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Correlation of Microvessel Density with Clinicothological Features of Hodgkin Lymphoma

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ABSTRACT

Background
Angiogenesis is the process of new blood vessel growth that has an important role in tumor development. Microvessel density (MVD) assessment is one of the methods to assess angiogenesis. A high MVD is associated with a poor prognosis in various types of cancer including Hodgkin lymphoma (HL). Although, HL incidence is lower in developing countries, the death rate is higher in these regions. Moreover, this type of lymphoma is higher among young and reproductive people. The aim of this study was to determine the association between microvessel density and HL clinicopathological characteristics.

Methods
This was an observational analytic study with a cross-sectional method, conducted at the Anatomical Pathology Department/Dr. Mohammad Hoesin Palembang. The samples were paraffin blocks diagnosed as HL for period 2016-2021 and had complete clinicopathological data according to the criteria of this study. The slides were immunostained with antibody anti-CD34. One microvessel was determined by observing the endothelial morphology and CD34 expression in endothelial cytoplasm and/or cell membrane, then was evaluated and calculated by Image J. Data was statistically analyzed by STATA version 15.

Results
Majority HLs in this study were discovered in the age group of <45 years (71.00%), male (61.30%), nodal location (80.60%) and lymphocyte rich classical HL (LRCHL) subtype (51.60%). Although there was no significant association between MVD and the clinicopathological characteristics of HL, high MVD tend to occur in the age <45 years, male, nodal location, and LRCHL subtype.

Conclusion
There was no significant association between microvessel density and HL clinicopathological characteristics.

Key words: hodgkin lymphoma, microvessel density, CD34, clinicopathological characteristics.

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INTRODUCTION

A large cluster of neoplasms derived from the immune system is known as a lymphoma. Ninety percent of lymphoma derives from lymphocyte B cells, while the rest is from lymphocyte T cells and natural killer (NK) cells.[1] Based on the existence of the Hodgkin cell, lymphoma is classified as either Hodgkin or non-Hodgkin lymphoma. Non-Hodgkin lymphoma accounts for 80-85% of all lymphoma cases, while Hodgkin lymphoma accounts for 10-15%.[2] Hodgkin lymphoma was the world's 27th most common malignancy, with 83,087 new cases and 23,376 deaths.[3]

The incidence of Hodgkin lymphoma tends to be higher in developed countries than in developing countries. Meanwhile, the mortality rate is relatively high in developing countries.[4] Hodgkin lymphoma is often found within the 15-30 years old range and increases in age beyond 55 years old.[5] Except for the NSCHL subtype, which has the same incidence ratio in men and women, it has a greater predilection in men.[6]

Hodgkin lymphoma is characterized by Reed-Sternberg cells, which are large cells with a multi-lobed nucleus, a prominent nucleolus, and wide and slightly eosinophilic cytoplasm that resembles an owl's eye.[7] Around 90% of Hodgkin lymphoma is classical Hodgkin lymphoma (CHL), and 10% or less is nodular lymphocyte predominant Hodgkin lymphoma (NSCHL), which is often found in developed countries and dominated by young adults. Meanwhile, the mixed-cellularity classical Hodgkin lymphoma (MCCHL) subtype is found in children from developing countries. The lymphocyte-depleted classical Hodgkin lymphoma (LDCHL) subtype has the worst prognosis, while the lymphocyte-rich classical Hodgkin lymphoma (LRCHL) has a better prognosis compared with other subtypes.[8]

Many studies have found that angiogenesis, which supplies oxygen from the circulatory system to tumor cells so that they can grow, is frequently found in tumor development.[9] Angiogenesis is the formation of new blood vessels, which are important in the growth of tumors and metastasis. At first, tumor cells obtain oxygen through diffusion. The increased number of tumor cells caused diffusion to no longer supply enough oxygen for tumor growth. This condition triggers the response of tumor and stromal cells in the microtumor environment to release proangiogenic factor, which stimulates the proliferation and migration of endothelial cells in the formation of new blood vessels.[10]

Angiogenesis is assessed by measuring microvessel density (MVD), which can be considered in predicting prognosis. It is believed that high-density microvessels are related to poor prognosis in many types of cancer.[11] A previous study found that increased angiogenesis and microvessel density were associated with a poor prognosis in CHL.[12] Inhibition of angiogenesis activity with anti-angiogenic therapy is expected to inhibit the growth and metastasis of tumors. Therefore, anti-angiogenic therapy can be one of the treatment choices for Hodgkin lymphoma.[13]

In Indonesia, there have been few studies on the relationship between microvessel density and clinicopathological features of Hodgkin lymphoma. Furthermore, similar studies in other countries showed different results, which is the reason for the author to conduct this study. The results of this study are expected to be beneficial as a prognostic marker and aid in determining antiangiogenic therapy as an effective adjuvant therapy for Hodgkin lymphoma in the future.

