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A Decade of Survival: Median Survival Time and Prognostic Factors of Non-Hodgkin Lymphoma in Elderly Patients in Kelantan (2008–2017)

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ABSTRACT

Non-Hodgkin lymphoma (NHL) is a major lymphoma subtype in Malaysia and a significant public health burden. Elderly patients often have poorer outcomes due to late presentation, comorbidities, and reduced treatment tolerance. This study examined median survival time and prognostic factors of death among NHL patients aged ≥60 years in Kelantan. A retrospective cohort was conducted using Kelantan Cancer Registry data from 2008–2017, with follow-up until December 2022. Mortality status was verified through the National Registration Department. Kaplan–Meier methods estimated survival, and Cox regression identified prognostic factors. Among 156 patients, 95 (60.9%) were male and 150 (96.2%) Malay. The median age was 67 years (IQR: 12). Most had Mature B-cell lymphoma (74.4%), and 89.1% were aggressive types. The overall median survival time was 4.18 months (95% CI: 2.26–6.08). Stage IV disease showed higher risk (Adj. HR: 2.33, 95% CI: 0.87–6.27, p=0.092). Patients without chemotherapy had significantly increased mortality (Adj. HR: 1.58, 95% CI: 1.02–2.43, p=0.040). Survival outcomes for elderly NHL patients were poor, highlighting the need for earlier diagnosis, improved access to chemotherapy, and lifestyle-based supportive care to enhance quality of life.

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

INTRODUCTION

Cancer is a multifaceted disease characterized by the uncontrolled proliferation of abnormal cells, which can invade surrounding tissues, form tumours, and disrupt normal biological processes (Jurlander, 2011). The World Health Organization (WHO) reported that cancer was responsible for nearly 10 million deaths globally in 2020, equivalent to one in six deaths worldwide (WHO, 2022). Among haematological malignancies, lymphomas are a major concern, arising in the lymphatic system when abnormal white blood cells proliferate uncontrollably (NSW, 2019). Lymphomas are divided into two main categories: Hodgkin lymphoma and non-Hodgkin lymphoma (NHL), with NHL constituting approximately 90% of cases and generally associated with poorer prognosis (National Cancer Registry Department, 2019).

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The global burden of NHL is considerable. A study showed that in Asia, NHL had the highest incidence rate at 44.4% and the highest mortality rate at 51.4% in 2020 (Miranda-Filho et al., 2019). In Southeast Asia, NHL ranks as the ninth most common cancer, while in Thailand and Singapore it is the sixth most common (Intragumtornchai et al., 2018; Miranda-Filho et al., 2019). In Malaysia, lymphomas are the fourth most common cancer, as documented by the Malaysia National Cancer Registry (National Cancer Registry Department, 2019).

NHL exhibits clinical heterogeneity and is graded into low-grade, intermediate-grade, and high-grade categories. Low-grade types such as Follicular Lymphoma progress slowly, while intermediate-grade types such as Diffuse Large B-cell Lymphoma (DLBCL) and high-grade types such as Burkitt Lymphoma progress rapidly, requiring prompt treatment (Sant et al., 2010). Survival outcomes are influenced by multiple factors, including patient demographics, histological subtypes, comorbidities, and treatment regimens.

Elderly patients represent a vulnerable group, as age itself is a determinant of poor prognosis. They often present with comorbidities, reduced treatment tolerance, and late-stage disease, which compromise survival (Shanbhag & Ambinder, 2018; Lees et al., 2019). Although lifestyle factors were not directly measured in this study, the findings highlight the importance of supportive care, preventive strategies, and healthier ageing practices in improving survival among elderly patients.

This study aimed to provide a comprehensive understanding of non-Hodgkin Lymphoma survival in Kelantan. Specifically, it sought to estimate the median survival time and determine the prognostic factors of death among patients aged 60 and above diagnosed with NHL between 2008 and 2017.

By addressing these objectives using population-based data from the Kelantan Cancer Registry (CanReg5), the study contributes to a more representative understanding among the elderly of NHL in the region. The findings are expected to guide clinicians and policymakers in improving management strategies, enhancing supportive care, and reducing disparities. In alignment with the Sustainable Development Goals (SDG 3: Good Health and Well-Being; SDG 10: Reduced Inequalities), this research underscores the importance of evidence-based planning to improve outcomes for NHL patients in Kelantan.

