SURVIVAL RATE AND PROGNOSTIC FACTORS OF DEATH AMONG PATIENTS WITH NON-HODGKIN LYMPHOMA IN KELANTAN FROM 2008-2017

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by

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LIST OF SYMBOLS

<	Less than
>	More Than
≤	Less than or Equal
≥	More Than or Equal
α	Alpha / Level of significance
n	Sample
%	Percentage

LIST OF ABBREVIATIONS

NHL	Non-Hodgkin Lymphoma
IARC	International Agency For Research Cancer (IARC)
MNCR	Malaysia National Cancer Registry
RS	Relative Survival
NNMR	National Medical Research Registry
OS	Observed Survival
HR	Hazard Ratio
MST	Median Survival Time
SD	Standard Deviation
SPSS	Statistical Packages For the Social Science
WHO	World Health Organization
MOH	Ministry of Health
USM	Universiti Sains Malaysia
JKN	Jabatan Kesihatan Negeri
DLBCL	Diffuse Large B Cell Lymphoma
FL	Follicular lymphoma
HR	Hazard Ratio
OS	Observed Survival
RS	Relative Survival
DLBCL	Diffuse Large B-cell lymphoma
CHOP	Cyclophosphamide, Adriamycin, Vincristine and Prednisolone
R-CHOP	Rituximab, Cyclophosphamide, Adriamycin, Vincristine and Prednisolone
NK Cell	Natural Killer Cell
HUSM	Hospital Universiti Sains Malaysia
HPE	Histopathological Examination
CI	Confidence Interval
SDG	Sustainable Developmental Goals
MEPS	Medical Expenditure Panel Survey
SEER	The Surveillance, Epidemiology, and End Results
RR	Relative Risk
ECOG	Eastern Cooperative Oncology Group
NHMS	National Health Morbidity Survey

IPI	International Prognostic Index
LDH	Lactate Dehydrogenase
NLR	Neutrophile Lymphocyte Ratio
ICD-0	International Classification of Disease for Oncology
SPSS	Statistical Package for Social Sciences
NOS	Not Otherwise Specified
MALT	Marginal Zone Lymphoma Type
ALK	Anaplastic Lymphoma Kinase
LR	Likelihood Ratio
LML	Log-Minus-Log
NMRR	National Medical Research Registry
SD	Standard Deviation
IQR	Interquartile Range
PET	Positron Emission Tomography
CT	Computed Tomography
GLOBOCAN	Global Cancer Observatory
AGRICOH	International Consortium of Agricultural Cohort Studies
AGRICAN	Agriculture and Cancer
CNAP	Calling Name Presentation
AHS	Agricultural Health Study
MACR	Malaysian Association for Cancer Research
CSC	Cancer Stem Cells
MTX	Methotrexate
WBRT	Whole Brain Radiation Therapy
REAL	Revised European American Lymphoma
FDG	Fludeoxyglucose
HIV	Human Immunodeficiency Virus

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ABSTRAK

KADAR JANGKA HAYAT, JANGKA HAYAT MEDIAN DAN FAKTOR-FAKTOR PROGNOSTIK DALAM KALANGAN PESAKIT BUKAN HODGKIN LIMFOMA DI KELANTAN DARIPADA TAHUN 2008-2017.

***Latar Belakang**:* Limfoma bukan Hodgkin merupakan kanser yang ke 12 didunia, yang ke empat di Malaysia, dan yang ke lima di Kelantan. Kajian berkenaan kadar jangka hayat, jangka hayat median dan faktor-faktor prognostic dapat memberikan pengetahuan yang bernilai kepada penduduk di Negeri Kelantan dan membantu dalam membangunkan program intervensi yang lebih baik. Memperbaik jangka hayat hidup bergerak sejajar dengan Matlamat Pembangunan Mampan 3.0, Bangsa Bersatu dengan tujuan untuk memastikan kehidupan yang sihat dan menggalakkan kesejahteraan untuk semua.

***Objektif**:* Kajian ini bertujuan adalah untuk menentukan kadar jangka hayat dan jangka hayat median pesakit limfoma bukan Hodgkin di Kelantan. Objektif kajian ini juga adalah untuk mengenalpasti faktor-faktor prognostik yang boleh mempengaruhi risiko kematian dalam kalangan pesakit limfoma bukan Hodgkin di Kelantan.

