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A POPULATION-BASED STUDY ON THE DEMOGRAPHIC AND CLINICAL PARAMETERS AMONG CHILDHOOD LEUKEMIA SURVIVAL

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ABSTRACT

Introduction: Leukemia is the commonest childhood cancer among children aged 0-19 years in Malaysia, constituting approximately 39.1% of all pediatric cancer cases in the country. **Aims:** This study aimed to measure the characteristics and survival of childhood leukemia among the local Malaysian population. **Methods:** This was a retrospective cohort study based on all the childhood leukemia patients aged 0-19 years registered in the Malaysian National Cancer Registry between 2010 and 2014 with the date of death before or on the 31st December 2019. The Kaplan-Meier method and life table were used to estimate five-year survival rates. Statistical analysis was performed using SPSS (version 27). **Result:** A total of 1,212 participants were included in this study. Their mean (SD) age was 8 (5.6) at the time of diagnosis. The highest five-year survival estimates were seen in females (58%, 95% CI: 54.5-63.1), children aged 1 to 4 (66%, 95% CI: 62.3-70.9), Indian (61.6%, 95% CI: 50.2-73.0), children diagnosed with acute lymphoid leukemia (ALL) (65.7%, 95% CI: 61.6-69.8), and those who had undergone chemotherapy at diagnosis (57.3%, 95% CI: 54.0-60.6). Patients with childhood leukemia in Malaysia reported a 5-year overall survival of 56.4 %. Survival was greater in children aged 1 to 4 years old, Indians, with ALL, and have had chemotherapy treatment at the time of diagnosis. **Conclusion**: The study demographic and clinical findings were comparable with other Asian countries.

Keywords: Childhood leukemia; cancer survival; ALL; AML

INTRODUCTION

Cancer is rare in children compared to adults. Among the types of cancer in children and adolescents (collectively termed “childhood”), leukemia ranks first globally and in Malaysia (GLOBOCAN: Cancer Today, 2020; Registri Kanser Kebangsaan Institut Kanser Negara, 2021). Furthermore, leukemia was the fourth leading cause of mortality in Malaysian children aged 0 to 14(Department of Statistics Malaysia, 2019). Leukemia refers to hematological cancers whereby blood cells fail to differentiate normally into various cell types. In comparison to adults, acute lymphoid leukemia (ALL) accounts for about 80% of childhood leukemia cases, whereas acute myeloid leukemia (AML) contributes the remaining 15%. However, the overall incidence of both subtypes varies greatly with age, gender, and socioeconomic status for both categories (Bonaventure et al., 2017; Allemani et al., 2018).

In addition, the five-year survival rate of leukemia also varies globally. In Southeast Asia, a study involving Malaysia, Thailand, and the Philippines reported a five-year observed survival (OS) between 32% and 49% (Redaniel et al., 2010; Wiangnon et al., 2014; Azizah et al., 2018). The rate was low in comparison to most of the European countries that had a childhood leukemia survival rate of more than 80% (Rascon and Smailytė, 2020). The study

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aimed to describe childhood leukemia survival characteristics in Malaysia between 2010 and 2014 and to assess their five-year survival rates, facilitating comparative analysis with other nations.

METHODS

Study Location

Malaysia is situated in the Southeast Asia region. It spans an approximate area of 330,289 square kilometers, encompassing Peninsular Malaysia and East Malaysia, which includes Sabah, Sarawak, and the Federal Territory of Labuan. It shares borders with Thailand, Singapore, Indonesia, and Brunei. There exist a combined total of 13 states and three federal territories, with a population exceeding 30 million.

Study Design

This retrospective investigation took place from June to August 2021, utilizing information sourced from the Malaysian National Cancer Registry, a nationwide cancer registry based on the population. Instituted in 2007, the registry comprehensively records cancer occurrences across all 13 states and three federal territories of Malaysia through 15 state-level cancer registries, where the Federal Territory of Kuala Lumpur and Putrajaya is treated as a single state.

