

## RESEARCH ARTICLE

# Histopathological Features of Lymphoma in Yogyakarta, Indonesia

Ery Kus Dwianingsih<sup>1\*</sup>, Indrawati<sup>1</sup>, Mardiah Suci Hardianti<sup>2</sup>, Rusdy Ghazali Malueka<sup>3</sup>, Riezka Rivani Iswar<sup>4</sup>, Stefani APPG Sutapa<sup>4</sup>, FX Ediati Triningsih<sup>1</sup>

### Abstract

The incidence and prevalence, the second most common lymphoid malignancy after leukemia, are both increasing. The distribution of lymphoma varies among sexes, age groups, and sites. In Indonesia, information about the incidence of lymphoma and its characteristics are insufficient. Therefore, this study was performed to evaluate the incidence of lymphoma and features based on age group, sex, site, clinical diagnosis, and histopathological type in Indonesia. This study is an observational analytical study with a cross-sectional design aimed to evaluate the histopathological profile of lymphoma in Yogyakarta from 2010-2014. It was based on secondary data from Anatomic Pathology Department's medical records from several hospitals and laboratories. The result showed an increased incidence of lymphoma in Yogyakarta in 2010-2014 ( $p=0.039$ ). Lymphoma mostly occurred in age range 45-64 years ( $p=0.004$ ), dominated by male with ratio 1.6:1. DLBCL was found to be the most common histopathological type (44.4%). Sex, age, and clinical diagnosis demonstrated statistically significant correlations with the histopathological type ( $p<0.001$ ). In conclusion, the incidence of lymphoma has significantly increased from 2010-2014. There are statistically significant correlations between gender, age, and clinical diagnosis with the histopathological type of lymphoma.

**Keywords:** Lymphoma - Hodgkin's - non-Hodgkin's - incidence - Yogyakarta, Indonesia

*Asian Pac J Cancer Prev*, 17 (9), 4213-4216

### Introduction

Lymphoma is a lymphatic system malignancy, the second most common lymphoid malignancy after leukemia (Longo, 2012). Based on the presence of Reed Sternberg cells, lymphoma is classified into two distinct groups: Hodgkin's lymphoma and non-Hodgkin's Lymphoma. The causes of Hodgkin's and non-Hodgkin's lymphoma are still mostly unknown (Hillman et al., 2011). Lymphoma is usually characterized by painless lymphadenopathy in the cervical and supraclavicular areas (Sabatine, 2011).

Lymphoma accounts for 3.37% of all malignancy worldwide. The incidence of malignant lymphoma exhibits a marked geographic variation; higher in North America, Australia/New Zealand, and Europe, and lower throughout Asia and Africa, except where Burkitt lymphoma (BL) is endemic (Huh, 2012; Bassig et al., 2016). In United States, the incidence of non-Hodgkin's lymphoma in 2005-2009, in the male population was 23.3 per 100,000, while in women was 16.2 per 100,000. Non-Hodgkin's lymphoma was the fourth leading cause of death from cancer in men aged 20-39 years and the fifth leading cause of cancer death in women aged greater than or equal to 80 years. The mortality rate of non-Hodgkin's

lymphoma for men was 8.4 per 100,000, while for women was 5.2 per 100,000 (Siegel et al., 2013). In the United States in 2010, Hodgkin's lymphoma had a prevalence of as many as 4,514 people in the pediatric population aged up to 19 years, 30,739 people above 20 years, and 35,253 people of all ages. Meanwhile, non-Hodgkin's lymphoma has a prevalence of as many as 6,442 people in the pediatric population aged up to 19 years, 16,301 people above 20 years, and 22,743 people of all ages (Ward et al., 2014).

In Indonesia, recent national epidemiology data regarding Hodgkin and non Hodgkin Lymphoma patients is not well provided (Soenarto et al., 1977; Timan et al., 2002; Reksodiputro, 2015). The incidence ratio of NHL : HL in Surabaya, Indonesia, for 24 years (1985-1990) was reported to fluctuate between 3.7 - 8.6 : 1 ratio, with higher incidence of non Hodgkin Lymphoma compared to Hodgkin Lymphoma (Boediwarsono, 2000). Study on epidemiology, survival and clonality of B-cell non Hodgkin's lymphoma patients in Indonesia has been reported previously (Reksodiputro, 2015; Antoro et al., 2016). However, the reports only addressed B-cell non Hodgkin's lymphoma. More information about the demographic description of all type of lymphoma in

<sup>1</sup>Department of Anatomic Pathology, <sup>2</sup>Department of Internal Medicine, <sup>3</sup>Department of Neurology, <sup>4</sup>Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta, Indonesia \*For correspondence: ery\_malueka@ugm.ac.id

Indonesia is needed. Therefore, information regarding the incidence of lymphoma and its description by age groups, sexes, sites, clinical diagnosis, and histopathological types of lymphoma is of clinical interest.