***Kaedah**:* Satu kajian rekod secara retrospektif telah dijalankan menggunakan data sekunder bagi pesakit yang telah didiagnosa sebagai penyakit limfoma bukan Hodgkin yang berumur ≥ 15 tahun dan keatas dari tahun 1 Januari 2008 sehingga 31 Disember 2017. Susulan tambahan selama lima tahun selepas pemilihan pesakit dijalankan iaitu daripada 1 Januari 2018 sehingga 31 Disember 2022. Kriteria inklusi termasuk pesakit Malaysia berumur 15 tahun atau lebih dengan limfoma bukan Hodgkin yang tinggal dan didaftarkan dalam Pendaftaran Kanser Kelantan antara 1 Januari 2008 dan 31 Disember 2017. Kriteria pengecualian termasuk data yang hilang lebih daripada 30% dan duplikasi data. Semua pesakit yang memenuhi kriteria

inklusi dan pengecualian dimasukkan dalam kajian ini. Data dan analisis dilakukan dengan menggunakan perisian SPSS versi 28. Kaplan Meier digunakan untuk mengira anggaran jangka hayat dan jangka hayat median. sementara Cox Proportional Hazard Model menentukan faktor prognostik.

***Keputusan**:* Sejumlah 448 pesakit dilibatkan didalam analisis ini. Purata (SD) umur ketika diagnosis ialah 50.19 (18.01) tahun. Kebanyakan pesakit adalah lelaki 60.7%, dan melayu 96.4. Kebanyakan jenis histology limfoma bukan Hodgkin ialah Mature B-Cell Neoplasm (74.3%) dan jenis Agresi mewakili (87.3%). Secara keseluruhan, kadar jangka hayat 5 tahun adalah 28.3 % (95%CI: 24.1,32.5). Jangka hayat median dalam kalangan pesakit limfoma bukan Hodgkin yang berumur 15 tahun dan keatas di Kelantan adalah 9.01 (95% CI: 5.95, 12.06) bulan. Dengan pemboleh ubah yang lain menggunakan "multivariable Cox Proportional Hazard Model", faktor-faktor prognostic yang bermakna yang boleh mempengaruhi kematian akibat limfoma bukan Hodgkin di Kelantan dari 2008 hingga 2017 adalah umur 60 tahun dan keatas menyebabkan faktor kematian 1.55 lebih tinggi (Adj. HR: 1.55; 95% CI: 1.24, 1.93; p = <0.001) berbanding pesakit yang berumur 60 tahun kebawah; berjantina lelaki menyebabkan faktor kematian 1.39 kali lebih tinggi (Adj. HR: 1.39; 95% CI: 1.12, 1.73; p= 0.003) berbanding Perempuan dan Kanser tahap IV menyebabkan faktor kematian 1.88 kali lebih tinggi (Adj. HR: 1.88; 95% CI: 1.17, 3.04; p= 0.010) berbanding tahap I dan II. Pesakit yang tidak menjalani rawatan kemoterapi menyebabkan faktor prognostik kematian 1.50 kali lebih tinggi (Adj HR: 1.50; 95% CI: 1.18, 1.92; p= 0.001) berbanding pesakit yang menjalani rawatan kemoterapi.

***Kesimpulan**:* Kadar jangka hayat 5 tahun secara keseluruhan adalah 28.3 % (95%CI: 24.1,32.5). Jangka hayat median dalam kalangan pesakit limfoma bukan Hodgkin

yang berumur 15 tahun dan keatas di Kelantan adalah 9.01 (95% CI: 5.95, 12.06) bulan. Faktor-faktor prognostik yang bermakna menyebabkan kematian adalah pesakit yang berumur 60 tahun dan keatas, berjantina lelaki, berada di tahap IV dan tidak menjalani rawatan kemoterapi. Hasil Kajian ini bergerak seiring dengan kajian limfoma Bukan Hodgkin didunia. Kajian ini menyediakan data penting untuk pembuat dasar merangka intervensi Kesihatan yang disasarkan, seperti program pengesanan awal dan rawatan, bagi meningkatkan kadar kelangsungan hidup, mengurangkan kematian akibat limfoma bukan Hodgkin, dan memperbaiki perkhidmatan penjagaan kanser darah di Kelantan.

