3-YEAR SURVIVAL RATE AND PROGNOSTIC FACTORS OF ACUTE LYMPHOBLASTIC LEUKAEMIA AMONG PAEDIATRIC PATIENTS ON UKALL PROTOCOL IN HOSPITAL UNIVERSITI SAINS MALAYSIA

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PARTIAL REQUIREMENT FOR MASTER OF MEDICINE (PAEDIATRIC) PROGRAMME

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LIST OF ABBREVIATIONS AND NOMENCLATURES

ALL	Acute lymphoblastic leukaemia
CSF	Cerebrospinal fluid
CNS	Central nervous system
Hospital USM	Hospital Universiti Sains Malaysia
WCC	White cell count
MRD	Minimal residual disease
UK	United Kingdom National Randomised Trial for Children and Young Adults with Acute Lymphoblastic Leukaemia and Lymphoma
OS	Overall survival
EFS	Event-free survival
COG	Children's Oncology Group
DCOG	Dutch Children's Oncology Group
EORTC	European Organization for Research and Treatment of Cancer

LISTS OF DEFINITION

Duration of survival is taken from the date of diagnosis

Overall survival is taken from time of diagnosis to death or last contact

Event-free survival is taken from time of diagnosis to the date of any event or the date when the patient was confirmed to be well, at the date of censor whichever occurred first

Event is considered as resistance disease, relapse, defaulted, death or major complications (presence of any recorded complications or secondary malignancy)

Relapse is any disease that recurs in bone marrow, central nervous system, or testes

Bone marrow relapse is present of 25% blast cells in bone marrow

CNS relapse is presence of any CNS manifestation without any other explanation or with or without presence of blast in cerebrospinal fluid

Testicular relapse is presence of testicular mass on examination or ultrasound

Good early response is absence of blast cells in peripheral blood on day 8 of treatment with steroid

Poor early response is the presence of blast cells in peripheral blood on day 8 of treatment with steroid

Minimal residual disease (MRD) is the presence of cancer cells after completed week 12 of treatment

Nutritional status refers to weight, height, and body mass index (BMI). Obese: weight >95th percentile for height and age, underweight: weight <10th percentile for height and age.

ABSTRACT

***Background*:** Paediatric patients with acute lymphoblastic leukaemia have shown better overall survival and event-free survival over the recent decades. This outcome is due to the advancement of diagnostic modalities, individualised patient treatment and improved supportive care. This study was done to determine common clinical presentations, the known prognostic factors associated with disease outcomes and the overall survival in paediatric ALL patients treated with UKALL protocol. ***Methods*:** This was a retrospective cohort study involving data interpretation from medical records of children diagnosed with ALL and received treatment with UKALL protocol in Hospital Universiti Sains Malaysia from 1st January 2008 until 31st December 2018. Kaplan-Meier analysis with log-rank test was performed to determine the 3-year survival probability. Multivariate analysis with simple and multiple Cox regression was performed to determine the significant prognostic factors of poor disease outcome. ***Results*:** A total of 97 patients were included in the study. The commonest clinical presentations were fever (83.5%), pallor (82.5%) and lethargy (52.6%). Clinical examinations also revealed that most patients had hepatomegaly (92.8%), splenomegaly (83.5%) and lymphadenopathy (82.5%). The 3-year OS is 72.2%. In this study, the Kaplan -Meier analysis showed that the weight percentile (p=0.002) and CSF involvement (p=0.023) were significant factors in leukaemia patients' survival. Multivariate analysis showed that the weight percentile of the 10^{th} – 95^{th} percentile significantly predicted the poor survival outcome (p=0.002). ***Conclusion*:** Most paediatric ALL patients usually present with common clinical presentations of acute leukaemia. Our overall survival is considered fair and comparable to other developing countries.

