ORIGINAL ARTICLE

The Determinants and Prognostic Factors of 5-year Survival of Childhood Leukaemia in Malaysia

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ABSTRACT

Introduction: Leukaemia is the fourth leading cause of death among children aged 0 to 14. This study aimed to determine the prognostic factors of death in childhood leukaemia in Malaysia. **Methods:** A retrospective cohort study was conducted for all childhood leukaemia patients aged 0 to 19 years diagnosed between 2010 and 2014 using data from the Malaysian National Cancer Registry database. Death dates were updated until 31st December 2019. The Cox proportional hazard model was used to determine the prognostic factors and hazard ratios. **Results:** Among the 1,212 children with leukaemia, females had a 19% (HR: 0.81, 95% CI: 0.68, 0.96) reduced risk of death than males. Meanwhile, patients aged less than one year, or between 10-14 and 15-19 years old reported adjusted hazard ratios of 1.7 ($p<0.05$), 1.7 ($p<0.001$), and 2.2 ($p<0.001$), respectively, when compared with patients aged 1-4 years old. Malay children with leukaemia had a 33% (HR: 1.33, 95% CI: 1.05, 1.68) higher risk of mortality than the Chinese. Patients with Mature B-cell (1a2) subtypes, acute myeloid leukaemia (AML) (1b) subtypes, and "unspecified and other" leukaemia (1e) subtypes showed 1.6 ($p<0.05$), 1.5 ($p<0.001$), and 1.6 ($p<0.001$) times the risk of death as compared to acute lymphoid leukaemia (ALL) (1a1) subtypes. **Conclusion:** Sex, age, ethnicity, and leukaemia subtypes were the four prognostic factors of mortality among pediatric patients. Early detection and treatment may improve childhood leukaemia survival.

Keywords: Childhood leukaemia; Acute lymphoid leukaemia; Acute myeloid leukaemia; Prognostic factors

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INTRODUCTION

Childhood leukaemia is the most common childhood malignancy, accounting for 30% of childhood cancer cases. Globally, it is also the commonest cause of death among children aged 0 to 19 (1). In Malaysia, 39.1% of all cancer cases among children 0-19 years were leukaemia. 48% of leukaemia cases are lymphoid leukaemia followed by myeloid (28%) and nonspecific leukaemia (24%). Males recorded a higher rate of childhood leukaemia than girls. Ethnicity-wise, Malay children were associated with a higher rate of leukaemia, followed by Chinese and Indians (2).

Upon diagnosis of leukaemia, clinical and laboratory symptoms can be used to predict the prognosis of the disease. The identification of prognostic factors affecting survival is one of the key ways to improve cancer survival and lower the overall burden(3,4). In developed countries, cytogenetic and molecular approaches are currently employed to evaluate prognosis (5). However, large-scale testing is not feasible in most resource-limited countries. The relevant evidence on the prognostication of childhood leukaemia remains sparse in Malaysia. It is vital to obtain country-specific prognostic variables as the impact of the major causes can differ greatly among patient populations in different countries. In addition, prognostic factors and their impact on all-cause mortality can help healthcare providers in Malaysia to better chart the best course of action for patients and caregivers in Malaysia as well as to convey disease progression to the patients and family members. This study aimed to determine the prognostic factors of death in childhood leukaemia in Malaysia.

MATERIALS AND METHODS

This was a retrospective cohort study using data from the Malaysian National Cancer Registry (MNCR), a population-based cancer surveillance system. Included were all Malaysian and permanent residents of Malaysia childhood leukaemia patients aged 0-19 years diagnosed with Groups 1a, 1b, and 1e leukaemia based on the International Classification of Childhood

Cancers Third Edition (ICCC-3) between 1 January 2010 and 31 December 2014. Chronic myeloproliferative diseases (ICCC-3 Group 1c), myelodysplastic syndrome, other myeloproliferative diseases (ICCC-3 Group 1d) and any inaccurate or incomplete information, such as registration based on a death certificate only (DCO) or autopsy, as well as those with invalid incidence dates (diagnosed less than two weeks from the patient's date of death), were excluded. For patients diagnosed with leukaemia more than once (duplicates) between 2010 and 2014, only the first record was kept.

