood stem cell transplantation

Autologous peripheral blood stem cell transplantation is an easily available source of hematopoietic stem cells, but with limited potential for the treatment of lymphoproliferative disease. Hassan *et al.* reported their series of 70 patients, half of whom

had lymphoma (19 NHL, 16 HL). The other half were patients with multiple myeloma.[75] Sixty five (92.9%) and 63 (90.0%) showing neutrophil and platelet engraftment, respectively. Patient's weight (< 60/≥ 60 kg), stage of disease at diagnosis and pre-transplant radiotherapy were significantly different for engraftment of both neutrophil and platelets. In addition, the number of previous chemotherapy cycles (< 8 v ≥ 8) was significant for neutrophil engraftment, while gender and CD34+ dosage (< 5.0 v ≥ 5.0 × $10^6$/kg and < 7.0 v ≥ 7.0 × $10^6$/kg) were significant for platelet engraftment.

Nur Adila Anuar *et al.* reported a promising outcome of non-Hodgkin's Lymphoma patients post high dose therapy with autologous haematopoietic stem cell transplant (AHSCT). They reported that the overall survival and event-free survival at three years were 68.9% and 60.8%, respectively of the post AHSCT.[77]

The median neutrophil engraftment time was faster than in patients with multiple myeloma than lymphoma, at 15 and 20 days, respectively. On the other hand, there was not much difference in platelet engraftment time (17 and 16 days) respectively. Among those who failed engraftment, five (out of six females with NHL) died within 30 days of transplant and had neutropenic sepsis within the first week of transplantation.[81]

AHSCT is of limited efficacy, whereas allogeneic HSCT may be useful in patients with stage III/IV and relapsed diseases if a remission can be achieved. Immunotherapy, including the use of antibodies against CD30, programmed cell death protein 1 and CD38, holds promises and should be considered for relapsed/refractory disease.[82]

**Outcomes in Lymphoma survivors**

Gan *et al.* evaluated the prevalence of erectile dysfunction (ED) in all types of male lymphoma survivors and reported that 81.7% of sexually active patients reported the presence of ED, with only 4.2% having severe ED. Prevalence of ED among younger patients (age ≤ 50 years old) was 64.5%. Their study prompted that the prevalence of ED and absence of sexual activity in lymphoma survivors was high and reminded that this should be considered by the treating clinician to offer early treatment and counselling.[83]

**Quality of Life**

Priscilla *et al.* used the European Organisation for Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30) questionnaire to study 105 patients at the Ampang Hospital, Kuala Lumpur who had haematological malignancies.[84] The haematological cancers included NHL (23.8%), acute myelogenous leukaemia (AML) (22.9%), acute lymphoblastic leukaemia (ALL) (14.3%), HL (10.5%), multiple myeloma (MM), (5.7%), other lymphomas (12.4%), other leukaemia (9.5%), and histiocytosis (1.0%). HL patients had more dyspnoea symptoms; and the NHL patients had reduced role functioning and more constipation, but they tended to be older than patients with the other cancers. The global quality of life of the female patients was much better than that of the male patients. Patients who were 40 years old or younger had a better global quality of life and physical functioning, as well as fewer symptoms of constipation, nausea, and vomiting. Employed patients were in less pain but showed greater impairments of cognitive function

than did unemployed patients. Patients who earned a monthly wage of RM1000 or less had reduced physical function, more symptoms of pain, and more financial difficulties compared with patients who earned more.[84]

**Limitations of the study:** This study does not represent the prevalence of lymphoma in Malaysia as it captures only what is published and many are case reports and series. We acknowledge that our literature search may miss out information despite our search efforts. It is hoped that this study is an indication of the gaps in literature that can guide investigators in moving forward.

## Conclusion

While progress has been made in the diagnosis and treatment of lymphoma, issues persist with classification changes, patient care, and treatment adherence. Immunotherapy shows promise for improving patient outcomes. In Malaysia, recent research on rare subtypes of lymphoma has provided important insights. Continued research in this field will lead to further improvements in lymphoma diagnosis and treatment worldwide.

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# Melioidosis septic arthritis with systemic dissemination: A case report

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Melioidosis is an infection caused by *Burkholderia pseudomallei* known to be endemic in large portions of Asia, Sub-Sahara, and North Australia. Despite its endemicity in Malaysia, prompt diagnosis and subsequent treatment remain elusive especially in the more peripheral medical centres. This coupled with increasing risk to the population because of worsening climate crises renders early recognition and treatment more justifiable than ever. Here we present a case of melioidosis septic arthritis with systemic dissemination and discuss the factors involved in disease contraction, worsening prevalence, and diagnostic methods.