Keywords: acute lymphoblastic leukaemia, overall survival, prognostic factors

ABSTRAK

Latar belakang: Pesakit kanak-kanak limfoblastik leukemia akut telah menunjukkan kadar jangka hayat keseluruhan lebih baik sejak dekad kebelakangan ini. Kesan jangka hayat keseluruhan yang lebih baik ini adalah disebabkan oleh kemajuan dalam modaliti diagnostik, rawatan yang lebih fokus kepada individu pesakit dan rawatan sokongan yang bersepadu. Kajian ini dijalankan untuk mengenal pasti tanda-tanda klinikal dan faktor-faktor prognostik yang berkemungkinan menyebabkan pengakhiran penyakit yang teruk dan menganalisa kadar jangka hayat secara keseluruhan pesakit ALL selepas menjalani rawatan kemoterapi UKALL. ***Kaedah:*** Kajian secara retrospektif ini melibatkan perolehan data daripada rekod perubatan pesakit kanak-kanak yang telah disahkan menghidap penyakit ALL dan menerima rawatan kemoterapi protokol UKALL di Hospital Universiti Sains Malaysia daripada 1 Januari 2008 hingga 31 Disember 2018. Analisa 'Kaplan-Meier' dan ujian 'Log-ranks' telah dijalankan untuk menentukan kadar jangka hayat keseluruhan bagi tempoh 3 tahun selepas rawatan. Analisa 'multivariate' dengan 'Cox-regression' mudah dan berganda telah dijalankan untuk menentukan faktor prognostik yang mempunyai signifikasi ke atas kesan penyakit yang teruk. ***Keputusan:*** Seramai 97 pesakit ALL telah menyertai kajian ini. Majoriti pesakit mempunyai gejala demam (83.5%), pucat (82.5%), dan keletihan (52.6%). Ujian fizikal menunjukkan kebanyakan pesakit mempunyai bengkak hati (92.8%), bengkak limpa (83.5%) and bengkak kelenjar limfa (82.5%). Kadar jangka hayat secara keseluruhan pada 3 tahun selepas rawatan adalah 72.2%. Analisa Kaplan-Meier menunjukkan 'weight percentile' (p=0.002), dan gangguan cecair cerebral (p=0.023) adalah faktor signifikan dalam meramal kesan jangka hayat keseluruhan pesakit ALL.

Pelarasan dengan fungsi 'Cox-regression' berganda menunjukkan '10^{th} - 95^{th} weight percentile' (p=0.002), sangat bersignifikasi dalam menjangka kesan teruk dalam jangka hayat keseluruhan pesakit ALL. ***Kesimpulan:*** Pesakit-pesakit ALL secara keseluruhan mempunyai ciri-ciri klinikal leukemia akut pada awal pengesanan penyakit. Malaysia sebagai negara membangun menunjukkan kadar jangka hayat keseluruhan yang memuaskan sejajar dengan negara-negara membangun yang lain.

CHAPTER II:
THE TEXT

Section A: Introduction

INTRODUCTION

Leukaemia accounts for 25 – 30% of childhood cancer. The vast majority of acute leukaemia was due to acute lymphoblastic leukaemia (ALL), which approximated around 80% of the cases. The peak incidence of paediatric ALL is between 2 – 5 years old [1].

Studies and research on risk factors and outcomes of ALL therapy have been done for decades to improve the survival of children affected by the illness. Hospital USM has been one of the oncology centres for east coast Malaysia and has been implementing multiple protocols and regimens for the treatment of childhood ALL since the early 1990s. In Malaysia, a few studies were done on treatment outcomes in paediatric ALL patients. For example, Nasir A. et al. (2020) and a recent study by Hamzah N. et al. (2021), which has yet to be published, were done in our centre on the overall outcome and survival of childhood ALL patients.