The time-to-event formula was used to determine the sample size (6). The significance level for α (two-sided) and power (1-β) of the study was set at 0.05 and 0.84, respectively. The hazard ratio for Malay compared to Chinese was 1.82 based on a previous study (7). Meanwhile, the proportion for both groups was fixed at 0.5 and missing values of 20% were anticipated. As a result, the final required sample size required was 470. Nonetheless, we included all the eligible cases in the registry to ensure that the population was accurately represented.

Data retrieved from the registry included registry number, age, sex, ethnicity, residential distance to tertiary care, leukaemia subtypes, vital status, date of death, date of the last follow-up, as well as chemotherapy, radiotherapy, and surgery received at diagnosis. Ethnicity was grouped as "Malay", "Chinese", "Indian," and "Others". "Others" is Bumiputera Sabah and Sarawak and all other ethnic groups. Meanwhile, age was classified as "<1", "1-4", "5-9", "10-14", and "15-19" as reported in most literature (8–10). Since childhood leukaemia patients require specialized care, the distance between the patient's home and the nearest tertiary care facility was measured. The residential addresses of patients were manually converted into World Geodetic System (WGS) coordinates before being loaded into the QGIS. The shapefile for tertiary healthcare facilities in Malaysia was divided into Peninsular Malaysia and East Malaysia. Subsequently, each residential area was measured for the shortest distance to the tertiary care centre by car. The distances were later categorized as "<10", "10-25", "25-50", "50-100", and ">100" km (11).

Statistical Analysis

Data were analyzed using SPSS version 27. The time-to-event was the outcome of interest in this study. All 1,212 patients who fulfilled the study criteria were followed up until the 31st of December 2019, resulting in a minimum of 5 years (60 months) of follow-ups for all patients. Those who were still alive at the end of the follow-up period were censored. Univariable Cox regression was used to investigate the association between each variable. Variables with p-values less than 0.25 (12) were subsequently included in the multivariable Cox regression analysis. A forward and backward likelihood ratio method was used to obtain the best predictors of death. The variables were chosen based on p-values less than 0.05 for variable inclusion and p-values greater than 0.1 for variable removal. The hazard functions and a log-minus-log plot were used to test the proportional hazard assumption against time. The final model included a hazard ratio, 95% confidence interval, and p-value. Covariates with p-values lesser than 0.05 were considered prognostic indicators for death in childhood leukaemia.

Ethics Approval

The Ethical Committee of the Faculty of Medicine and Health Sciences at Universiti Malaysia Sabah (UMS) (JKEtika 1/21 (10)) and the Medical Review and Ethical Committee of the Ministry of Health Malaysia NMRR-21-385-58568 (IIR) granted clearance for the study. Following that, approval was also obtained 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 usage of pediatric leukaemia data and healthcare facility geospatial data. Patient consent was not required because there was no identifiable patient data.

RESULTS

Characteristics of Patients

From 2010 to 2014, the event (death) was met in 548 cases while the remaining 664 cases were alive (censored). Table I provides an overview of the characteristics and present status (alive or dead) of the childhood leukaemia patient population in this study.

Cox Regression Analysis

The univariable Cox regression analysis was done for all variables. The significant factors of p-value less than 0.25 were sex, age groups, ethnicity, leukaemia and chemotherapy at diagnosis (Table II). However, multiple Cox regression analysis (Table III revealed that sex ($p<0.05$), age at diagnosis ($p<0.001$), ethnicity ($p<0.05$), and leukaemia subtypes ($p<0.001$) were important predictive factors for death. Females had a 19% (HR: 0.81, 95% CI: 0.68, 0.96) reduced likelihood of death than males. Meanwhile, patients aged less than one year, 10-14, and 15-19 years old had 1.7 ($p<0.05$), 1.7 ($p<0.001$), and 2.2 ($p<0.001$) times the risk of death compared to patients aged 1-4 years old. Malay children with leukaemia had a 33% (HR: 1.33, 95% CI: 1.05, 1.68) higher risk of death than Chinese patients. Mature B-cell (1a2) subtypes, AML (1b) subtypes, and unspecified and other leukaemia (1e) subtypes had 1.6 ($p<0.05$), 1.5 ($p<0.001$), and 1.6 ($p<0.001$) times the likelihood of dying from childhood leukaemia as compared to ALL (1a1) subtypes.