METHODS

This study was designed as a retrospective cohort study to determine the survival rate, median survival time, and prognostic factors of death among elderly patients with non-Hodgkin lymphoma (NHL) in Kelantan. The methodology was structured to ensure accuracy, reproducibility, and reliability of findings.

Study Duration and Location

The study was conducted between November 2023 and May 2024 at the Non-Communicable Disease (NCD) Unit, Kelantan State Health Department. Kelantan is located in northeastern Peninsular Malaysia and comprises ten districts: Kota Bharu, Pasir Mas, Tumpat, Bachok, Pasir Puteh, Machang, Tanah Merah, Jeli, Kuala Krai, and Gua Musang. Cancer notification forms were voluntarily submitted by all health facilities across these districts to the NCD Unit, ensuring comprehensive surveillance data for the state.

Study Population

The reference population was all elderly (≥60 years old) patients with NHL in Kelantan. The source population consisted of NHL patients registered in the Kelantan Cancer Registry during the study period. The sampling frame included all NHL cases recorded in the registry between January 1, 2008, and December 31, 2017.

Study Sample and Criteria

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The study sample comprised patients aged ≥60 years who were diagnosed with NHL between 2008 and 2017 and who met the inclusion and exclusion criteria.

- **Inclusion criteria:**
  1. NHL cases identified by ICD-O classification, diagnosed between January 1, 2008, and December 31, 2017.
  2. Malaysian citizens.
- **Exclusion criteria:**
  - Cases with more than 30% missing data or duplicate records.

Sample Size

The sample size was estimated using PS software for survival analysis. While no calculation was required for the descriptive objective (median survival time), sample size determination was performed for the prognostic factor analysis (objective two). Parameters for calculation included median survival time estimates and hazard ratio assumptions. A 20% adjustment was applied for potential dropout. However, because the pooled data available (n = 156) were smaller than the required sample size, all eligible cases were included in the study.

Research Tools and Data Collection

Data were extracted from the Kelantan Cancer Registry using the CanReg5 software. Extracted variables included sociodemographic characteristics (age, gender, ethnicity), clinical details (morphology, histological subtype, stage), and treatment information (chemotherapy). Dates of diagnosis and death were verified in collaboration with the National Registration Department to ensure accuracy.

A proforma checklist guided data extraction and ensured completeness of variables. Data entry was performed using SPSS version 28.0, with validation and cleaning steps to check for missing values, outliers, and normality of numerical variables.

Data Analysis

Descriptive Analysis

Descriptive statistics were used to summarise sociodemographic and clinical characteristics. Numerical variables such as age were presented as median and interquartile range, while categorical variables were reported as frequencies and percentages.

Survival Analysis

Survival time was defined as the period from diagnosis until death or the end of follow-up on December 31, 2022. Patients alive at the end of follow-up were censored. The Kaplan–Meier method was applied to estimate median survival times.

Univariable and Multivariable Analyses

Cox proportional hazards regression was used to assess prognostic factors of death. **Univariable analysis:** Simple Cox regression estimated crude hazard ratios (HR) with 95% confidence intervals. Variables with $p < 0.25$ or clinical relevance were retained. **Multivariable analysis:** Multiple Cox regression was used to obtain adjusted hazard ratios. Model building employed Backward LR and Forward LR approaches, and all potential two-way interactions and proportional hazard assumptions were tested before finalising the model.

Ethical Considerations

Confidentiality was maintained by anonymising all data. The registry provided pooled data with no identifiable patient information. Ethical approval was obtained from the Human Research Ethics Committee, Universiti Sains Malaysia (USM/JEPem/16120585), and the National Medical Research Registry (NMRR) NMRR ID: 23-03433-Z2X (IIR), with authorisation from the Kelantan State Health Department.

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RESULTS

This study analysed 156 patients aged 60 years and above who were diagnosed with non-Hodgkin lymphoma (NHL) in Kelantan between January 2008 and December 2017 with a total of 14 cases were excluded due to duplication and incomplete data (>30% missing).