**Materials and Methods**

This is an observational analytical study with a cross-sectional design. This study was based on secondary data from the medical records of patients at the Anatomic Pathology Department of DR. Sardjito Hospital, Panti Rapih Hospital, Bethesda Hospital, and Waskita Laboratory in Yogyakarta during the period of 2010-2014 who were diagnosed by histopathological examination and fulfilled the inclusion and exclusion criteria. Inclusion criteria included patients who were diagnosed with lymphoma by histopathological examination, registered in 2010-2014, and had a complete medical record (there was evidence of age, gender, clinical diagnosis, and histopathological diagnosis). Exclusion criteria were incomplete, unreadable, or missing medical records.

The dependent variables of the study were sex, age, predilection, and clinical diagnosis. The instrument used was data from medical records. The independent variable was the histopathology of lymphoma.

The data were analyzed by statistical software. A Kruskal-Wallis test was used to show the correlation between the dependent variable and independent variable.

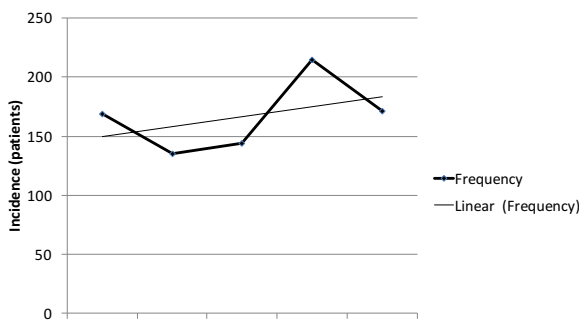
The research ethics committees of the Medical Faculty of Gadjah Mada University, Dr. Sardjito Hospital, Panti Rapih Hospital, Bethesda Hospital, and Waskita Laboratory approved this study.

**Results**

This research was conducted at Dr. Sardjito Hospital, Panti Rapih Hospital, Bethesda Hospital, and Waskita Laboratory in Yogyakarta. The subjects were those who had a histopathological analysis registered from 1 January 2010 until 31 December 2014.

*Incidence of lymphoma*

The incidence of lymphoma in Yogyakarta fluctuated but tended to increase during the years 2010-2014 (Figure 1). This study showed that the annual incidence of lymphoma was 169 in 2010, 135 in 2011, 144 in 2012, 215 in 2013, and 171 in 2014 (p=0.039).



**Figure 1. Annual Incidence of Lymphoma in Yogyakarta from 2010-2014.** Incidence of lymphoma was 169 in 2010, 135 in 2011, 144 in 2012, 215 in 2013, and 171 in 2014

There is an increased incidence of lymphoma by age. Lymphoma is more common in the age group of 45-64

**Table 1. Distribution of the Incidence of Lymphoma Based on Sex, Age Group, Predilection, Clinical Diagnosis and Histopathological Type in Yogyakarta During the Years 2010-2014**