These state registries received cancer case notifications from private and government hospitals, laboratories, university hospitals, hospices, the National Registration Department (NRD), and the Health Informatics Centre of the Ministry of Health (MOH) (Azizah et al., 2018). This research encompassed solely Malaysian citizens and permanent residents aged 0 to 19 years diagnosed with Groups 1a, 1b, and 1e leukemia, as per the International Classification of Childhood Cancers Third Edition (ICCC-3), during the period from January 1, 2010, to December 31, 2014. Conditions such as chronic myeloproliferative diseases (ICCC-3 Group 1c), myelodysplastic syndrome, and other myeloproliferative diseases (ICCC-3 Group 1d) were not considered in the study. The National Death Registry was searched through until 31 December 2019 using the unique national identification card number of the patients identified in the cancer registry. Demographic (age, gender, ethnicity, and residential distance) and clinical (subtypes, surgery, radiation, and chemotherapy status) data were retrieved from the patient records. All data were organized using Microsoft Excel. For patients diagnosed with leukemia more than once (duplicates) between 2010 and 2015, only the first record was kept. Concurrently, any imprecise or partial details, such as registrations solely based on a death certificate (DCO) or autopsy, along with cases featuring invalid incidence dates (diagnosed within two weeks of the patient's date of death), were omitted from the study.

Statistical Analysis

The analysis of data was conducted utilizing SPSS version 27. The time-to-event was the outcome of interest in this study. The duration of survival was computed as the period between the diagnosis date (time) and the date of death (event) from any cause. For all patients, a minimum of five years of follow-up was achieved by the end of December 2019. Individuals who were still alive by the end of the study were considered censored. The five-year survival rate was computed using Kaplan-Meier methodology and life tables. Since more than half of the status was unrecorded, the Kaplan-Meier estimates were performed for all variables, except for being a recipient of radiotherapy and surgery at diagnosis. The log-rank test was employed to ascertain the statistical distinction between the survival curves, where a p-value below 0.05 denoted statistical significance.

Ethics Approval

Clearance for the study was obtained from the Ethical Committee of the Faculty of Medicine and Health Sciences at Universiti Malaysia Sabah (UMS) under JKEtika 1/21 (10) and the Medical Review and Ethical Committee of the Ministry of Health Malaysia (NMRR-21-385-58568 (IIR)). Additionally, approval was secured from the National Cancer Institute's Director (Reference No.: IKN.CRC/760-2/4/1 JLD.2 (38)) and Malaysia's National Geospatial Centre's Director (Reference No.: KeTSA.600-4/2/2) for the utilization of pediatric leukemia data and healthcare facility geospatial data.

RESULTS

Characteristics of Patients

Of the 1,424 patients who were identified from the registry, 212 were excluded due to records based solely on a death certificate only (DCO), invalid date of diagnosis, incomplete address, uncertain date of the last contact, and patients with combination therapy. Only 1,212 childhood leukemia patients diagnosed between 2010 and 2014 were included in the final analysis. At diagnosis, the mean (SD) age was 8 (5.6) years old. The majority of leukemia occurred in children aged 1 to 4 years old (38.3%), followed by children aged 5 to 9 years old (23.3%), 10 to 14 years old (17.5%), 15 to 19 years old (17.0%), and less than one-year-old (4.0%). The patients were primarily male (58.2%) and Malay (63.4%). The median distance to the nearest hospital was 9.9 km, with an interquartile range of 11.84 km. Half of the patients lived within 10 kilometers of the nearest hospital.

The most prevalent leukemia subtype was precursor cell or ALL (43.7%), followed by AML (27.0%), and "unspecified and other" leukemia (22.9%). The least common leukemia subtypes were mature B-cell (4.0%), lymphoid leukemia NOS (2.1%), and mature T-cell and NK cell (less than 1%). In terms of treatment, almost three-quarters of the patients (71.5%) received chemotherapy at diagnosis. Meanwhile, more than half of all surgeries and radiotherapy received at diagnosis were unrecorded.

Five-Year Observed Survival

In Malaysia, the five-year overall survival (OS) rate for childhood leukemia was 55.6% (95% CI: 52.9-58.3). Survival differed significantly by age group at diagnosis ($p<0.001$), ethnicity ($p<0.05$), leukemia subtypes ($p<0.001$), and patients who received treatment at diagnosis ($p<0.05$). However, there was no significant association found in sex ($p=0.064$) or distance to the tertiary healthcare facility ($p=0.856$). Table 1 shows the five-year observed survival of childhood leukemia in Malaysia. Even though there was no significant difference in survival by sex, females diagnosed with leukemia (58.8%, 95% CI: 54.5-63.1) recorded a slightly higher five-year survival than males (53.3%, 95% CI: 49.6-57.0).