The median age at diagnosis was 67 years (IQR = 12). The majority of patients were male (95 cases, 60.9%) and Malay (150 cases, 96.2%). Stage IV was the highest among those with known staging (22 cases, 14.1%).

The predominant histological subtype was Mature B-cell lymphoma (116 cases, 74.4%). Most patients presented with aggressive types of NHL (139 cases, 89.1%).

Table 3.1: Descriptive Analysis among ≥60 years old Non-Hodgkin Lymphoma Patients in Kelantan from 2008-2017 (n=156)

Characteristic	Total n(%)	Censored n(%)	Death n(%)
Age (Year old)			
60-74	121(77.6)	14 (11.6)	107 (88.4)
≥75	35 (22.4)	5 (14.3)	30 (85.7)
Gender			
Male	95 (60.9)	11 (11.6)	84 (88.4)
Female	61 (39.1)	8 (13.1)	53 (86.9)
Ethnicity			
Malay	150 (96.2)	17 (11.3)	133 (88.7)
Non-Malay	6 (3.8)	2 (33.3)	4 (66.7)
Stages of Lymphoma			
Stage I	5 (3.2)	2(40.0)	3 (60.0)
Stage II	2 (1.3)	0 (0.0)	2 (100.0)
Stage III	13 (8.3)	4 (30.8)	9 (69.2)
Stage IV	22 (14.1)	2 (9.1)	20 (90.9)
Unknown	114 (73.1)	11 (9.6)	103 (90.4)
Histological Subtypes			
Mature B-Cell neoplasm	116 (74.4)	15 (12.9)	101 (87.1)
Mature T Cell Lymphoma and NK-cell Neoplasm	9 (5.8)	2 (22.2)	7 (77.8)

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Table 3.1. Continued

NHL Precursor Lymphoid Neoplasm	5 (3.2)	0 (0.0)	5 (100.0)
Malignant Lymphoma (NOS)	26 (16.7)	2 (7.7)	24 (92.3)
Grades of Lymphoma			
High Grade (Very Aggressive)	5 (3.2)	0 (0.0)	5 (100.0)
Moderate Grade (Aggressive)	139 (89.1)	19 (13.7)	120 (86.3)
Low Grade (Indolent)	12 (7.7)	0 (0.0)	12 (100)
Chemotherapy			
Yes	37 (23.7)	7 (18.9)	30 (81.1)
No	96 (61.5)	7 (7.3)	89 (92.7)
Unknown	23 (14.7)	18 (78.3)	5 (21.7)

Median Survival Time

The overall median survival time for non-Hodgkin lymphoma patients aged ≥ 60 years in Kelantan (2008–2017) was 4.18 months (95% CI: 2.26, 6.08). Details are shown in Table 4.6, with the Kaplan–Meier curve presented in Figure 4.1.

Table 3.2: Overall Median Survival Time among ≥60 years old Non-Hodgkin Lymphoma Patients in Kelantan from 2008-2017