***Keywords:*** *Melioidosis, B.pseudomallei, septic arthritis, systemic dissemination.*

## Introduction

Melioidosis is an infectious disease caused by *Burkholderia pseudomallei*; an environmental Gram-negative bacillus found in contaminated soil and water[1] which can infect humans and animals through inhalation, ingestion, and inoculation, first described in Burma (now Myanmar) in 1912,[2] then Malaya in 1925.[3] It has since been considered endemic in at least 45 countries, predominantly in Asia, Sub-Sahara, and Northern Australia regions.[4-7]Additionally, case importation into non-endemic countries is fast gaining ground.[4,5]

The infection is estimated to affect 5.0 per 100,000 population per year in endemic countries.[4] In Malaysia, actual numbers are not readily known because melioidosis is not required by law to be notifiable under the Preventable and Control of Communicable Diseases Act 1988 (Act 342)[8,9] although Pahang, a particularly endemic state within Peninsular Malaysia, did report an incidence of 6.1 per 100,000 population in 2003.[9] The disease is endemic in the Northern states as well.[8] Clinical presentation is highly varied, earning this infection the monicker, "the great imitator": from localized to systemic and disseminated disease. Here, we describe a patient who contracted melioidosis septic arthritis of the knee joint with subsequent systemic dissemination.

## Case report

A 30-year-old male with newly diagnosed type 2 diabetes mellitus was referred to Hospital Tuanku Jaafar Seremban, a tertiary hospital in Negeri Sembilan, Malaysia, from a district hospital after presenting to their emergency department with complaints of intermittent high-grade fever, breathlessness and worsening right knee pain and swelling for the past one month. He had initially been treated twice as an outpatient with oral non-steroidal analgesics for "non-specific arthritis". Associated symptoms included lethargy, chills and rigor, anorexia, and diarrhoea. He denied any trauma, nor any other significant social history. The patient had worked in a variety of odd jobs since stopping school at age 13, one of which being involved in palm oil agriculture for ten years until he was 24.

Clinically, the patient was tachypnoeic with respiratory rate of 30 breaths/min, SpO2 93% at room air, and febrile (39.2°C). He was tachycardic with a heart rate of 111 beats/minute, blood pressure 116/67 mmHg, and a random blood glucose of 16.0mmol/L. The right knee was swollen and erythematous, warm to touch with severe tenderness and effusion on palpation, and limited range of motion. A summary of preliminary laboratory findings is given in Table I.

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**Table I. Summary of relevant preliminary laboratory findings**

| LABORATORY TESTS | RESULTS | REFERENCE VALUES |
|---|---|---|
| White cell count | 12.4 x $10^3$/µL<br>Monocyte 1.2 x $10^3$/µL<br>Neutrophil 10.5 x $10^3$/µL | 4 – 10 x $10^3$/µL<br>0.2 – 0.8 x $10^3$/µL<br>2 – 8 x$10^3$/µL |
| Haemoglobin | 11.2g/dL | 13 – 17g/dL |
| Platelet | 100 x $10^3$/µL | 150 – 400 x $10^3$/µL |
| Aspartate transaminase | 98U/L | 5 – 30U/L |
| Bilirubin | 3.4µmol/L | 0 – 6µmol/L |
| C-reactive protein | 189.56mg/L | < 5mg/L |
| Leptospirosis IgM | Negative | Negative |
| Dengue NS1. IgM and IgG | Negative | Negative |
| Covid-19 rapid test | Negative | Negative |
| Serology for HIV Hepatitis | Negative | Negative |
| Anti-cyclic citrullinated peptides (anti-CCP) | Negative | Negative |
| Rheumatoid factor | Negative | Negative |

X-ray of right knee joint showed soft tissue swelling and possible effusion (Figure I). Ultrasound of the abdomen revealed hepatosplenomegaly, with liver span of 18.6cm and spleen measuring 16.2cm. Chest X-ray revealed bilateral consolidation of perihilar region, more prominent on the right. Computed tomography (CT) pulmonary angiogram revealed scattered patchy consolidation in both lungs with minimal right pleural effusion.

The patient underwent multiple arthrotomies on days 1, 7, and 13 along with washout and wound debridement. Blood, tissue and synovial fluid samples from the first two surgeries were taken for culture and sensitivity (C&S) using routine blood agar and MacConkey agar. All reported positive for *B.pseudomallei* sensitive to Amoxicillin-clavulanate, Ceftazidime, Doxycycline and Trimethoprim-Sulfamethoxazole. The total white cell count in knee synovial joint fluid was >1000x$10^3$/µL. These findings confirmed a diagnosis of melioidosis manifesting as right knee septic arthritis. Considering the systemic findings, a case of disseminated melioidosis was considered. The patient was started on IV Ceftazidime 2g QID and Tab. Sulfamethoxazole-Trimethoprim 400/80mg 4 tablets BD. Sinus pockets were found during the third procedure (D13) but culture from tissue samples showed no further bacterial growth. His surgical wounds were dressed in negative pressure wound therapy followed by povidone gauze packing. The patient improved clinically with complete remission of fever.

Our patient was admitted for a total of six weeks, the first week of which was in the acute intensive care unit for his breathlessness likely due to melioidosis dissemination to his lungs. His antibiotic regime was continued upon discharge with oral Sulfamethoxazole-Trimethoprim 4 tabs BD for the following 3 months.