KataKunci: Limfoma Bukan Hodgkin, Kadar Jangka Hayat, Kadar Jangka Hayat Media, Faktor prognostik

ABSTRACT

SURVIVAL RATE AND PROGNOSTIC FACTORS OF DEATH AMONG PATIENTS WITH NON-HODGKIN LYMPHOMA IN KELANTAN FROM 2008-2017

Background: Non-Hodgkin lymphoma is the 12th most common cancer globally, the 4th in Malaysia, and the 5th in Kelantan. Studying the survival rate, median survival time, and prognostic factors of non-Hodgkin Lymphoma can provide valuable insights specific to the Kelantan population and assist in developing better intervention programs. Improving the survival rate aligns with Sustainable Development Goal 3.0, which aims to ensure healthy lives and promote well-being.

Objectives: This study aimed to describe Kelantan's non-Hodgkin lymphoma survival rate and median survival time. This study also aimed to determine the prognostic factors for death among non-Hodgkin lymphoma patients in Kelantan.

Methodology: A retrospective record review was conducted using secondary data among the patients diagnosed with non-Hodgkin lymphoma from January 1st, 2008, until December 31st, 2017. An additional five-year follow-up until December 31, 2022, was done to verify the patient's status. The inclusion criteria included Malaysian patients aged 15 years or older with Hodgkin lymphoma who resided and registered in the Kelantan Cancer Registry between January 1st, 2008, and December 31st, 2017. The exclusion criteria included missing data greater than 30% and duplicate data. All patients who fulfilled the inclusion and exclusion criteria were included in the study. The data were analysed using SPSS version 28. Kaplan-Meier was used to calculate survival estimates, while the Cox proportional hazards model was used to determine prognostic factors.

Results: There were 448 patients included in this analysis. The mean (SD) age at diagnosis was 50.19 (18.01). Most patients were male, 60.7% and Malay 96.4%. The most common histological subtypes were Mature B-cell neoplasm (74.3%) and the aggressive type (87.3%). The 5-year overall survival rate was 28.3% (95% CI: 24.1, 32.5). The median survival time of ≥ 15-year-old non-Hodgkin lymphoma patients in Kelantan was 9.01 (95% CI: 5.95, 12.06) months, respectively. The proportional Hazard Cox model showed that age more than 60 years old had a higher hazard of death of 1.55 (Adj. HR:1.55; 95% CI: 1.24, 1.93; p=<0.001) times compared to age less 60 years old; being male had a higher hazard ratio of death of 1.39 (Adj. HR: 1.39; 95% CI: 1.12, 1.73; p =0.003) times compared to female; and being in stage IV had a higher hazard ratio of death of 1.88 (Adj. HR: 1.88; 95% CI: 1.17, 3.04; p=0.010) times compared to stages I and II. When other variables were adjusted, the patient who did not undergo chemotherapy treatment had a significantly higher hazard of death of 1.50 (Adj. HR: 1.50; 95% CI: 1.18, 1.92; p = 0.001) times compared to the patient who received chemotherapy.

Conclusion: The overall 5-year survival rate was 28.3% (95% CI: 24.1, 32.5). The median survival time of ≥ 15-year-old non-Hodgkin lymphoma patients in Kelantan was 9.01 (95% CI: 5.95, 12.06) months. The significant factors of death among non-Hodgkin lymphoma patients in Kelantan were age ≥ 60, male gender, stage IV, and patients who did not receive chemotherapy treatment, which was consistent with other studies globally. This study provides essential data for policymakers to design targeted health interventions, such as early detection and treatment programs, to increase survival rates, reduce non-Hodgkin lymphoma mortality, and improve Kelantan's blood cancer care services.

Keywords: Non-Hodgkin Lymphoma, Survival, Median Survival time, Prognostic Factors of Death

CHAPTER 1

INTRODUCTION

1.1 Lymphoma

Cancer is a set of diseases that are multifarious and characterised by the uncontrolled proliferation of abnormal cells. These cells have the potential to invade adjacent tissues and develop tumours, thereby disrupting normal biological processes (Jurlander, 2011). The World Health Organisation (WHO) has identified cancer as a predominant cause of mortality on a global scale, accounting for nearly 10 million fatalities in 2020, which accounts for almost one in six deaths worldwide (WHO, 2022). Haematological malignancies, including leukaemia, lymphoma, and myeloma, are cancers of the hematopoietic and lymphoid tissues Jurlander (2011).