The five-year survival rates for infants less than one year old (43.7%, 95% CI: 29.6-57.8), 10 to 14 years old (47.0%, 95% CI: 40.1-53.9), and 15 to 19 years old (34.9%, 95% CI: 28.4-41.4) were significantly lower than that of age groups 1 to 4 (66.6%, 95% CI: 62.3-70.9) and 5 to 9 years old (61.4%, 95% CI: 55.7-67.1) Survival estimates were higher in Indians (61.6%, 95% CI: 50.2-70.0), those diagnosed with ALL (65.7%, 95% CI: 61.6-69.8), and those who had chemotherapy at the time of diagnosis (57.3%, 95% CI: 54.0-60.6). The Kaplan-Meier curve (overall) is presented in Figure 1. Meanwhile, Figure 2 shows the Kaplan-Meier curves for age groups, ethnic groups, leukemia subtypes, and chemotherapy treatment.

Table 1. Five-year Observed Survival of Childhood Leukemia in Malaysia (n=1,212).

Variables		**OS (%)**	**95% CI**	***p*-value**
Sex				0.064
	Male	53.3	49.6-57.0	
	Female	58.8	54.5-63.1	
Age				<0.001
	< 1 year old	43.7	29.6-57.8	
	1 to 4 years old	66.6	62.3-70.9	
	5 to 9 years old	61.4	55.7-67.1	
	10 to 14 years old	47.0	40.1-53.9	
	15 to 19 years old	34.9	28.4-41.4	
Ethnicity				0.009
	Malay	52.0	48.5-55.5	
	Chinese	59.3	52.6-66.0	
	Indian	61.6	50.2-73.0	
	Others	65.0	57.6-72.4	
Distance (km)				0.856
	<10	55.2	51.3-59.1	
	10-25	56.1	51.4-60.8	
	25-50	54.5	45.3-63.7	
	50-100	62.2	41.4-83.0	
	>100	60.0	17.1-102.9	
Leukemia subtypes				<0.001
	Lymphoid leukemia			
	Precursor-cell (ALL;1a1)	65.7	61.6-69.8	
	Mature B-cell (1a2)	45.9	31.8-60.0	
	Mature T-cell and NK cell (1a3)	25.0	-17.5-67.5	
	Lymphoid leukemia NOS (1a4)	67.0	48.2-85.8	
	Acute myeloid leukemia (AML; 1b)	47.2	41.7-52.7	
	Unspecified and other leukemia (1e)	47.3	41.4-53.2	
Treatment				
	Chemotherapy			0.018
	Yes	57.3	54.0-60.6	
	No	51.3	41.9-60.7	
	Unrecorded	51.0	44.5-57.5	

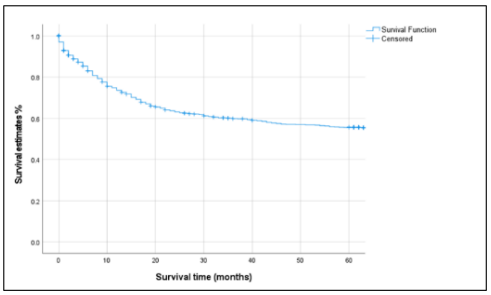

Figure 1. Kaplan-Meier Survival Curve for five-year Overall Survival Rate for patients in Malaysia.