Variable	Median Survival time (month)	(95%CI)
Overall	4.18	2.26, 6.08

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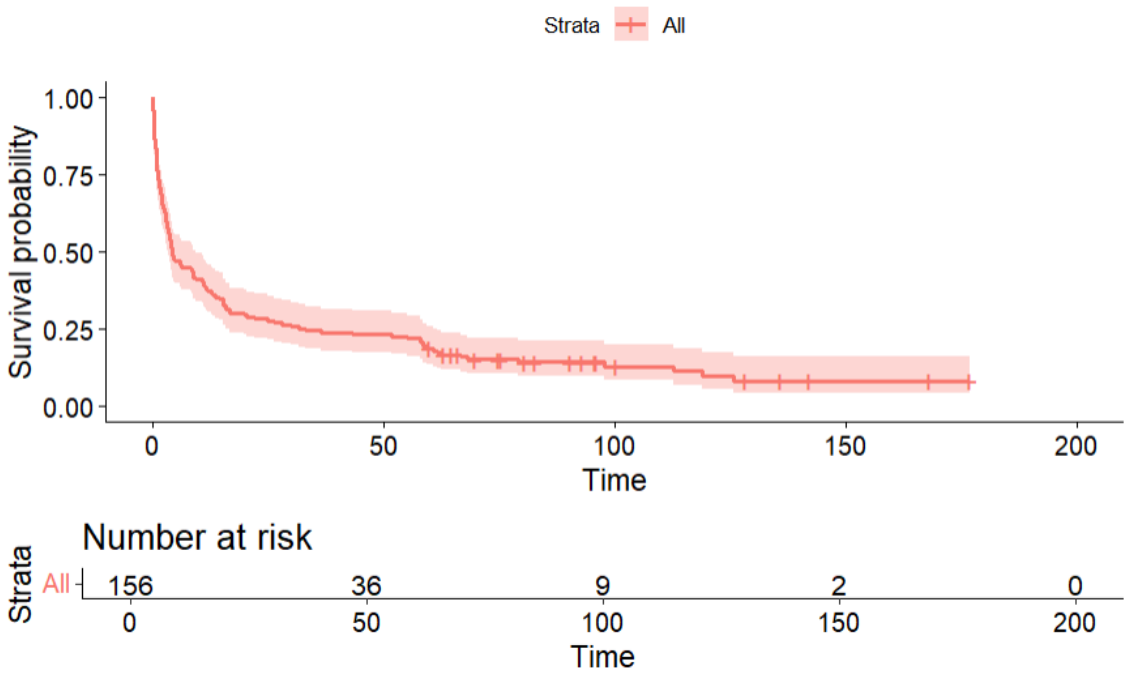

Figure 3.1: Kaplan Meier curve for survival estimates among ≥ 60-year-old non-Hodgkin Lymphoma in Kelantan 2008-2017.

Prognostic Factors of Death

Cox regression showed that age ≥60 (HR 1.61; 95% CI: 1.30–2.00), male sex (HR 1.34; 95% CI: 1.07–1.66), stage IV disease (HR 1.73; 95% CI: 1.08–2.79), and absence of chemotherapy (HR 1.51; 95% CI: 1.20–1.88) were significant predictors of death. Full results are presented in Table 4.7.

Table 3.3: Prognostic Factors of Death Among > 60 years old Non-Hodgkin Lymphoma Patients in Kelantan from 2008-2017 by simple COX proportional hazard regression (n=448)

Variable	B	Wald	Crude HR (95%CI)	p-value
Age	0.01	0.231	1.01 (0.98, 1.03)	0.631
Gender				
Female			ref	
Male	0.17	0.94	1.19 (0.84,1.68)	0.333
Ethnicity				
Malay			ref	
Non-Malay	-0.67	1.75	0.51 (0.19, 1.38)	0.186
Grade of NHL				
Indolent			ref	
Aggressive	-0.09	0.09	0.91 (0.50, 1.66)	0.768
Very Aggressive	0.24	0.22	1.28(0.45, 3.66)	0.642
Histological subtypes				
Bcell			ref	
Tcell/NK	-0.01	0.00	0.99 (0.46, 2.13)	0.979

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Precursor Cells	0.38	0.42	1.47(0.46,4.67)	0.515
Malignant Lymphoma (NOS)	0.36	0.70	1.43 (0.62,3.34)	0.403
Stage				
Stage 1-11			ref	
Stage III	-0.20	0.01	0.98 (0.33, 2.92)	0.967
Stage IV	0.86	2.91	2.35 (0.88, 6.28)	0.088
Unknown	0.63	1.91	1.89 (0.77,4.62)	0.168
Chemotherapy				
Yes			Ref	
No	0.48	5.19	1.62 (1.07, 2.46)	0.023
Unknown	0.07	0.06	1.08 (0.60, 1.93)	0.808

Table 3.4: Prognostic Factors of Death among ≥ 60 years old non-Hodgkin Lymphoma Patients in Kelantan from 2008-2017 by Multiple Cox Regression.

Variable	B	Wald	Adjusted HR (95%CI)	p-value
Stage				
Stage 1-11			ref	
Stage III	-0.09	0.03	0.91 (0.30, 2,74)	0.872
Stage IV	0.85	2.83	2.33 (0.87, 6.27)	0.092
Unknown	0.52	1.21	1.67 (0.67, 4.19)	0.271
Chemotherapy				
Yes			Ref	
No	0.45	4.22	1.58 (1.02, 2.43)	0.040
Unknown	-0.00	0.00	1.00 (0.55, 1.82)	0.890

DISCUSSION

This retrospective cohort study examined survival outcomes and prognostic factors of non-Hodgkin lymphoma (NHL) patients in Kelantan using population-based data from the Kelantan Cancer Registry. The registry's integration with the National Registration Department ensured accurate survival status, making the dataset representative and reliable for analysis. Survival analysis was selected as it accounts for censored data and allows valid estimation of median survival times, and prognostic factors of death.