Characteristics	Frequency	(%)
<b>Sex</b>		
Male	511	61.3
Female	323	38.7
N	834	100
<b>Age</b>		
≤14 years	34	4.1
15-24 years	30	3.6
25-44 years	151	18.1
45-64 years	353	42.3
≥65 years	266	31.9
N	834	100
<b>Predilection</b>		
Tonsil	45	5.4
Sinonasal and pharyngeal	85	10.2
Orbita	68	8.2
Abdomen	130	15.6
Colli	129	15.5
Lymph node	65	7.8
Multiple	50	6
Others	262	31.4
N	834	100
<b>Clinical Diagnosis</b>		
Lymphoma	336	40.3
Non Lymphoma	498	59.7
N	834	100
<b>Histopathological Type of Lymphoma</b>		
<b>Non-Hodgkin's Lymphoma (NHL)</b>		
Small lymphocytic lymphoma	115	13.8
B cell prolymphocytic leukemia	1	0.1
Lymphoplasmacytic lymphoma	3	0.4
Mantle cell lymphoma	6	0.7
Follicular lymphoma	7	0.8
Extranodal marginal zone lymphoma	9	1.1
Diffuse Large B Cell lymphoma (DLBCL) (multiple subtype)	370	44.4
Burkitt lymphoma	20	2.4
T-ALL	7	0.8
Mycosis fungoides/ Sezary syndrome	2	0.2
Angioimmunoblastic T Cell lymphoma	3	0.4
<b>lymphoma</b>		
Anaplastic large cell lymphoma	17	2.0
Panniculitis-like T cell lymphoma	1	0.1
Adult T cell lymphoma	1	0.1
Extranodal NK/T cell lymphoma	30	3.6
<b>Hodgkin's Lymphoma (HL)</b>		
Hodgkin's Lymphoma, Nodular Sclerosis	27	3.2
Hodgkin's Lymphoma, Mixed Cellularity	21	2.5
18. Hodgkin's Lymphoma, Lymphocyte Rich	6	0.7
Hodgkin's Lymphoma, Lymphocyte depletion	4	0.5
Hodgkin's Lymphoma, Lymphocyte predominance	3	0.4
Others	181	21.7
N	834	100

years ( $p=0.004$ ) (Table 1). Lymphoma is more common in males than females ( $p=0.253$ ). The most common site of lymphoma is the “others” group and followed by abdomen and colli ( $p<0.001$ ). Based on clinical diagnosis, non-Hodgkin’s lymphoma is more common than Hodgkin’s lymphoma. The most common type of lymphoma is Diffuse Large B Cell lymphoma (DLBCL), which had 370 cases.

#### *Correlation between Age and Histopathological Type of Lymphoma*

The study showed that there is a significant correlation between age and the histopathological type of lymphoma (Kruskal-Wallis,  $p<0.001$ ).

#### *Correlation between Sex and Histopathological Type of Lymphoma*

The study showed that there is a significant correlation between sex and the histopathological type of lymphoma (Kruskal-Wallis,  $p<0.001$ ).

#### *Correlation between Clinical Diagnosis and Histopathological Type of Lymphoma*

The study showed that there is a significant correlation between clinical diagnosis and the histopathological type of lymphoma (Kruskal-Wallis,  $p<0.001$ ).

## **Discussion**

The study revealed an increasing incidence of lymphoma during 2010–2014 ( $p=0.039$ ). The World Health Organization (WHO) stated that there has been an increase in cases of lymphoma in the world and that the greatest increase in cases occurred in developed countries (Morton et al., 2006; Fan et al., 2012). The incidence of NHL has doubled over the past two decades in the United States (US) and most other western countries (Naz et al., 2011). An increasing incidence of lymphoma in Indonesia in the previous years is assumed to be associated with the increasing number of infections (EBV, CMV, HIV, and Human Herpes Virus). EBV and Herpes virus are transmitted among the human population by mucosal secretion (Wada et al., 2008). These viruses will introduce foreign genes into target cells. EBV infection usually occurs subclinically early in life, but may be symptomatic if first contact is delayed until adolescence. HIV infection tends to increase the risk of lymphoma by 8–10 fold (Gloghini et al., 2013).

The incidence of lymphoma is apparently more frequent in males than in females, with a ratio of 1.6:1 ( $p=0.253$ ). This phenomenon was explained by women’s resilience, which is better than men (Hoppe et al., 2007). Some studies stated that  $17\beta$ -estradiol may decrease the production of IL6 spontaneously, causing IL6 levels in the serum to decline. The high level of IL6 will reduce the body’s immune response and act as a growth factor for lymphoma; therefore, a decrease in the serum levels of IL6 has a protective effect. Indirectly, sex hormones also affect the immunologic T helper 1 and T helper 2 cells. The balance of Th1 and Th2 has a very important role in the development of lymphoma. Th1 cytokine secretion

during cellular immunity can act against intracellular pathogens and cancer cells. Th2 will control humoral immunity by regulating the production of antibodies. Another mechanism showed that estrogen has direct anti-proliferative effects on lymphoid cells via estrogen receptor  $\beta$  signaling (Horesh and Horowitz, 2014). Men are suspected to be at greater risk of developing lymphoma due to smoking habit, occupational factors and environmental exposure to pesticides even though studies to identify patterns of exposure with the occurrence of lymphoma have not been performed yet (Morton et al., 2005; Wada et al., 2008; Boffetta, 2011; Reksodiputro, 2015). Some jobs that are often associated with higher risk include farming, forestry, and agriculture. This was caused by exposure to herbicides and organic solvents. In Indonesia, farmers, forest workers, and agriculture workers are mostly male.