Multiple studies have found that 5-year overall survival (OS) varied between developed and developing or non-developed countries. For example, recent studies showed 5-year OS of 80% to 90-95% in developed countries, and in Asia, the 5- year OS varied from 44.3% to 80% [2,3]. Malaysian Study on Cancer Survival (MySCan) over five years from 2007 to 2011 reported the 5- year OS in paediatric leukaemia is 62.3%[4].

Multiple studies have identified prognostic factors affecting ALL patients' OS and event-free survival (EFS). Adverse prognostic factors include male gender, age younger than one year old or older than ten years old, high white cell count on presentation, T-cell immunophenotype, abnormal cytogenetic such as hypoploidy and Philadelphia chromosome, high level of minimal residual disease (MRD) at day 28 of chemotherapy and poor early response at day 8 of induction with steroid.

Over the years, multiple treatment protocols were developed to cater to and improve the outcome of paediatric ALL patients. Hospital USM has been implementing the United Kingdom National Randomised Trial for Children and Young Adults with Acute Lymphoblastic Leukaemia and Lymphoma (UKALL) treatment regimens for our patients. This protocol was started in Hospital USM in 2007 and was fully implemented on ALL new cases by 2008. Patients on UKALL protocol were stratified according to the disease risk factor and specific treatment regimen. UKALL protocol has undergone multiple upgrades since its introduction. Though the medications used did not have many changes, the overall disease stratification for patients' treatment had significant improvement since the introduction of cytogenetic analysis and minimal residual disease (MRD) analysis. ALL patient has better outcomes due to the advancement of diagnostic modalities, better and more specific risk stratification strategies and improvement in treatment approach and supportive care.

This study is to determine the clinical characteristics and prognostic factors involved in the outcome of paediatric ALL patients on UKALL regimen. We will also look at the 3-year survival rate of patients with ALL. In addition, this study would include other factors not discussed in our centre's previous study, such as patient nutritional status and cytogenetic outcome.

Section B:
Study Protocol

Document submitted for ethical approval

RESEARCH PROPOSAL FOR MASTER OF MEDICINE

PARTIAL REQUIREMENT FOR MASTER OF MEDICINE (PAEDIATRIC) PROGRAMME

UNIVERSITI SAINS MALAYSIA

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INTRODUCTION

Leukaemia accounts for 25 – 30% of childhood cancer. Within this portion, acute leukaemia constitutes about 97% of all childhood leukaemia. The vast majority of acute leukaemia was due to acute lymphoblastic leukaemia (ALL), which approximated around 80% of the cases [1]. Peak incidence is between 2 – 5 years old. However, infants less than one year old and children above ten years old may be affected with a more unfavourable prognosis.

Studies and research on risk factors and outcomes of ALL therapy have been done for decades to improve the survival of children affected by the illness. Hospital USM has been the oncology centre for east coast Malaysia. We have implemented multiple protocols for the treatment of childhood ALL since the early 1990s. Studies done in our centre were by Nasir A. et al. (2020) and a recent study by Hamzah N. et al. (2021), which has yet to be published; both were looking at the outcome and survival of childhood ALL patients. The earlier study was based on a different treatment protocol that was used before the year 2008. 5-year overall survival (OS) varies between developed and developing or non-developed countries. OS of 80% to 90-95% is seen in a developed country, and in Asia, the OS varies from 44.3% to 80% [2,3].

Multiple studies have identified prognostic factors that could affect the OS and EFS in ALL patients. These factors are essential to define risk categories and predict the risk of relapse. Prognostic factors include demographic-related risks such as age at presentation, gender, weight, height and socioeconomic status. Disease-related risks include initial TWC level at diagnosis, immunophenotypes, cytogenetic abnormalities, mediastinal mass, hepatosplenomegaly and CNS involvement. Treatment-related risks include early response to steroids, toxicity to anti-cancer medication and minimal residual disease (MRD) [7].