Table I : Characteristics of childhood leukaemia patients included in the study (n=1,212)

Characteristics	n	Alive (%)	Dead (%)
Total	1,212	664 (54.8)	548 (45.2)
Sex			
Male	705	366 (51.9)	339 (48.1)
Female	507	298 (58.8)	209 (41.2)
Age			
< 1 year old	48	21 (43.8)	27 (56.3)
1 to 4 years old	464	306 (65.9)	158 (34.1)
5 to 9 years old	282	170 (60.3)	112 (39.7)
10 to 14 years old	212	101 (47.6)	111 (52.4)
15 to 19 years old	206	66 (32.0)	140 (68.0)
Ethnicity			
Malay	768	395 (51.4)	373 (48.6)
Chinese	211	125 (59.2)	86 (40.8)
Indian	72	43 (59.7)	29 (40.3)
Others	161	101 (62.7)	60 (37.3)
Distance (km)			
<10	612	328 (53.6)	284 (46.4)
10-25	457	256 (56.0)	201 (44.0)
25-50	116	63 (54.3)	53 (45.7)
50-100	22	14 (63.6)	8 (36.4)
>100	5	3 (60.0)	2 (40.0)
Leukaemia subtypes			
All lymphoid leukaemia (1a)	608	388 (63.8)	220 (36.2)
Precursor-cell (ALL;1a1)	530	347 (65.5)	183 (34.5)
Mature B-cell (1a2)	49	23 (46.9)	26 (53.1)
Mature T-cell and NK. cell (1a3)	4	1 (25.0)	3 (75.0)
Lymphoid leukaemia NOS (1a4)	25	17 (68.0)	8 (32.0)
Acute myeloid leukaemia (AML; 1b)	327	150 (45.9)	177 (54.1)
Unspecified and other leukaemia (1e)	277	126 (45.5)	151 (54.5)
Treatment			
Chemotherapy			
Yes	867	492 (56.7)	375 (43.3)
No	109	55 (50.5)	54 (49.5)
Unrecorded	236	117 (49.6)	119 (50.4)
Radiotherapy			
Yes	5	2 (40.0)	3 (60.0)
No	384	193 (50.3)	191 (49.7)
Unrecorded	823	469 (57.0)	354 (43.0)
Surgery			
Yes	15	8 (53.3)	7 (46.7)
No	385	193 (50.1)	192 (49.9)
Unrecorded	812	463 (57.0)	349 (43.0)

n: number of cases, %: Percentage, Alive: Censored, Dead: Event

Table II : Univariable Cox Regression Analysis for Prognostic Factors for Death of Childhood Leukemia, Malaysia, 2010-2014 (n=1,212)

Variables	Crude HR (95% CI)	*p*-value
Sex		0.066
Male	1	(ref.)
Female	0.85 (0.72, 1.01)	0.066
Age		<0.001
1 to 4 years old	1	(ref.)
< 1 year old	1.97 (1.31, 2.97)	0.001
5 to 9 years old	1.21 (0.95, 1.54)	0.127
10 to 14 years old	1.74 (1.37, 2.22)	<0.001
15 to 19 years old	2.43 (1.94, 3.06)	<0.001
Ethnicity		0.011
Chinese	1	(ref.)
Malay	1.30 (1.03, 1.64)	0.030
Indian	1.11 (0.75, 1.63)	0.938
Others	0.98 (0.65, 1.50)	0.513
Distance (km)		0.861
<10	1	(ref.)
10-25	0.94 (0.78, 1.12)	0.478
25-50	1.04 (0.78, 1.40)	0.778
50-100	0.75 (0.37, 1.51)	0.420
>100	0.96 (0.24, 3.84)	0.948
Leukemia subtypes		<0.001
Lymphoid leukemia		
Precursor-cell (ALL;1a1)	1	(ref.)
Mature B-cell (1a2)	1.77 (1.18, 2.68)	0.006
Mature T-cell and NK cell (1a3)	3.09 (0.99, 9.69)	0.052
Lymphoid leukemia NOS (1a4)	0.90 (0.44, 1.82)	0.766
Acute myeloid leukemia (AML; 1b)	1.85 (1.51, 2.28)	<0.001
Unspecified and other leukemia (1e)	1.88 (1.52, 2.33)	<0.001
Treatment		
Chemotherapy		0.020
Yes	1	(ref.)
No	1.31 (0.98, 1.74)	0.064
Unrecorded	1.29 (1.05, 1.58)	0.017

