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ORIGINAL RESEARCH

Clinical and Biomarker Characteristic of Lymphoma Patients in Hasan Sadikin Lymphoma Registry

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Background: No specific data have been systematically collected regarding lymphoma patient characteristics, while non-Hodgkin lymphoma (NHL) is identified as the 7th most common cancer and Hodgkin lymphoma (HL) is the 28th. Inflammation plays an important role in the pathogenesis and progression of lymphoma. Malnutrition is an adverse prognostic factor in lymphoma. Systemic Inflammatory Index (SII), Prognostic Nutritional Index (PNI), and Advanced Lung Cancer Inflammation Index (ALI) were biomarkers depicting inflammation and nutritional status. This study aims to describe the clinical and biomarker characteristics of both HL and NHL patients.

Methods: This descriptive study used a cross-sectional design, and data were collected from Hasan Sadikin Hospital lymphoma registry from January 2020 to November 2023. Demographic, staging, and histopathological data were extracted. Three biomarkers were evaluated. Survival curves were drawn using Kaplan–Meier curve analysis, and the log rank test was used for comparison of survival between early and advanced stage.

Results: A total of 271 patients were recruited as participants, and the majority (80.5%) had NHL, with diffuse large B-cell lymphoma (DLBCL) being the most common histopathological type (50.5%). Early disease was observed in two-thirds of patients, and low-risk International Prognostic Index (IPI) score was the most common prognostic score found (95%). SII was slightly higher in early compared to advanced stages. Treatment response was evaluated from 101 patients, and complete response was observed in 44.5%. Two-year overall survival (OS) was 93.1%, with median survival 22.7 (95% CI 21.9–23.5) months. In early stage, the median survival was slightly longer than in advanced stage [23.0 (95% CI 22.2–23.8) vs 21.6 (95% CI 19.3–23.8) months, P=0.09].

Conclusion: Hodgkin lymphoma and DLBCL had similar clinical and biomarker characteristics. There were slight differences between the three biomarkers SII, ALI, and PNI based on the disease stage. Almost all patients still survived at 2-year follow-up.

Keywords: lymphoma, non-Hodgkin lymphoma, Hodgkin lymphoma, registry

Background

Lymphoma is a malignancy affecting lymphocytes and lymphoid tissues, particularly the lymph nodes and associated organs such as the spleen. These cancers are classified based on cellular origin, with molecular diagnostics playing an increasingly significant role. Currently, more than 80 different entities are recognized in this classification system.[1]

In 2020, 83,087 cases of Hodgkin lymphoma (HL) constituted 0.4% of newly reported cancer occurrences and accounted for 0.2% of cancer-related deaths worldwide. The global age-standardized incidence rate for HL was 0.98 per 100,000 people.[2,3] Meanwhile, non-Hodgkin lymphoma (NHL) imposes a significant global burden, with the incidence increasing rapidly in recent decades. In 2020, NHL was identified as the 11th most frequently diagnosed cancer, with

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nearly 545,000 new cases and ranking as the 11th leading cause of death, resulting in approximately 260,000 fatalities. According to GLOBOCAN data, NHL ranks as the 7th most common cancer in Indonesia, while HL is at the 28th position.[2]

The etiology and development of lymphoma are significantly influenced by inflammation.[3] According to Park et al, malnutrition is a poor predictive factor for lymphoma.[4] Biomarkers that represented inflammation and nutritional status included Systemic Inflammatory Index (SII), Prognostic Nutritional Index (PNI), and Advanced Lung Cancer Inflammation Index (ALI).[5]

There has been no systematic collection of specific data on lymphoma patient characteristics. By assembling a standardized minimum dataset that progressively incorporates patient-reported results, registries prove highly beneficial, particularly for diseases or interventions posing challenges for clinical trials. Even in large referral centers where patient numbers may be limited, registries play a crucial role, providing a means to detect variations in medical practices. Additionally, registries function as efficient platforms for executing observational studies and interventional trials, facilitating the establishment of optimal management methods and enabling health economics analyses through the use of "real world" data.[6]

The purpose of this study is to characterize the clinical features and biomarkers of inflammation and nutritional status of lymphoma patients in our hospital.