Since the 1980s, studies on the chromosome and genetic abnormality have been more prominent as ALL was found to be a heterogeneous disease at cytogenetic and genetic levels [5]. Many acquired genetic abnormalities have been described in the bone marrow cells of patients with ALL, including chromosomal translocations, aneuploidy, deletions and amplifications. In addition, several genetic aberrations are pathognomic of the disease and can be used to monitor treatment response. Along with treatment regimen, age, white cell count and minimal residual disease (MRD) detection, the genetic profile of leukaemia is the primary determinant of clinical outcome, especially the risk of relapse [6].

1. PROBLEM STATEMENT

Malaysian Study on Cancer Survival (MySCan), published in the year 2018, reported that the number of new cases of leukaemia from 2007 to 2011 in Malaysia was 1,179 patients, with a relative 5-year survival of 62.3% [4].

There are many clinical presentations among children with ALL. The most common presentations are fever, anaemia, lymphadenopathy, hepatosplenomegaly, or splenomegaly. However, a patient may also be present with other symptoms such as anorexia/weight loss (29%), abdominal pain (12%), and abdominal distension (11%). Other presentations can also involve musculoskeletal and bleeding manifestations such as mucosal bleeding (25%), joint pain (11%), and limping (15%) [7].

Acute lymphoblastic leukaemia has been found to vary in overall survival and event-free survival as multiple prognostic factors such as the age of onset, gender, initial TWC, ALL subtypes or cytogenetic subtypes. These factors would determine the patient disease risk stratification, severity of the disease and risk of relapse or poor treatment response.

ALL patients' survival depends on the clinical presentations and prognostic factors to better stratify the disease at initial presentation and throughout the treatment phase.

Therefore, early detection of clinical signs and symptoms suggestive of acute leukaemia in children, the laboratory parameters and the prognostic factors are critical for a timely diagnosis and early and individualised intervention to improve patient outcomes.

1.1 Study Justification

Survival analysis to determine overall or event-free survival in ALL patients is not an uncommon ongoing study of interest. With time and improvement in the diagnosis and treatment of ALL patients, multiple studies are done to evaluate the response and outcome of the patient. Though this is not a new study, this study is planned as an extension of previous studies in our centre and Malaysia. The study will include prognostic factors and other determinants for patient survival or outcomes that were not discussed in previous studies, such as the effect of nutrition on disease outcome and the outcome of a patient with a specific chromosome or cytogenetic abnormality. From 2007 onward, our centre has applied UKALL protocol for our newly diagnosed ALL patients. UKALL protocol has undergone multiple improvements since its introduction to cater to new risk stratifications and advancement in ALL treatment. This study will determine the 3-year survival probability of patients on UKALL protocol only to reduce study bias. Since the advancement of genetic studies in ALL, treatment protocols such as BFM, COG or UKALL 2003 have included cytogenetic and abnormal chromosomes associated with ALL in the disease risk factors. Later, the use of MRD is added to predict the risk of relapse. This information is essential to analyse our current treatment regimen, predict the outcome of the disease in the future and help in better implementation of disease intervention.

1.2 Research Questions

1) What are the clinical characteristics (clinical presentations and haematological parameters) of children with ALL in Hospital USM?

2) What are the prognostic factors, including cytogenetic subtypes and nutritional status, regarding survival outcomes among children with ALL in Hospital USM?

3) What is the 3-year survival rate of paediatric ALL in Hospital USM?

1.3 Objectives

1.3.1 General objectives:

To determine the common clinical characteristics, prognostic factors and 3-year survival probability of ALL in children in Hospital USM.

1.3.2 Specific objectives:

1. To identify the clinical characteristics (clinical presentations and haematological parameters) of children with ALL in Hospital USM.

2. To determine the prognostic factors, including cytogenetic subtypes and nutritional status among children with ALL in Hospital USM.