This study revealed that the incidence of lymphoma increases with age. The peak incidence is observed in the 45–64 age group. There is a decreased incidence of lymphoma in the  $\geq 65$  age group. The incidence of non-Hodgkin’s lymphoma is higher in the age group of 50–70 years and all lymphoid neoplasms increase by age in all races and all sex groups (Morton et al., 2006). This study showed a decreased incidence of lymphoma at age  $\geq 65$  years. However, according to the Ministry of Health of the Republic of Indonesia, there is a growing elderly population in Indonesian. This is evidenced by the data published by the Central Bureau of Statistics of Indonesia that life expectancy in Indonesia in 2010–2015 increased from 69.1 to 70.1. However, according to the Indonesian Ministry of Health, the elderly population is dominated by females. As was noted earlier, women are more protected from the risk of lymphoma.

The three most common sites of predilection are in the abdomen (15.6%), colli (15.5%), and sinonasal and pharyngeal (10.2%). Previous study in Indonesia and Pakistan revealed similar result that nodal presentation of cervical lymph node involvement was the most common, while extra nodal origin was mostly from abdominal nodes (Naz et al., 2011; Reksodiputro, 2015).

Based on the clinical diagnosis, this study revealed that most of the diagnosed cases of lymphoma were originally not diagnosed as such by the clinicians (59.7%). There is a low level of clinical suspicion to lymphoma because lymphoma is quite rare in Indonesia (Boediwarsono, 2000). In addition, based on the National Treatment Guidelines Non Hodgkin Lymphoma Cancer, published by the National Committee of Cancer Prevention (KPKN) in 2015, the common symptoms in patients with lymphoma are generally not specific. The clinical signs of lymphoma are a high fever of 38 degrees Celsius for 1 week without an obvious cause, night sweats, weight loss of 10%, and anterior mediastinal adenopathy. In addition, there is a weakness in this study. Incomplete writing of the clinical diagnosis also affected the results of the data analysis. Incomplete clinical diagnoses that did not contain the word ‘lymphoma’ on the medical records were considered as non-lymphoma.

Regarding the histopathological types of lymphoma, the most common type found in this study is DLBCL

(Diffuse Large B Cell Lymphoma), which accounts for 44.4%. The second most common type is SLL (Small Lymphocytic Lymphoma), which accounts for 13.8%. The histopathological type used in the study was based on the latest update of the WHO classification in 2008. Previous study showed that among all of the incidence of lymphoma, non-Hodgkin's lymphoma (NHL) provides the dominant contribution where DLBCL accounts for 31% (Longo, 2012). In Indonesia, DLBCL accounted for 69% of non-Hodgkin's lymphoma cases (Reksodiputro, 2015). DLBCL has also been reported as the most frequent lymphoid malignancy in Asians (29%) (Morton et al., 2006). The most common lymphoma in adults comes from the Germinal Center (GC) and post-GC of B-cells follicles. This conclusion was drawn from the molecular analysis, which showed that most B-cell lymphoma experiencing somatic hyper-mutation activity was limited to the center of B cell follicles. The follicular center B cells also undergo a change of immunoglobulin class along with somatic hyper-mutation, which produces regulated genomic instability that causes B cells to have a relatively high risk for mutations that can trigger the transformation (Kumar et al., 2013).

The study also revealed the correlation between age, sex, clinical diagnosis and the histopathological type of lymphoma. Using the Kruskal-Wallis test, this study showed that there are statistically significant correlations between sex, age, and clinical diagnosis with the histopathological type of lymphoma ( $p < 0.001$ ). The male predominance in B-cell neoplasms can be caused by environmental factors and smoking. The latest is known to have an association with non-Hodgkin's lymphoma, particularly follicular lymphoma (Morton et al., 2005; Morton et al., 2006). Specific correlation between age and the histopathological type of lymphoma remains unclear. Previous study showed that non Hodgkin's Lymphoma and Hodgkin's lymphoma nodular sclerosing type occurred more frequently in young adults, while the Hodgkin's lymphoma mixed cellularity type occurs more frequently in older adults (Howlader et al., 2010; Naz et al., 2011).

There is a high number of mismatches between the clinical diagnoses with the histopathological type. This mismatch can be caused by several factors. One of them is the unspecific clinical signs of lymphoma that do not lead to lymphoma. Moreover, the histopathological type of lymphoma that is not in accordance with the classification established by WHO may also cause a mismatch.