Method

A cross-sectional design was applied in this descriptive study, using lymphoma registry data collected from the Oncology clinic at Dr Hasan Sadikin General Hospital in Bandung from January 2020 to November 2023. Participants were selected through a total sampling method, with the following inclusion criteria: patients suspected or diagnosed with lymphoma, confirmed by histopathology, and engaged in a minimum of one chemotherapy cycle. Furthermore, the variables explored were age, gender, sex, age at diagnosis, year of diagnosis, baseline hematologic profile, histological type, Ann Arbor stage, and treatment modalities. Death confirmation relied specifically on medical records from Hasan Sadikin Hospital. Additionally, multiple information-gathering steps were carried out, including raw data collection, data abstraction and coding, initial verification, data input, secondary verification, data analysis, and reporting. Patient lists were obtained from medical records and the hospital information system, filtered for duplication, hand-searched for correspondence, and subjected to data abstraction and coding. The demographic, diagnostic, staging, and histopathological data were collected.

The following formulas were utilized to calculate these values: NLR (neutrophil lymphocyte ratio: peripheral blood levels of absolute neutrophil count/absolute lymphocyte count; ALI: body mass index (BMI) × blood albumin level (g/dL)/NLR; PNI: 10 × serum albumin (g/dL) + 0.005 × total lymphocyte count/mm^3; SII: platelet count × NLR.[5] Unpaired *t* testing or Mann–Whitney *U* testing was used to compare continuous variables, while categorical data were compared using χ^2 testing or Fisher exact testing to differentiate characteristics between HL and DLBCL patients. Two-year survival curves were drawn using Kaplan–Meier curve analysis, and we used the log rank test for comparison between early and advanced stage. A P value <0.05 was considered statistically significant.

All the data were analyzed using Microsoft Excel and SPSS version 25.0.

The permission to conduct this study was obtained under the Ethical Approval Number DP.04.03/D.XIV.2.2.1/197/2024.

Result

A total of 271 patients with lymphoma, of whom 161 (63.1%) were males, were included in this study, and the demographic characteristics were assessed as presented in Table 1. Approximately two-thirds of participants were 60 years old or younger, with a median BMI in normal limits before treatment. Only 11.4% were underweight, and hematological parameters observed before treatment remained in normal limits. The majority (80.5%) had NHL, with diffuse large B-cell lymphoma (DLBCL) being the most common histopathological type. T-cell lymphoma was found in only 3/271 (1.1%) patients. Early-stage disease (stages I and II) was observed in two-thirds of patients, and most had good performance status (ECOG 0 and 1). The low-risk IPI score was the most common prognostic score found, and approximately half of patients received an R-CHOP or CHOP chemotherapy regimen. Four biomarkers including SII, PNI, ALI, and LMR/LDH ratio showed slight differences between early and advanced stages.

Table 1 Clinical Characteristics

Characteristic	
Participants (*n*)	271
Demographic Characteristics	
Age, median (IQR), years	50 (34–62)
≤60 Years (*n*, %)	198 (73.1)
>60 Years (*n*, %)	73 (26.9)
Male sex (*n*, %)	161 (63.1)
Clinical Characteristics	
Body Mass Index (BMI) before Treatment [Median (IQR), kg/m^2]	21.9 (19.8–24.6)
Underweight (BMI<18.5) (*n*, %)	31 (11.4)
Normoweight (BMI≥18.5) (*n*, %)	240 (88.6)
Hematological Parameters, Median (IQR)	
Hemoglobin (g/dL)	12.7 (11.0–14.1)
White blood cells (/mm^3)	7800 (6200–10,500)
Neutrophil count (/mm^3)	4896 (3560–6896)
Lymphocyte count (/mm^3)	1675 (1054–2420)
Platelets count (/mm^3)	323,500 (252,000–397,000)
Pathology Anatomy (*n*, %)	
Hodgkin lymphoma	53 (19.5)
Non-Hodgkin lymphoma	218 (80.5)
– Diffuse large B-cell lymphoma	137 (50.5)
– Follicular lymphoma	35 (12.9)
– Marginal zone lymphoma	11 (4.0)
– Mantle cell lymphoma	4 (1.5)
– T cell lymphoma	3 (1.1)
Stage	
– I	82 (30.2)
– II	131 (48.4)
– III	42 (15.5)
– IV	16 (5.9)
ECOG	
– 0	215 (79.3)
– 1	53 (19.5)
– 2	2 (0.8)
IPI Score	
Low risk (0–1)	258 (95.0)
Low intermediate risk (2)	13 (5.0)
High intermediate risk (3)	0
High risk (4–5)	0
Chemotherapy regimen	
– CHOP	113 (41.7)
– R-CHOP	115 (42.5)
– ABVD	43 (15.8)
Biomarker, Median (IQR)	
– SII	
Early stage	947,760 (537,762.5–1,681,826)
Advanced stage	854,031 (363,701.5–1,778,635.2)