3. To determine the 3-year survival rate of children diagnosed with ALL in Hospital USM.

1.4 Research Hypothesis

There is an association between selected clinical characteristics, prognostic factors and survival outcomes among children with ALL in Hospital USM. The hypothesised clinical characteristics and prognostic factors to poor survival outcome with ALL include age of < 1 and ≥10 years, male, initial high WCC > 50 x 10^9/L, CNS involvement, presence of liver and spleen enlargement > 5cm (measured below subcostal margin at presentation), poor response to treatment, and high-risk group patient. Other factors include ALL immunophenotype, cytogenetic or chromosomal abnormality and nutritional status.

2. LITERATURE REVIEW

2.1 Clinical presentation of childhood ALL

The presenting clinical features of paediatric acute leukaemia are mainly attributed to ineffective haematopoiesis, presenting with anaemia, thrombocytopenia, and a range of constitutional symptoms. Typical physical findings in childhood malignancy include pallor, lethargy, bruises, and bleeding tendency. Other features include hepatosplenomegaly, lymphadenopathy, testicular swelling, arthritis, acute renal failure, meningeal syndrome (features of increased intracranial pressure, papilloedema, retinal haemorrhage), and anterior mediastinal mass are due to organ infiltration by the leukaemic cells [6,7].

Five common features were presented in more than 50% of children: hepatomegaly (64%), splenomegaly (61%), pallor (54%), fever (53%) and bruising (52%). Additional features were presented in a third to a half of children, including recurrent infections (49%), fatigue (46%), limb pain (43%), hepatosplenomegaly (42%), petechiae (42%), lymphadenopathy (41%), bleeding tendency (38%) and rash (35%). About 6% of children were asymptomatic at diagnosis [7].

A study performed in Riyadh showed that fever (70%), pallor (54%), lymphadenopathy (50%), and hepatosplenomegaly (50%) were the commonest presenting signs and symptoms, followed by weight loss (22%), bleeding and bruising (18%), bone pain and arthralgia (10%), neurological symptoms (6%), abdominal distension (6%), and nausea and vomiting (4%) [8].

Another study in Palestine, published in 2021, also found that patients mostly presented with pallor (70%), fever (53%), hepatosplenomegaly (49%) and bruises (21%) [9].

A local study from Malaysia performed by Nasir A. et al. (2020) revealed that children with ALL mostly presented between the ages of 1.1 to 4.9 years (55.8%) with a mean age of 4.9 ± 2.8 years old. 32.9% were from 5.0 to 9.9 years old, 8.9% from 10 to 12 years old and the remaining were infants. Most of them presented with TWC of 100 x 10^9/ L and below (75.8%), 21.4% with TWC of more than 100.0 x 10^9/L and 2.4% was not documented at initial diagnosis. The mean TWC at the first presentation was 77.0 x 10^9/L. Additionally, 28.1% had liver enlargement, and 21.4% had spleen enlargement 5 cm below the subcostal margin[1].

2.2 Prognostic factors

Known adverse prognostic indicators in paediatric ALL includes male gender, age less than one year or more than ten years, high WCC count at presentation, the size of liver and spleen > 5 cm at diagnosis, presence of mediastinal mass at diagnosis, CNS involvement, poor response to induction therapy, T – cell immunophenotype, unfavourable cytogenetic, such as the presence of Philadelphia chromosome, hypoploidy or Down syndrome, and a high level of minimal residual disease (MRD) at day 28 of starting chemotherapy [1,6].

The risk category is further divided into standard risk (SR), intermediate risk (IR) or high risk (HR). SR is defined when the age at presentation is between 1 to 10 years old, with the initial TWC < 50 x 10^9/L, in the absence of high-risk features.

The high-risk features include CNS and testicular involvement, T cell immunophenotype, M3 marrow on Day 15, or M2/ M3 marrow on Day 36. M2 marrow is defined as the presence of 5% to 25% of blast cells in the bone marrow (partial remission), while M3 marrow is defined as the presence of more than 25% blast cells in bone marrow (not in remission) [10,11].