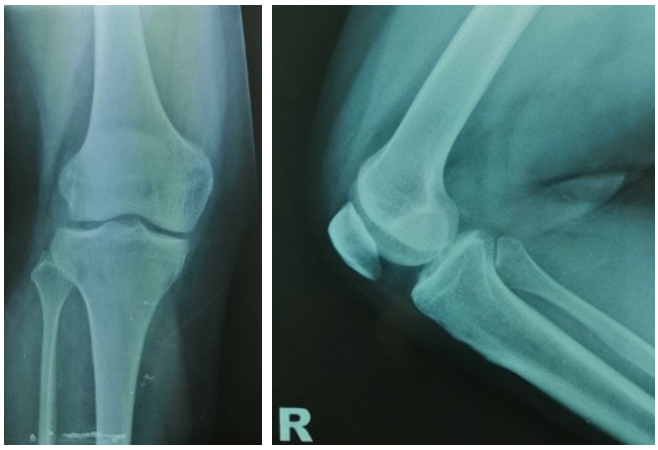


*Figure I: Anteroposterior (left) and lateral (right) view of the right knee on the day of admission. Extensive soft tissue swelling was noted with effusion.*

*Figure II: Sequential portable supine chest radiographs on Day 1(left), Day 3 (centre), and Day 7 (right) of admission. Progressive increased interstitial and hilar markings were noted.*

*Figure III: Wound condition on Day 16 of admission after three arthrotomies (left). Wound condition on Day 28 of admission. Slough and pus discharge were much reduced (right).*

**Discussion**

Melioidosis carries a high mortality rate unless recognized and managed promptly. Septic arthritis due to melioidosis is a rare but well-recognised manifestation of melioidosis. We encountered reports mentioning musculoskeletal manifestation ranging from 4.6% - 13.2%[7,8,10,11] of patients presenting with *B.pseudomallei* infection.

Our patient exhibited several risk factors for disease contraction. He previously worked in a palm oil plantation, the soil of which was typically sandy and/or silty clay, which drained poorly. This is prime grounds for *B.pseudomallei* habitation[4] and patient contact. With an incubation period of 1-21 days,[12] the organism is fastidious enough to remain latent in the body for up to 26 years.[1] The patient might have acquired the infection years prior, remaining silent until the patient inadvertently became diabetic three months prior to admission – thus, "activating" the disease onset.

Diabetes is a clear risk factor in melioidosis[1,6-11,13] with some authors placing this predisposing factor as occurring in 48% of patients with *B.pseudomallei* bacteraemia[14] and others estimating an increased risk of 100-fold.[7]

Our patient underwent multiple arthrotomy procedures and wound debridement before the progression was arrested. Multiple procedures were required as the wound for the knee joint continued to drain persistently. It is unlikely that antibiotics alone and/or wound dressings would have resolved such a deep-seated infection. We suspected the patient initially presented with localized melioidosis confined to the right knee joint, but the delay in treatment led to subsequent systemic dissemination and multi-organ involvement. He received the appropriate antibiotic treatment as suggested by multiple reports[1,9-12,15,16] with strong advice for compliance to prevent relapse.

Our intentions of highlighting this case are multi-fold: Firstly, despite the infection being endemic in Malaysia, there is still a lack of clear guidelines for diagnosis. The delay encountered in this patient is a testament to this. Clearly, greater efforts ought to be taken in both patient and healthcare professional education. Secondly, the return of eco-tourism since the lifting of COVID-19 restrictions places foreign and local tourists alike in danger of disease contraction, particularly in endemic countries such as Malaysia. Thirdly, climate change has made local rainy and monsoon seasons far more unpredictable and violent,[17] leading to flash floods and aerosolized bacteria,[7,11] placing susceptible persons at risk of inhalation, inoculation, or ingestion of the organism. Consequently, rescue workers during flood relief efforts are at risk as indicated by reports of melioidosis-related deaths.[9,10] Finally, co-infection with Leptospirosis and scrub typhus is a particular problem in areas with *B.pseudomallei* endemicity[9] and appropriate prophylaxis and personal protective equipment ought to be mandatory.[8,9,16]

The gold standard in diagnosis remains the isolation of the organisms from adequately and appropriately collected specimens. However, isolation and identification of *B.pseudomallei* may take up to several days, perhaps more if crucial specimen handling techniques are not observed[1,18] leading to diagnostic and treatment delays. One way of overcoming this limitation is with serology. Despite the possibility of cross reactivity, it is particularly useful for culture-negative cases.[11,16,18] However, serology for *B.pseudomallei* is currently only available to certain tertiary centres in Malaysia. More extensive availability of this diagnostic tool coupled with increased awareness of disease manifestation amongst medical personnel is required to combat this hardy organism.

**Conclusion**

A case of melioidosis septic arthritis leading to disseminated disease deserves mention because it highlights the necessity of due diligence in disease recognition and prompt treatment. The endemicity of *B.pseudomallei* in Malaysia and other Southeast Asia countries will most probably rise due to ongoing climate change which has led to more frequent and deadly floodings and aerosolized bacteria, placing the public, rescue workers and other ancillary personnel at risk. The availability of bacterial culture, serological test and increased awareness in more peripheral health facilities will help control this endemic infection.

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