(*Continued*)

Table 1 (Continued).

Characteristic	
– PNI	
Early stage	39.2 (10.1–47.4)
Advanced stage	40.3 (13.1–48.7)
– ALI	
Early stage	8.5 (1.7–32.5)
Advanced stage	14.4 (8.7–43.7)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; SII, Systemic Immune Inflammatory Index; PNI, Prognostic Nutritional Index; ALI, Advanced Lung Cancer Inflammation Index.

Table 2 shows the comparison of clinical characteristics between HL and DLBCL patients. There was no significant difference in demographic, clinical, and biomarker characteristics between the groups.

At the time of analysis, half of the patients had completed chemotherapy, with the majority achieving a complete response. Out of 271 patients, 56 (20.6%) failed to complete follow-up, and 14 (5.2%) deaths were recorded during treatment; patient's outcome are shown in Table 3.

Table 2 Clinical Characteristics Difference Between HL and DLBCL

Characteristic	HL n=53	DLBCL n=137	p
Demographic Characteristics			
Age, median (IQR), years	48 (37–60)	52 (40–63)	0.231
≤60 Years (*n*, %)	49 (92.4)	55 (40.2)	
>60 Years (*n*, %)	4 (7.6)	82 (59.8)	
Male sex (*n*, %)	26 (49.1)	87 (63.5)	
Clinical Characteristics			
Body Mass Index (BMI) Before Treatment [median (IQR), kg/m^2]	18.1 (17.6–25.8)	17.9 (17.6–28.7)	0.266
Underweight (BMI<18.5) (*n*, %)	9 (16.9)	15 (10.9)	
Normoweight (BMI≥18.5) (*n*, %)	44 (83.1)	122 (89.1)	
Hematological Parameters, Median (IQR)			
Hemoglobin (g/dL)	12.5 (10.6–14.0)	12.4 (11.0–14.1)	0.848
White blood cells (/mm^3)	7500 (5400–11,640)	7800 (6200–10,245)	0.679
Neutrophil count (/mm^3)	4480 (3027–6751)	4960 (3572–6890)	0.347
Lymphocyte count (/mm^3)	1596 (1015–2272)	1692 (1053–2558)	0.464
Platelet count (/mm^3)	341,000 (266,000–398,500)	328,000 (255,500–409,000)	0.959
Stage			
– Early	109 (79.5)		0.540
– Advanced	28 (20.5)		
ECOG	52 (98.1)		
– 0–1		137 (100)	1.000
– 2–3	1 (1.9)	0 (0)	
Biomarker, Median (IQR)			
SII	978,000 (520,791–2,290,962)	1,009,810 (514,948–1,677,870)	0.938
PNI	9.3 (5.6–12.9)	8.9 (6.3–14.1)	0.492
ALI	0.4 (0.0–1.7)	0.53 (0.0–1.44)	0.813

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; SII, Systemic Immune Inflammatory Index; PNI, Prognostic Nutritional Index; ALI, Advanced Lung Cancer Inflammation Index.

Table 3 Outcome of Treatment

Outcome	n (%)
Completed Chemotherapy	118 (43.5)
Chemotherapy Response [a](*n*=101)	
– CR	45/101 (44.5)
– PR	20/101 (19.8)
– SD	27/101 (26.7)
– PD	9/101 (8.9)
Drop out	56 (20.6)
Death before completed chemotherapy	14 (5.2)

Notes: [a]chemotherapy response could not be evaluated in 17 patients due to loss to follow-up.
Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

After 2 years of follow-up, we demonstrated a 2-year overall survival (OS) of 93.1% with median survival 22.7 (95% CI 21.9–23.5) months. In early stage, the 2-year OS and median survival were slightly better than in advanced stage [94.9% vs 85.7% and 23.0 (95% CI 22.2–23.8) months vs 21.6 (95% CI 19.3–23.8) months, $P = 0.09$] (Figure 1).