Ng et al. (2000) determined several adverse prognostic indicators in children with acute leukaemia that included male gender (OR: 1.75, 95%, CI: 1.23 - 2.50), age less than one year or above ten years (OR: 4.34, 95% CI: 1.56 – 12.11), high WBC count at diagnosis (OR: 1.77, 95% CI: 1.17 – 3.52) and Hb > 11g/dL (OR: 2.11, 95% CI: 1.26 – 3.52) [12].

Nasir A. et al. (2020) showed that CSF involvement (HR: 2.36, 95% CI: 1.15 – 4.85), poor response to induction therapy (HR: 1.54, 95% CI: 1.15 – 4.85), and high-risk group (HR: 1.56, 95% CI: 1.08 - 2.25) were predictive of poor survival outcome [1].

Multiple studies have been done to look at a patient's outcome regarding the nutritional status, mainly the patient's weight or BMI, at diagnosis and during treatment. Children's Oncology Group (COG) reported that 14 % of obese (weight > 95^{th} percentile for age and height) children had inferior outcomes compared to non obese patients: 5-year EFS 64% vs 74%). A retrospective study at a single institution also found that obesity was linked to an increased risk of MRD at the end of induction. Another study involving 373 patients did not find an association between weight and MRD, the cumulative incidence of relapse or EFS. However, OS was lower in high BMI patients, primarily resulting from treatment-related mortality and inferior salvage after relapse [13].

On the other spectrum, Dutch Children's Oncology Group (DCOG) reported that patients who were underweight at diagnosis (8% of the population) had an almost two-fold higher risk of relapse compared with patients who were not underweight (after adjusting for risk group and age). Patients with a decrease in BMI during the first 32 weeks of treatment had similar relapse rates as other patients. However, they had significantly worse OS because of poorer salvage rates after relapse [3].

2.3 Outcome of childhood ALL

In developed countries, the survival rate of childhood acute lymphoblastic leukaemia (ALL) has improved by more than 80% to 90%. The implementation of current treatment protocols could contribute to this success, optimal application of risk stratification, risk-directed multi-agent chemotherapy regimens, and improved supportive care.

Low- and Middle- Income-Countries (LMICs), the estimated 5-year survival rates range between 44.3% and 80.0%, respectively. The Intercontinental-BFM2002 study, conducted in 15 upper-middle and high-income countries, reported 5-year event-free survival (EFS) of 74% and overall survival (OS) rates of 82%. Several factors that contributed to the poor survival rates among the LMICs included delay in presentation, diagnostic inaccuracy, restricted budget for risk-stratification and appropriate treatment, treatment abandonment, and socioeconomic status [2].

A study in Korea by Lee JW et al. published in 2017 found a 10-year EFS of 78.5% and OS of 81.9%, respectively [14].

Local studies performed in Malaysia by Ng et al. (2000) reported a two-year survival rate of 67%, while Nasir A. et al. (2020) showed an overall survival rate at 1, 3, and 5 years of 77.7%, 66.9%, and 63.5% for ALL, respectively [1,12].

In 2021, based on a study from Malaysia-Singapore 2003 and 2010 trials, B-ALL cytogenetic subtypes were determined. Examples of the genetic subtype are as listed: hyperdiploidy (chromosome >50), hypodiploidy (chromosome <45) and Philadelphia chromosome (BCR-ABL1). Each subtype will determine the risk group stratification for ALL patients, and the 5-year overall survival for each subtype mentioned were 98.8%, 50% and 75%, respectively [3].

3. METHODOLOGY

3.1 Conceptual framework

The diagram shows the conceptual framework for this study. All patients younger than 13 years old diagnosed with ALL from 2008 to 2018 were included in the study. This study included variables such as age, gender, ethnicity, clinical presentation, initial haematology parameters and various prognostic factors of ALL. In addition, the 3-year survival analysis was calculated, and the prognostic factors identified earlier were verified.