Univariable analysis using simple Cox regression model; HR: Hazard ratio; 95% CI: 95% confidence interval; n: number of cases, (ref.): reference

DISCUSSION

In this study, data from the MNCR was retrieved to identify the predictive determinants for death among childhood leukaemia patients who were diagnosed between 2010 and 2014. Sex, age, ethnicity, and leukaemia subtypes substantially impacted the survival rate. According to the results, sex was a significant prognostic factor, with females having a 19% lower risk of death than males. Differences in biological and genetic factors between males and females may contribute to varying outcomes in leukaemia patients.

Table III : Multivariable Cox Regression Analysis for Prognostic Factors for Death of Childhood Leukaemia, Malaysia, 2010-2014 (n=1,212)

Variables	Adjusted HR (95% CI)	*p*-value
Sex		0.018
Male	1	(ref.)
Female	0.81 (0.68, 0.96)	0.018
Age		<0.001
< 1 year old	1.66 (1.10, 2.50)	0.017
1 to 4 years old	1	(ref.)
5 to 9 years old	1.25 (0.98, 1.60)	0.071
10 to 14 years old	1.70 (1.33, 2.18)	<0.001
15 to 19 years old	2.24 (1.77, 2.84)	<0.001
Ethnicity		0.031
Malay	1.33 (1.05, 1.68)	0.020
Chinese	1	(ref.)
Indian	0.95 (0.62, 1.46)	0.824
Others	1.04 (0.75, 1.46)	0.801
Leukaemia subtypes		<0.001
Lymphoid leukaemia		
Precursor-cell (ALL;1a1)	1	(ref.)
Mature B-cell (1a2)	1.63 (1.07, 2.47)	0.022
Mature T-cell and NK cell (1a3)	2.52 (0.79, 8.04)	0.120
Lymphoid leukaemia NOS (1a4)	0.91 (0.45, 1.85)	0.786
Acute myeloid leukaemia (AML; 1b)	1.52 (1.22, 1.89)	<0.001
Unspecified and other leukaemia (1e)	1.60 (1.28, 2.00)	<0.001
Treatment		
Chemotherapy		0.187
Yes	1	(ref.)
No	1.21 (0.90, 1.63)	0.201
Unrecorded	1.19 (0.96, 1.47)	0.119

HR: Hazard ratio; 95% CI: 95% confidence interval; n: number of cases, (ref.): reference

Hormonal influences, immune responses, and genetic predispositions can affect disease progression and response to treatment. The finding that females had a lower risk of death than males suggests potential underlying biological mechanisms influencing leukaemia survival. The disparity between sexes might also be related to leukaemia lineage, especially in ALL, as reported in a recent study (4).

In addition, children below the age of one year and between 10-19 years showed a higher risk of death than children between the ages of 1-4 years. In the literature, infancy was strongly associated with a poor prognosis of childhood leukaemia due to genetic damage, poor response to induction treatment in babies, especially with ALL, as well as the presence of CD10 negativity and Pro-B immunophenotype (13–15). In comparison, adolescents were more likely to die from leukaemia if they were diagnosed with biologically high-risk leukaemia (16), did not participate in clinical trials and were treated with adult regimens (17). It is also important to note that the reasons behind the higher mortality risk among these age groups are multifactorial. Hence, to address the higher risk of death among infants and adolescents diagnosed with leukaemia in Malaysia, several solutions can be implemented. These include improving early detection and diagnosis, enhancing specialized pediatric oncology services, optimizing treatment protocols for infants, promoting treatment adherence

and participation in clinical trials, strengthening supportive care services, and enhancing public health education. Collaboration among healthcare providers, policymakers, researchers, and the community is essential for the successful implementation of these solutions.