Discussion

Clinical and pathological features of 271 lymphoma cases in Hasan Sadikin General Hospital were assessed from 2020 to 2023 during this study. The patients were younger than the age reported for those with Western lymphoma, and most were not malnourished. Additionally, NHL was the dominant case found, with DLBCL being the most common type. In two-thirds of patients, the early disease stages I and II were observed, and the majority had good performance status. Moreover, the most prevalent predictive score discovered was a low-risk IPI Score. R-CHOP or CHOP regimens were administered to about half of the patient population who had finished chemotherapy, with the majority showing complete response.

The median age of lymphoma patients was 50 (IQR, 34–62) years, correlating with the range of 45–65 years among 834 participants reported by Dwianingsih et al in Yogyakarta, Indonesia, from 2010–2014.[7] In 203 DLBCL patients in Surabaya from 2015–2017, the mean age recorded was 51 ± 12.9.[8] In Singapore, 18 to 94 (mean 55.0±16.2) years was observed,[9] which was younger than the median 63 years reported during previous study by Mugnaini and Ghosh in the United States from 2009 to 2013. Similarly, in Australia and New Zealand, the median age of 64.3 (range, 52.1–73.5) years was identified.[10,11] The median age of those with NHL in Asia is significantly lower, compared to the population-based registration in Western countries. Risks for developing NHL include immunosuppression, a causal connection between infectious agents and

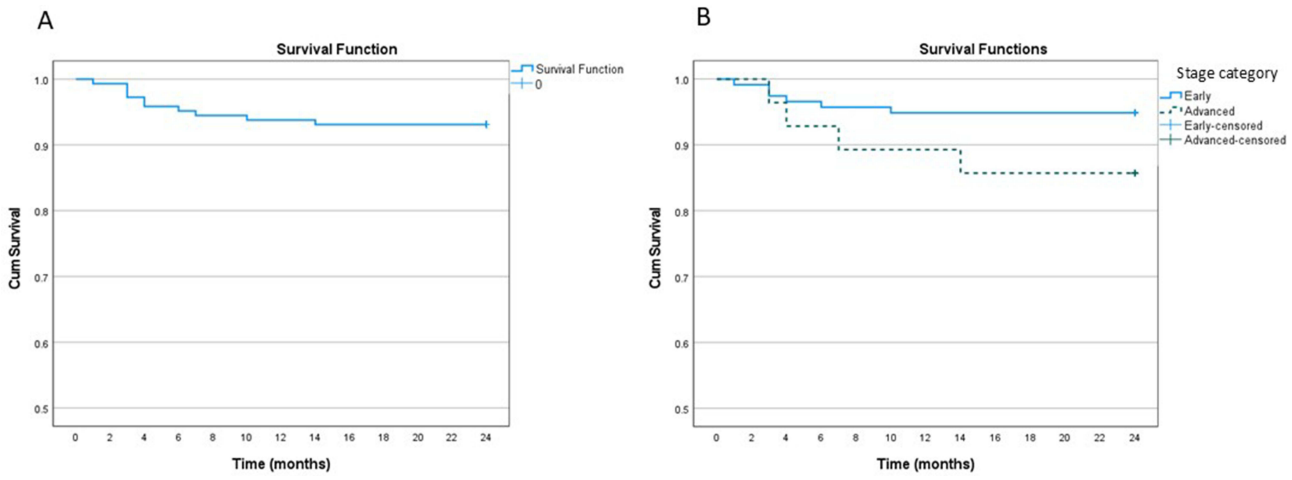

Figure 1 Survival curve for 145 patients in 2 years of follow-up. (**A**) All patients. (**B**) Early vs advanced stage.