Lymphomas are cancers that begin in the lymphatic system when abnormal white blood cells proliferate uncontrollably (NSW, 2019). Hodgkin lymphoma and non-Hodgkin lymphoma are the two principal types of lymphoma. The 5-year prevalence rate of Lymphoma was 41.4% globally, while in Asia, non-Hodgkin lymphoma had the highest incidence rate at 44.4% and the highest mortality rate at 51.4% in 2020 (Miranda-Filho *et al.*, 2019). Non-Hodgkin Lymphoma is the ninth most common cancer in Southeast Asia and the sixth most common in Thailand and Singapore. (Intragumtornchai *et al.*, 2018; Miranda-Filho *et al.*, 2019) In Malaysia, lymphomas are the fourth most common cancer, as the Malaysia National Cancer Registry reported (National Cancer Registry Department, 2019). Non-Hodgkin Lymphoma accounts for 90% of cases and typically has a worse prognosis than Hodgkin lymphoma.

Classification of Non-Hodgkin Lymphoma

Non-Hodgkin Lymphoma encompasses a wide range of diverse groups of lymphoid malignancies categorized based on the specific form of lymphocyte involved (B cells, T cells, or natural killer (NK) cells) and specific genetic, histological, and clinical characteristics. The World Health Organization (WHO) classification system identified approximately more than 60 distinct subtypes of non-Hodgkin Lymphoma, and the classification kept increasing when classifications were updated, each with unique prognostic and therapeutic implications (Swerdlow *et al.*, 2016). The diffuse large B-cell lymphoma (DLBCL) was the most common subtype of B-cell lymphoma, which was the most prevalent form of Non-Hodgkin Lymphoma, and the DLBCL was the most responsive subtype to treatment, resulting in better prognosis post-treatment, followed by follicular lymphoma and Burkitt lymphoma (Smith *et al.*, 2015). Meanwhile, T-cell lymphomas, including peripheral T-cell lymphoma and anaplastic large-cell lymphoma, were less frequent, generally more aggressive, and had a poor prognosis, in contrast to Diffuse Large B-cell lymphoma (Smith *et al.*, 2015).

Non-Hodgkin Lymphoma is also graded based on the aggressiveness of the disease and is classified into three categories: low-grade, intermediate-grade, and high-grade. Low-grade (indolent) non-Hodgkin Lymphoma types, such as Follicular Lymphoma and Small Lymphocytic Lymphoma, grow slowly, allowing patients to live for many years without symptoms. Intermediate-grade non-Hodgkin Lymphoma , including Diffuse Large B-cell Lymphoma (DLBCL), have a faster growth rate and require prompt treatment. High-grade (very aggressive type) non-Hodgkin Lymphoma, such as Burkitt Lymphoma and Lymphoblastic Lymphoma, spread rapidly and need immediate treatment for a better prognosis (Sant *et al.*, 2010).

Various factors, such as sociodemographic factors, histological subtypes, grades of malignancy, patient health, and treatment regimens, influence survival rates, median survival times, and patient prognosis. This study examines the survival rate, median survival time, and prognostic factors of death among non-Hodgkin Lymphoma patients aged 15 years and older in Kelantan from 1st January 2008 until 31st December 2017.

1.1.1 Malaysia National Cancer Registry and Kelantan Cancer Registry

The Kelantan Cancer Registry was established in 1998. The National Cancer Registry was established in 2002 as part of the Clinical Research Centre. In 2007, it amalgamated with another organization and became known as the Malaysia National Cancer Registry (MNCR). The Public Health Division of the Ministry of Health currently maintains the MNCR. All states utilized the CanReg5 computer program for this purpose. The data from the Kelantan Cancer Registry must be transmitted to the MNCR every three months, as the National Cancer Institute monitors it.

The non-communicable disease branch of the state health department manages the Kelantan Cancer Registry, a population-based registry system that the government maintains. This registry records notification and documents all types of cancer either through active notification or passive notification, utilizing the patients' addresses as a basis for registration. Patients residing in the state of Kelantan diagnosed with cancer will be enrolled in this registry using the offline database Can Reg V5 software system developed by the International Agency for Research on Cancer (IARC), thus enabling the Kelantan Cancer Registry to generate an epidemiological profile of cancer in Kelantan the patient's personal identification number was employed to register cases in the database, thereby preventing duplication. The primary lesion will serve as the basis for entering all pertinent information about cancer, including its topography,

morphology, stage, and potential treatment options. The cancer cases must be reported voluntarily using the notification form. The management team will complete the form and then submitted to the Non-communicable Disease Unit of the State Health Department. The managing team of health facilities in Kelantan comprises 15 hospitals, including nine public hospitals, one university hospital (HUSM), and five private hospitals.