METHODS

This study used a cross-sectional observational analytic design, was conducted in the Department of Anatomical Pathology in the Faculty of Medicine of Sriwijaya University/RSUP Dr. Mohammad Hoesin Palembang. The population included all cases diagnosed pathologically as Hodgkin lymphoma during 2016-2021. Samples were obtained through non-probability sampling, namely the purposive sampling technique.

The samples were part of the population that fulfilled the inclusion and exclusion criteria. The inclusion criteria included an archive of hematoxylin-eosin (HE) and immunohistochemistry (IHC) preparations and a paraffin block diagnosed as Hodgkin lymphoma with complete medical record data including age, gender, tumor location, and subtype. The exclusion criteria included archives of HE preparations and paraffin blocks with signs of cell damage due to inadequate fixation, and the paraffin block did not contain enough tumor tissue for IHC examination using anti-CD34 antibodies and recurrent cases. There were 31 samples that fulfilled the criteria.

Observation and measurement of microvessels were carried out using an Olympus BX51

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binocular light microscope equipped with a DP-21 digital camera. The images from the camera were analyzed and measured with the Image J software. Microvessels were identified by observing single or clustered endothelial cells that were separated from the surrounding tumor cells and stained brown by an anti-CD34 antibody with or without a lumen; each blood vessel did not have more than eight erythrocytes inside the lumen; each blood vessel did not have a muscle layer; and it was not located in the sclerotic area.[14] Figure 4.1 depicts an identified microvessel structure (black arrow).

Microvessel density was assessed by choosing three areas with the densest microvessel in a small field of view (100 times), then choosing the five densest areas in a large field of view (400 times). Afterward, the mean value was calculated by adding the results of the five areas above, divided by 5 in each sample. The collected data were statistically analyzed using STATA software version 15 to determine the clinicohistopathological characteristics distribution of Hodgkin lymphoma, as well as the correlation between microvessel density and clinico-histopathological characteristics using Chi-Square and a significant result of $p<0.05$.

RESULTS

Microvessel morphology

Identifying a microvessel microscopically is carried out by paying attention to the following characteristics: (1) single or clustered endothelial cells separated from the surrounding tumor cells and stained brown by anti-CD34 with or without a lumen; (2) each blood vessel does not contain more than eight erythrocytes inside the lumen; (3) each blood vessel does not have a muscle layer; (4) the blood vessel is not located in a sclerotic area.[14,27] Figure 1 shows an identified microvessel structure (black arrow).

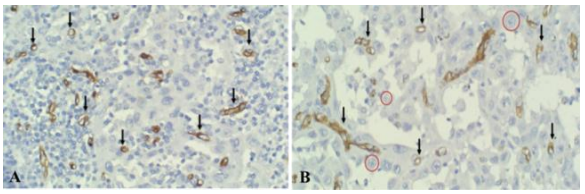

Figure 1. Immunohistochemistry staining with anti-CD34 antibody. A. High microvessel density in the tumor microenvironment (black arrow); B. Low microvessel density in the tumor microenvironment (black arrow). 400 times magnification.

Clinicopathological characteristics of hodgkin lymphoma

The age range in this study was 7-77 years old, with an average age of 36 years old. Patients aged <45 years old had more diagnoses of Hodgkin lymphoma, comprising 22 samples (71.0%). There were more men than women, comprising 19 samples (61.30%). Nodal locations were seen more often in 25 samples (80.60%). The LRCHL subtype, with 16 samples (51.60%), was the most common (Table 1).

Table 1. Clinicopathological characteristics of hodgkin lymphoma.

Clinicopathological characteristics	n (%)
Age	
<45 years old	22 (71.00)
≥45 years old	9 (29.00)
Gender	
Men	19 (61.30)
Women	12 (38.70)
Tumor location	
Nodal	25 (80.60)
Extranodal	6 (19.40)
Subtype	
NSCHL	6 (19.40)
MCCHL	9 (29.00)
LDCHL	0 (0.00)
LRCHL	16 (51.60)

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Distribution of microvessel density in Hodgkin lymphoma

The distribution of microvessel density in Hodgkin lymphoma is divided into two categories: high microvessel density and low microvessel density. The Shapiro-Wilk test was conducted beforehand and revealed normally distributed microvessel density data (p>0,05). Because the data is normally distributed, the mean value is considered the cut-off value. The mean value of microvessel density is 18.26 and it is determined as the cut-off value, where microvessel density above 18.26 is considered high and density below 18.26 is considered low (Table 2).