In conclusion, the incidence of lymphoma in Yogyakarta has increased during the years 2010-2014, which is statistically significant. Lymphoma is more common at age 45-64, and DLBCL is the most common histopathological type. There are statistically significant correlations between sex, age, and clinical diagnosis with the histopathological type of lymphoma.

## References

Antoro EL, Dwianingsih EK, Indrawati, et al (2016). The polymerase chain reaction in diagnosis of small B-cell non-Hodgkin lymphomas. *Asian Pac J Cancer Prev*, **17**, 491-5.  
 Bassig BA, Au WY, Mang O, et al (2016). Subtype-specific

incidence rates of lymphoid malignancies in Hong Kong compared to the United States, 2001-2010. *Cancer Epidemiol*, **42**, 15-23.  
 Boediwarsono (2000). A problem of malignant lymphoma management in Indonesia. *Folia Medica Indonesiana*, **36**, 32-7.  
 Boffetta P (2011). Epidemiology of adult non-Hodgkin lymphoma. *Ann Oncol*, **22**, 27-31.  
 Fan R, Zhang LY, Wang H, et al (2012). Multicentre hospital-based case-control study of diffuse large B-cell lymphoma in Shanghai, China. *Asian Pac J Cancer Prev*, **13**, 3329-34.  
 Glohini A, Dolcetti R, Carbone A (2013). Lymphomas occurring specifically in HIV-infected patients: from pathogenesis to pathology. *Semin Cancer Biol*, **23**, 457-67.  
 Hillman RS, Ault KA, Leporrier M, et al 2011. Hematology in Clinical Practice, USA, McGraw-Hill.  
 Hoppe RT, Mauch PT, Armitage JO, et al 2007, Hodgkin Lymphoma, Philadelphia, Lippincott Williams & Wilkins.  
 Horesh N, Horowitz NA (2014). Does gender matter in non-hodgkin lymphoma? Differences in epidemiology, clinical behavior, and therapy. *Rambam Maimonides Med J*, **5**, e0038.  
 Huh J (2012). Epidemiologic overview of malignant lymphoma. *Korean J Hematol*, **47**, 92-104.  
 Kumar V, Abbas AK, Aster JC (2013). Hematopoietic and lymphoid system. In 'Robbins Basic Pathology', Eds Elsevier Saunders, Canada, 429-58  
 Longo DL (2012). Malignancies of lymphoid cells. In 'Harrison's principle of internal medicine', Eds Mc Graw Hill, USAMc Graw Hill, USA, 919-35  
 Morton LM, Hartge P, Holford TR, et al (2005). Cigarette smoking and risk of non-Hodgkin lymphoma: a pooled analysis from the International Lymphoma Epidemiology Consortium (interlymph). *Cancer Epidemiol Biomarkers Prev*, **14**, 925-33.  
 Morton LM, Wang SS, Devesa SS, et al (2006). Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. *Blood*, **107**, 265-76.  
 Naz E, Mirza T, Aziz S, et al (2011). Frequency and clinicopathologic correlation of different types of non Hodgkin's lymphoma according to WHO classification. *J Pak Med Assoc*, **61**, 260-3.  
 Reksodiputro AH (2015). Multicentre epidemiology and survival study of B cell non Hodgkin lymphoma patients in Indonesia. *J Blood Disorders Transfusion*, **6**, 1-5.  
 Sabatine MS 2011. Pocket Medicine, Philadelphia, Lippincott Williams & Wilkins.  
 Siegel R, Naishadham D, Jemal A (2013). Cancer statistics, 2013. *CA Cancer J Clin*, **63**, 11-30.  
 Soenarto D, Soekamto S, Koesoemowardoyo (1977). Malignant lymphoma in Surabaya. *Mod Med Asia*, **13**, 5-6.  
 Timan IS, Aulia D, Atmakusma D, et al (2002). Some hematological problems in Indonesia. *Int J Hematol*, **76**, 286-90.  
 Wada N, Ham MF, Fujita S, et al (2008). Malignant lymphomas in Waldeyer's ring in Asian countries: Association with histologic types and Epstein-Barr virus. *Mol Med Rep*, **1**, 651-5.  
 Ward E, DeSantis C, Robbins A, et al (2014). Childhood and adolescent cancer statistics, 2014. *CA Cancer J Clin*, **64**, 83-103.