lymphomagenesis. These have been determined, particularly for human T-cell leukemia/lymphoma virus type1 (HTLV-1), Epstein–Barr virus (EBV), *Helicobacter pylori* infections, and hepatitis C viruses (HCV), which are frequently detected in Asia.[12] These factors could be the potential reason for the younger age of lymphoma patients in Asia. The age group <60 years constituted 73.1% in this study, corresponding to previous investigations by Reksodiputro who reported NHL patients constituting 78% (117/153) from 2004–2005. Similarly, 78.8% (119/203) of individuals with DLBCL receiving R-CHOP chemotherapy during 2015–2017 in Surabaya[8,13] and 78.8% (598/791) in India were <60 years.[14]

The assessed patients were predominantly male (63.1%), comparable to the previous report of 60.8% and 61.3% of those with lymphoma in Jakarta and Yogyakarta being male, respectively.[7,13] In Singapore, the gender ratio of lymphoma patients among male and female was 1.3:1.[9] In Australia and New Zealand, 59.6% of the total population suffering from lymphoma was male.[9] Among DLBCL patients, Dilliawan reported 63.6% male in Surabaya,[8] while a 61.7–67.1% male gender distribution was found in India.[14,15] The precise reasons for the sex-based disparities in lymphoma occurrence are unknown, but immunological and hormonal abnormalities, body size, tumor biology, and different exposures to environmental contaminants have been suggested as the causes.[16,17]

Malnutrition, defined as BMI <18.5, was found in 11.4% of the lymphoma patients, which was lower than 47.4% observed during a previous study conducted in 2017.[18] The 47.4% value was higher than the BMI <18.5 reported in the US among only 1% of lymphoma patients.[19] This disparity can be caused by different socioeconomic status, and it is possible for tumor impact or body systemic reaction against the tumor to trigger high production of pro-inflammatory cytokines. An important clinical investigation for lymphoma stated the function of interleukin-6 (IL-6) in generating malnutrition in lymphoma.[20]

Lymphoma is broadly classified into HL (10%) and NHL (90%) pathological subtypes.[10] The distribution of these subtypes (NHL vs HL: 80.5% vs 19.5%) in Hasan Sadikin General Hospital registry is consistent with reports from another Indonesian region (Yogyakarta), India, and Australia.[7,11,14] Singapore had a slightly higher percentage of NHL patients compared to HL at 90.8% and 6.9%, respectively.[21] The most common lymphoma type detected among the patients in this study was DLBCL (50.5%), which correlated with a previous report of 53% DLBCL from 2004–2005 in Jakarta.[13] In other regions of Indonesia, DLBCL was found at a level of approximately 44.4%.[7] The proportion of DLBCL patients recorded in the registry was similar to 55% and 53.3% cases reported in India and Singapore, respectively.[9,14] However, it was higher than the proportion reported in Korea (31%), Japan (33%), and China (36%).[5,22,23] This might represent variations in genetic and environmental exposures among Asian communities.[9] Follicular lymphoma in 12.9% (35/271) patients was the second most common type identified, exceeding the 0.8% and 8.0%-11.5% found in Yogyakarta and Singapore, respectively.[7,9,21] However, the value was smaller compared to the 15.4% recorded in Australia,[11] suggesting that T cell lymphoma in this study (1.1%) was lower than the reports in Japan (10%).[23]

The majority of patients (78%) were in the early stages I and II, correlating to another study by Reksodiputro which reported early-stage disease among 68.97%.[13] These results contradicted a previous report of early-stage disease among 43.5% in India from January 2005 to December 2009, suggesting the possibility of differences between periods of data collection.[14] Based on ECOG values of 0–1, good performance status (PS) was found among 98.8% of patients, exceeding 86.7% reported by Reksodiputro, as well as the observed 69.9% in India and 88.8% in Australia.[11,13,14] These differences could be significantly influenced by subjective measures affecting PS assessment.

Most patients had a low-risk IPI score of 0–1 (95.0%), which was higher than the values reported in China (44.3%) and India (70%).[14,15,24,25] This discrepancy could be attributed to different lymphoma types included in this current study, while Nimmagadda studied only DLBCL patients.