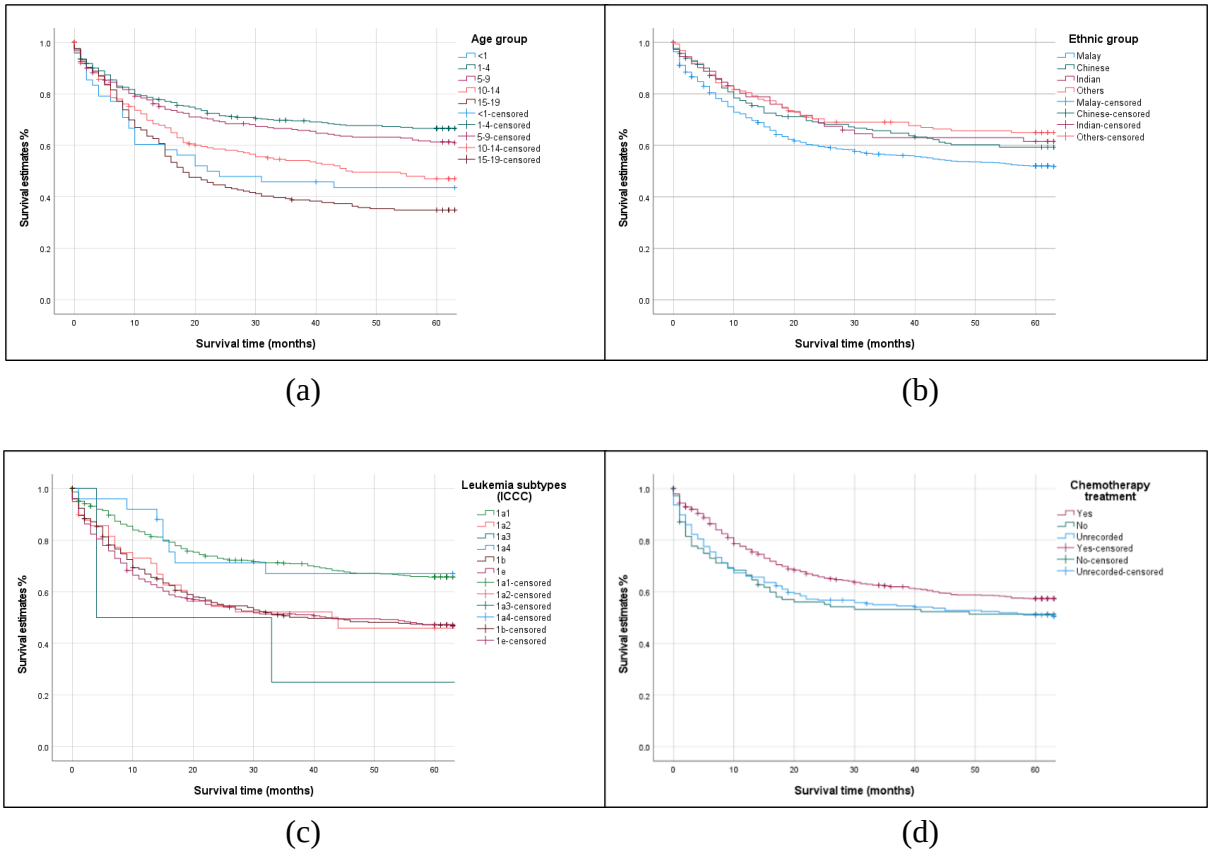

Figure 2. Kaplan-Meier Survival Curve for five-year Overall Survival Rate among childhood leukemia patients in Malaysia, i.e., for (a) Patients according to the age group; (b) Patients according to the ethnic group; (c) Patients according to the leukemia subtypes; (d) Patients according to the chemotherapy treatment.

DISCUSSION

This study examined the attributes of pediatric leukemia patients in Malaysia and appraised their survival rates. Our patient cohort's demographic and clinical features exhibited similarities with those observed in previous studies conducted in Malaysia and other Asian countries (Demanelis et al., 2015; Asthana et al., 2017; Registri Kanser Kebangsaan Institut Kanser Negara, 2021). The five-year rate in this study was 55.6%. In comparison, the five-year survival rates in other Asian countries ranged from 49% in Thailand (Wiangnon et al., 2014), 70.5% in China (Zheng et al., 2015), 75.4% in South Korea (Park et al., 2016), 80.1% in Brunei (Leong et al., 2020), and 71-83% in Japan (highest) (Nakata et al., 2018). Conversely, in certain developed nations, the five-year survival rate may reach as high as 90% (Bonaventure et al., 2017). This disparity could be attributed to differences in management techniques such as diagnostic and treatment modalities, as well as underlying healthcare delivery, socioeconomic position, and the existence of cancer registries (Park et al., 2016; Force et al., 2019). Nevertheless, it is imperative to exercise caution when making direct comparisons with survival rates documented in other nations. Disparities in age groups, study durations, and analytical methodologies employed should be taken into account.

To our knowledge, there are limited studies on childhood leukemia survival rates in Malaysia. Our study indicated a higher five-year survival rate than a previous study by the Malaysia National Cancer Registry (Azizah et al., 2018).

Despite similarities in exclusion and inclusion criteria, the lower survival rate in earlier studies could be attributed to a low notification rate, as most state cancer registries were only established after 2007 (Azizah et al., 2016). Furthermore, treatment factors such as a lack of participation in the ALL clinical trial, poor risk-reduction strategy, and low cure rate could also be the reason (Hany et al., 2020; Reedijk et al., 2020).

Additionally, boys were more likely than girls to develop childhood leukemia. Nonetheless, in this study, no substantial disparity in the five-year survival rate was observed between male and female patients, mirroring findings from a study conducted in the United States. (Whelan and Alva, 2018). According to research comparing Filipino residents, Asian Americans, and Caucasians, boys recorded a slightly higher five-year survival rate than girls (Redaniel et al., 2010). In contrast, a worldwide comparison of childhood leukemia (ALL and AML) survival studies found that girls outlived boys (Bonaventure et al., 2017). Survival disparities between sexes could be linked to sex chromosomes, hormone levels, and sex-biased biochemical changes in general (Zhu et al., 2019).