The Non-Communicable Disease unit performed a regular investigation to identify current instances, such as cross-referencing patients who had been discharged from the hospital's medical record unit with the histopathological examination (HPE) results obtained from the pathology department in tertiary hospitals. Identified unregistered cases will be reported to the appropriate hospital. A Non-Communicable Disease Unit Public Health Specialist will authenticate notifications before entering them into the Kelantan Cancer Registry.

1.2 Problem Statement

A previous systematic review of non-Hodgkin lymphoma research in Malaysia, excluding B-cell lymphomas, could not represent the prevalence of lymphoma in the country because many studies were case reports and case series (Lim *et al.*, 2023). The classification of non-Hodgkin Lymphoma has changed several times, from the Revised European American Lymphoma classification in 1994 to the WHO classifications in 2001, 2008, 2016, and the latest 5th edition in 2022 (Alaggio *et al.*, 2022).

No study has been done in Kelantan on survival and prognostic factors of death using CanReg 5 (Population-based system), which liaised with National Cancer

Registry data. A previous study conducted in Kelantan in 2010 examined the survival rates of non-Hodgkin Lymphoma patients from 1996 to 2006 using data from Hospital Universiti Sains Malaysia, which cannot represent the Kelantan state accurately because it gathered data from only one facility and this study combined survival rates of Hodgkin Lymphoma and Non-Hodgkin Lymphoma and childhood and adult (Nur Sabrina Che, 2010). Therefore, this study was warranted and essential to acquire an accurate survival analysis in Kelantan and be able to make a comparison. This study will become a foundation for non-Hodgkin Lymphoma studies as its classification increases over time. Hodgkin Lymphoma had a better prognosis (Shanbhag and Ambinder, 2018) compared to non-Hodgkin Lymphoma (Lees *et al.*, 2019). Malaysian study on cancer survival showed that the survival rate for lymphoma among adults was 40.1% (95%CI: 38.7, 41.6) and 46.3% (95%CI: 40.0, 52.4) among children (National Cancer Registry Department, 2018).

Previous studies hindered clinicians and policymakers in Kelantan from fully understanding the epidemiology and evaluating the current treatment status of non-Hodgkin Lymphoma in Kelantan, which might potentially affect management strategies. When compared to the United States, survival improved over time.

1.3 Rationale of study

This study addresses the research gap from the previous study by conducting an analysis of non-Hodgkin Lymphoma cases in Kelantan from 2008 to 2017 that were 15 years of age or older, providing a comprehensive and representative understanding of non-Hodgkin Lymphoma in this population using CanReg 5 data gathered from all hospital facilities (both public and private) in Kelantan. CanReg 5, adopted by the

International Association of Cancer Registries in partnership with WHO, is used by the other 15 states and accurately reflects the population of Kelantan. The study focused on the survival rate, median survival time, and prognostic factors of death among ≥ 15-year-old non-Hodgkin Lymphoma patients in Kelantan. Fifteen years and above were considered as the cut-off point because lymphoma was the most common cancer among individuals aged 15-24, affecting both males and females, and it was a similar cut-off point used in the Malaysia National Cancer Registry. Furthermore, the childhood classification was grouped until 14 years old, and the overall survival rate in lymphoma among childhood was 44.1, which was better than that of adults at 31.1% (National Cancer Registry Department, 2018).

Furthermore, the findings of this study aimed to assist clinicians and policymakers in planning screening and prevention and evaluating the current management strategies. Additionally, the study described all non-Hodgkin lymphoma classifications according to subtypes and grades, providing insights into which subtypes predominantly affect the Kelantan population. This study will hopefully be used as a foundation of reference in Kelantan for future non-Hodgkin Lymphoma research on the progress of survival in current treatment and further investigations into non-Hodgkin Lymphoma subtypes. Understanding the survival rate, median survival time, and prognostic factors of death among non-Hodgkin Lymphoma patients aligns with the Sustainable Development Goals (SDGs), particularly with emphasis on SDG 3.0 (Good Health and Well-Being) and SDG 10.0 (Reduced Inequalities). By providing essential data for improving healthcare strategies and addressing disparities in health outcomes, this study contributes to the overall goal of enhancing the quality of life among non-Hodgkin lymphoma in Kelantan.