Ethnicity has been established as a predictor of death in childhood leukaemia in many studies (18–20). However, one earlier study found that ethnicity did not affect survival (21). The Malaysian population is made up of three main ethnicities: Malay, Chinese, and Indian, each with its distinctive history, culture, and social standing. In our study, ethnicity is a predictor of death. Malay children had a 33% higher risk of dying from childhood leukaemia compared to Chinese children. Similar results were found in another local study (7). In East Malaysia, specifically in regions such as Sabah and Sarawak, the presence of distinctive socioeconomic (22,23), educational (24,25), and cultural (26) intricacies may contribute to the exacerbation of disparities in health outcomes and access to leukaemia care for children, despite the insignificance of 'Other' ethnicity as prognostic factors for death. Moreover, ethnicity is one of the major social health factors contributing to disparities in health outcomes, particularly among disadvantaged populations (27). Delays in diagnosis and abandonment of therapy as a result of socioeconomic disadvantages often lead to disease progression and recurrence (28). Additionally, other cultural factors such as parents' educational level, health perception, and health-seeking behaviour also contributed to the ethnic disparities in the prognosis and outcomes of childhood leukaemia (29–31). Therefore, to address ethnic disparities in health outcomes, particularly in childhood leukaemia, in Malaysia, several approaches can be taken. These include improving access to healthcare, increasing awareness and education, enhancing culturally sensitive healthcare services, reducing socioeconomic barriers, and supporting patient advocacy groups. These strategies aim to promote equitable access to healthcare, address cultural beliefs and barriers, and improve overall health outcomes for all ethnic groups in Malaysia.

Regarding leukaemia subtypes, childhood leukaemia patients with AML showed almost two times greater risk of death than those with ALL. Our result corresponded with a study in California, United States (20). The poor prognosis in AML patients is often attributed to relapse, disease complications, and medication adverse effects (32–34). In this study, chemotherapy treatment was not a prognostic factor for death. Even though it was significant in the univariable analysis, it was not significantly associated with mortality once adjusted in the multivariable analysis. However, different methods of evaluating the treatment could have impacted the study outcomes. For instance, in a recent study (35), the outcomes of different subtypes of leukaemia kinds were assessed based on specific treatment methods.

The strength of our study is the large population-based data on childhood leukaemia from the MNCR. Hence, the results represent a reliable overview of the overall cancer care for childhood leukaemia in Malaysia. In addition, the completeness of the alive/dead status at the end of the follow-up period was another key strength. However, there are also several limitations in our study. Since the study relied on secondary registry data, chemotherapy types, socioeconomic status, treatment adherence, follow-up status, and residence type (rural or urban) were not analysed. Moreover, there was a high number of missing data on radiotherapy and surgical treatment because this section of notification was voluntary in the registry, thus updates on treatment following diagnosis were scarce. Hence, future studies need to seek alternative strategies to address this limitation. Nevertheless, despite these limitations, this study provided important baseline evidence on the prognostic factors for death among childhood leukaemia patients in Malaysia

CONCLUSION

In conclusion, four major prognostic factors of death among pediatric leukaemia patients were identified in this study, namely gender, age, ethnicity, and the subtypes of leukaemia. Chemotherapy treatment at diagnosis was not a significant predictor of death. However, early detection and treatment may improve survival. Future research should expand the collection of all other relevant variables. Like-minded researchers should aim to fill the gaps in current evidence on the prognostication of pediatric leukaemia, especially in terms of leukaemia subtype-specific treatment types, individual and neighbourhood-level socioeconomic disparities, and access to health care services among different ethnicities.

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