In terms of age group, our study showed significant disparities in survival with children aged 1-4 years old having the highest survival with adolescents aged 15-19 having the lowest. Research conducted in the United States revealed that adolescents aged 15-19 years exhibited the least favorable survival outcomes, whereas the younger cohort aged 1-4 years demonstrated the highest survival rates over an extended duration (Holmes et al., 2012). In alignment with research conducted in the Philippines, it was observed in this study that children falling within the age groups of 1-4 years and 5-9 years exhibited a higher five-year survival rate compared to other age cohorts (Redaniel et al., 2010). A literature review found that infancy was related to shorter survival due to genetic damage and poor response to induction treatment, particularly in newborns with ALL (Gao et al., 2019; Candelli et al., 2021). Meanwhile, decreased survival in adolescents may be attributed to a diagnosis of physiologically high-risk leukemia (Tricoli et al., 2011) or treatment with adult regimens (Kent et al., 2009; Alken et al., 2020).

In the current study, Malay children recorded the highest number of childhood leukemia cases (63.4%) and the lowest five-year survival rate compared to other ethnicities. In contrast, Indians showed the greatest five-year survival rate (61.6%). While the precise origins of ethnic disparities remain uncertain, it is postulated that both genetic and non-genetic factors contribute to variations in survival outcomes (Yang et al., 2011; Jobayer, Xie and Caywood, 2015).

In terms of leukemia subtypes, ALL (43.7%) is the most common among pediatric leukemia patients, followed by AML (27.0 %), and "unspecified and other" leukemia subtypes (22.9%). ALL patients had a greater five-year survival rate (65.7%) than AML (47.2%). The same pattern was observed in Thailand (Wiangnon et al., 2014), India, and various European countries (Gatta et al., 2014). The variation in survival rates between ALL and AML could be ascribed to the treatment modality, including its type and duration. In many instances of AML, more intensive chemotherapy regimens are commonly administered within a shorter timeframe, which may consequently increase the likelihood of experiencing side effects. (Creutzig et al., 2012; Du Plessis, Rassekh and Mammen, 2018). In contrast, lower chemotherapy doses are administered over a longer time in the cases of ALL (American Cancer Society, 2019).

Furthermore, more than half of the patients who underwent chemotherapy in our study showed a better survival rate (57.3%). Several studies have proposed that enhanced standard protocols for risk assessment and active involvement in clinical trials have contributed to improved

survival rates among pediatric patients. (Wiangnon et al., 2011; Hunger et al., 2012; Nakata et al., 2018; Reedijk et al., 2020). In Malaysia, the intensification of therapy for high-risk leukemia patient groups resulted in a notable elevation of the overall five-year survival rate, escalating it from 69% to 91% (Hany et al., 2020). Globally, treatment outcomes of leukemia have improved dramatically over the 30 years. For instance, single-center research conducted in Lithuania recorded a five-year OS growth from 36.1% in 1982 to 66.9% in 1991 (Rascon and Smailytė, 2020).

Even though half of the patients in our study resided less than 10 kilometers from the hospital, there was no significant difference in survival. In contrast, an Australian study found a substantial relationship between geographical remoteness and OS (p=0.004) (Jessop et al., 2021). Previous studies have found that most patients would have moved to nearby hospitals for treatment continuation (Fluchel et al., 2014; Kelly et al., 2016), thus blurring the distance categorization. Distance association could also be more significant in single-center than multi-centered studies, as revealed by Fluchel et al. (2014).

The primary constraint of our investigation stemmed from our reliance on secondary data. Owing to a notable proportion of missing data pertaining to variables such as distance, surgery, and radiotherapy, we were unable to comprehensively explore the underlying causes behind the diminished survival rates. Nevertheless, the robust aspect of our study emanates from its utilization of nationwide population-based data, which effectively captured a representative overview of childhood leukemia in Malaysia. Another significant aspect of our research was the completeness of follow-up data and the death confirmation due to the linkage with the national death registry. To the best of our understanding, this represented the first population-based investigation to scrutinize the five-year survival rate within the demographic of children, aged 0 to 19, afflicted by leukemia in Malaysia. Further research is needed to investigate factors like familial and socioeconomic characteristics impacting childhood leukemia survival in diverse populations and uncover underlying mechanisms behind these survival disparities.

CONCLUSIONS

This study comprehensively summarized the survival outcomes and characteristics of Malaysian children diagnosed with leukemia, revealing a 5-year overall survival (OS) rate of 56.4%. Our findings suggest that children aged 1 to 4 years old, Indian, those diagnosed with ALL, and had chemotherapy treatment at diagnosis are vital factors influencing the survival of children with leukemia.

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