This study highlights the poor prognosis of elderly patients (≥60 years) with non-Hodgkin lymphoma (NHL) in Kelantan, where the overall median survival time was only 4.18 months. This finding is considerably shorter compared to the median survival of 15.7 months observed in a single-centre study conducted at Hospital USM from 1996–2006 (Nur Sabrina Che, 2010). The discrepancy may be attributed to several factors. First, the present study focused exclusively on elderly patients, who are known to have reduced treatment tolerance, multiple comorbidities, and age-related physiological decline, all of which negatively impact outcomes (Fougère et al., 2017; Akhtar et al., 2022). Second, this population-based study included cases from across Kelantan, encompassing both urban and rural areas, in contrast to the USM cohort that reflected a tertiary referral population from an urban centre with greater access to specialized treatment. Studies from China and the United Kingdom similarly demonstrate that limited accessibility to healthcare, particularly in rural populations, is strongly associated with delayed treatment initiation and poorer survival outcomes (Liu et al., 2022; Smith, 2021).

Several prognostic factors of death were identified in this study, consistent with global literature. Stage IV disease was associated with an adjusted hazard ratio (HR) of 2.33, nearly doubling the risk of death compared to early-stage disease, although this did not reach

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conventional statistical significance (p = 0.092). This aligns with previous studies where advanced stage consistently predicted poorer survival (Qiu et al., 2021; Jiang & Sun, 2016). Stage IV NHL reflects systemic dissemination, including bone marrow, liver, pleural, or central nervous system involvement (Armitage, 2005). Late presentation is a common challenge in Malaysia, and is compounded by low awareness of early symptoms, sociocultural stigma, and delays in seeking medical care. The high proportion of patients presenting with advanced stage disease in our cohort underscores the urgent need for earlier detection and more effective referral pathways.

Chemotherapy emerged as a significant protective factor. Patients who did not receive chemotherapy had a 58% higher risk of death (Adj. HR: 1.58, 95% CI: 1.02–2.43, p = 0.040), reinforcing its central role in NHL management. This finding is consistent with evidence from the United States and other high-income countries, where chemotherapy, particularly in combination with rituximab, has significantly improved survival across NHL subtypes (Zhang et al., 2020; Zhou & Chen, 2023). Without treatment, aggressive subtypes such as diffuse large B-cell lymphoma often result in death within weeks to months (Smith, 2021). However, elderly patients are less likely to receive chemotherapy due to frailty, comorbidities, or concerns about tolerability. Moreover, socioeconomic and geographic barriers may limit timely access to therapy in Kelantan, reflecting broader inequalities in cancer care across low- and middle-income countries (Frederiksen et al., 2012; Gopal & Sharpless, 2021). Bridging these gaps through financial protection schemes, decentralised oncology services, and targeted support for elderly patients is essential to improve outcomes.

Age itself remains a critical determinant of survival in NHL. Biological ageing involves immune senescence, chronic inflammation, and diminished physiological reserves, which not only increase susceptibility to lymphoma but also limit the body's ability to tolerate treatment (Burton, 2009; Fougère et al., 2017). Elderly patients frequently present with multiple comorbidities, such as cardiovascular disease, diabetes, and chronic respiratory conditions, which complicate management and preclude intensive therapies (Smith, 2021). Studies in Western populations have similarly reported significantly higher mortality risks among older age groups, even after adjusting for disease subtype and stage (Zhou & Chen, 2023; Zhang et al., 2020). These findings suggest that while biological ageing is inevitable, improved supportive care, comorbidity management, and tailored treatment protocols could mitigate its adverse effects on survival.