The chemotherapy regimen mainly applied in this study was CHOP, while R-CHOP was provided to 42.5%. Similarly, a previous investigation identified CHOP as the most commonly administered (84%), and 42.7% of those suffering from DLBCL were treated using rituximab.[26] In Surabaya, Salma reported the provision of CHOP and R-CHOP for 79.48% and 20.52% of patients with NHL, respectively.[27] R-CHOP only was given in 42.5% due to the availability of rituximab in our government's health insurance which only approved this monoclonal antibody for DLBCL.

Our study found the median age of HL patients was 48 (IQR, 37–60) years. This was older than previous study in Taiwan that reported the median age of HL was 26 (range, 3–84) years.[28] In our DLBCL patients, the median age was 52 (IQR, 40–63) years. This finding was similar with previous finding that reported the median age of DLBCL patients in 57

(range, 7−85) years.[29] Our study did not find difference in clinical and biomarker characteristics between HL and DLBCL patients.

The chemotherapy responses were complete response (CR) in 44.5% of cases and partial response (PR) in 19.8%, which was similar to CR (52.38%), PR (26.19%), and minimal response (14.2%) reported among the Indonesian population in 2011.[11] Based on the data from 2011–2015 in Surabaya, 51.3% of NHL patients had CR, and 28.2% achieved PR.[27] These response rates were lower compared to previous external studies conducted, such as in China, where the overall response rate (CR+PR) was 83.3%, and 67 (11.8%) patients achieved stable disease (SD) or suffered from progressive disease (PD) after receiving CHOP-like or R-CHOP-like regimen.[26]

Exploration of simple biomarkers in lymphoma has become an essential area of study. Previous investigations evaluated SII, PNI, and ALI among DLBCL patients, identifying slightly higher SII in early compared to advanced disease stages. However, in the early stages, both PNI and ALI showed slightly decreased levels. ALI and PNI may serve as easily available markers to predict clinical results in DLBCL patients, while SII can predict overall survival (OS) only in univariate analysis.[25] Our study found that, compared with early stage, SII was higher, whereas PNI and ALI were lower in advanced stage. This reflected that in advanced stage of lymphoma there were higher inflammation and lower nutritional status. The systemic immune-inflammation index (SII), based on neutrophil, platelet, and lymphocyte counts, is a prognostic biomarker and in some solid cancers may reflect the inflammatory status and tumor activity. Prognostic nutrition index (PNI), a variable based on serum albumin concentration and total lymphocyte count in peripheral blood, is a scoring system that reflects the nutritional status and immune status of patients.[30] The Advanced Lung Cancer Inflammation Index (ALI) has been demonstrated to be a prognostic factor of survival in some solid cancers and lymphoma.[31] Serum albumin, as an important nutritional indicator, plays an important role in improving the body's immunity, inflammatory state, and anti-tumor activity.[5]

At the time of analysis, 2-year OS was 93.1%. The 2-year OS in early stage was higher than in the advanced stage group (94.9% vs 85.7%). Previous study reported estimated 2-year OS of 61.6% (95% CI 54.1–68.2%) in DLBCL patients.[32] This difference could be caused by subject's variation between the studies: we included all lymphoma patients, while previous study only evaluates DLBCL.

Study Limitations

Some of the strengths and limitations associated with this study are described as follows. This is the first investigation conducted on the characteristics and biomarkers of lymphoma patients, including treatment response, in Hasan Sadikin General Hospital over a three-year period. However, due to the retrospective nature of this study, there is a possibility that the information extracted from the case charts may not be entirely accurate or comprehensive. A substantial portion of the patient population was lost to follow-up, and not all chemotherapy response was evaluated using appropriate imaging. Despite these limitations, the analysis performed is expected to provide a significant contribution to the literature of lymphoma in Indonesia.

Conclusion

In conclusion, this study showed similarities between demographic characteristics of lymphoma patients with features reported from many developing nations, but differences were observed in the distribution of PS and IPI-score. The chemotherapy response was comparable with the rates found in other investigations, while the biomarkers SII, PNI, and ALI were essential parameters requiring exploration. At 2-year follow up, almost all patients were still alive. Subsequently, a more robust system of lymphoma registry should be effectively established. The registry could be used as a platform for observational studies and clinical trials, enabling effective, long-term follow-up.

Ethics Statement

This study was approved by the ethics committees of the Hasan Sadikin General Hospital and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from patients.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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