Psychosocial and socioeconomic barriers also disproportionately affect elderly patients. Limited mobility, financial constraints, and lack of caregiver support reduce adherence to complex treatment regimens (Mohd Rosnu et al., 2022). Cognitive decline and psychological distress, including depression and anxiety, are common in this age group and may further undermine treatment compliance (Seol et al., 2021; WHO, 2023). In addition, stigma surrounding cancer in some rural communities may delay health-seeking behaviour, contributing to late presentation. These findings highlight the need for holistic approaches that integrate medical treatment with psychosocial and community-based interventions tailored to the elderly.

Lifestyle factors are increasingly recognised as important determinants of cancer outcomes. Poor nutrition, sedentary behaviour, smoking, and obesity can worsen comorbidities and reduce tolerance to chemotherapy. Conversely, lifestyle-oriented supportive interventions such as nutritional counselling, physical activity adapted for elderly capacity, and structured caregiver involvement can enhance resilience and improve quality of life during treatment (Peng et al., 2024). Psychosocial support is equally critical, as social isolation and ageism exacerbate vulnerability in older cancer patients (WHO, 2023). A comprehensive model of care that addresses not only medical treatment but also lifestyle,

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social, and psychological dimensions may offer the best chance of improving survival and well-being for elderly NHL patients.

Strengths and Limitations

A key strength of this study is its use of population-based data from the Kelantan Cancer Registry. This registry captures all reported NHL cases within the state, providing a comprehensive and representative dataset that minimizes selection bias. By including all NHL patients aged ≥60 years diagnosed between 2008 and 2017, the study offers a broad overview of disease burden and outcomes among elderly patients, reflecting both urban and rural populations. The integration of mortality data from the National Registration Department, Kelantan Branch, further enhances the reliability of survival estimates by ensuring complete ascertainment of vital status up to December 2022.

The use of CanReg5, a cancer registry software developed by the International Agency for Research on Cancer (IARC), is another methodological strength. Its standardized data entry protocols promote consistency and comparability, reducing variability in reporting and strengthening the validity of the analyses. Additionally, data extraction and cleaning were conducted by trained personnel experienced with the registry, which reduced the likelihood of duplication, misclassification, and data inconsistency. This systematic approach improved overall data quality and supports the credibility of the study findings.

Despite these strengths, several limitations should be acknowledged. First, the study relied on secondary data, which restricted the scope of variables available for analysis. Reporting of NHL cases to the Kelantan Cancer Registry was not mandatory during the study period, raising the possibility of underreporting and case omission. The accuracy and completeness of registry data are dependent on individual healthcare providers' reporting practices, which may have varied across facilities.

Second, NHL is a heterogeneous disease encompassing more than 60 subtypes, each with distinct clinical behaviour and prognosis (Smith et al., 2015). Classification systems also evolved during the study period, transitioning from the REAL classification to the WHO 2008 and 2016 updates (Swerdlow et al., 2016). This may have resulted in some misclassification of subtypes and limited the comparability of outcomes across time. For example, aggressive subtypes such as diffuse large B-cell lymphoma differ markedly in prognosis compared to indolent subtypes such as follicular lymphoma, which may survive for years without urgent treatment.

Third, the treatment data lacked detail regarding chemotherapy regimens. While the registry documented whether chemotherapy was received, it did not specify regimen type, dosage, or the use of targeted therapies such as rituximab. This limited the ability to evaluate the effect of specific treatment approaches on survival. Given that treatment protocols evolved substantially during the study period, the absence of such detail constrains interpretation of chemotherapy outcomes.

Finally, lifestyle and psychosocial variables which may play an important role in elderly patients' outcomes, such as nutritional status, physical activity, and social support were not captured in the registry. This restricts the ability to directly quantify their contribution, although evidence from other studies indicates that they likely influence survival and treatment tolerance (Mohd Rosnu et al., 2022; WHO, 2023).

CONCLUSION

In summary, this study demonstrates that elderly patients with NHL in Kelantan have poor survival outcomes, with stage at presentation and receipt of chemotherapy emerging as key prognostic factors. The findings underscore the importance of early diagnosis, equitable treatment access, and comprehensive supportive care that incorporates lifestyle and psychosocial dimensions. Addressing these challenges through integrated healthcare strategies is essential to improve survival and quality of life for elderly NHL patients in Malaysia.

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