Table 2. Distribution of microvessel density in hodgkin lymphoma.

	Mean	Std. Deviation	Min	Max	*p*
Microvessel density	18.26	5.47	10.40	32.10	0.13

Correlation between microvessel density and clinicopathological characteristics of Hodgkin lymphoma

There is a statistically insignificant correlation between microvessel density and clinicopathological characteristics of Hodgkin lymphoma (age, gender, tumor location, subtype) (p>0.05). However, high microvessel density tends to be occurred in the 45 years old age group (p=0.60), men (p=0.88), nodal location (p=0.08), and LRCHL subtype (p=0.84) as seen in Table 3.

Table 3. Correlation between microvessel density and clinicopathological characteristics of Hodgkin lymphoma.

Clinicopathological characteristics	Microvessel density		P-value
	High	Low	
Age			
<45 years old	10	12	0.60
≥45 years old	5	4	
Gender			
Men	9	10	0.88
Women	6	6	
Tumor location			
Nodal	14	11	0.08
Extranodal	1	5	
Subtype			
LRCHL	7	9	0.84
LDCHL	-	-	
MCCHL	5	4	
NSCHL	3	3	

DISCUSSION

Angiogenesis is the process of new blood vessel tissue formation that is important in the growth of tumors and metastasis. Angio-genesis is a response of tumor cells and stroma cells in the tumor microenvironment in releasing pro-angiogenic factor that stimulates the proliferation and migration of endothelial cells (ECs) required in forming new blood vessels.[10] One of the methods to quantify new blood vessels inside tumor tissues is by measuring microvessel density (MVD) with immunohistochemistry (IHC) staining.[11] This study used anti-CD34 as a microvessel marker.[14]

A recent study indicated that microvessel density can be used to predict the prognosis of lymphoma because high microvessel density is correlated with a poor prognosis in CHL cases.[12]

Age is an important factor in predicting the overall prognosis and is an independent factor to assess progression-free survival in Hodgkin lymphoma patients.[15] The age distribution of Hodgkin lymphoma patients varies according to ethnicity and socioeconomic status in a region. In general, Hodgkin lymphoma often occurs in patients aged 15-30 years and older than 55 years.[16] The patient's age in this study is around 7-77 years old (mean age of 36.32 years old). The youngest age in this study was younger than the study by Hewamana *et al*, who had an age interval of 12-83 years old.[17] This may be because, in developing countries, Hodgkin lymphoma is more often found in children.[8]

Analysis of the correlation between microvessel density and age in this study showed a statistically insignificant correlation (p=0.60). However, high microvessel density was most likely found in patients younger than 45 years old. This is in line with Koh *et al*, who studied the correlation between clinicopathological characteristics and microvessel density and stated that there is no significant correlation between age and microvessel density (p=0.56), with a similar tendency of high microvessel density in the <45 years old age group.[18] There is a decrease in HIF-1 expres-sion and angiogenic factors such as VEGF in elderly patients, as well as changes in the extracellular matrix in the tumor micro-environment. Meanwhile, in the angiogenesis process triggered by hypoxic conditions in tumor tissues, this HIF-1 expression is required to induce various angiogenic factors such as VEGF. Therefore, microvessel density is usually lower in older patients and higher in younger patients.[19-21]

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In this study, Hodgkin lymphoma is more often found in men (61.30%) compared to women (38.70%), with a ratio of 1.6:1. This is in line with an epidemiologic study by the WHO, which stated that Hodgkin lymphoma is more often found in men.1 This study also confirms the findings of Wen-Yan Yu, *et al*, who obtained a ratio of Hodgkin lymphoma incidence of 1.67:1 between men and women.[22]

Statistical analysis indicated an insignificant correlation between microvessel density and gender (p=0.88), with a tendency for higher microvessel density in men compared to women. This is in line with Panico *et al* and Makboul *et al*, who stated that there is no statistically significant correlation between gender and microvessel density.[23,24] Koh *et al* also suggested a similar tendency for high microvessel density in men (p=0.07).[18] This is due to higher androgen levels in men compared to women. Androgen improves the angiogenesis process through an increased response of proliferation and migration of endothelial cells by inducing the regulation of genes related to angiogenesis, such as HIF-1α and SDF-1α, and pro-angiogenic factors such as VEGF and VEGFR2.[25,26]

Almost all Hodgkin lymphoma cases are found in the lymph nodes. Therefore, this disease is also known as a nodal disease. Hodgkin lymphoma can also develop to infiltrate the spleen, liver, and other extranodal locations.[8] In this study, Hodgkin lymphoma is more often found in nodal (80.60%) compared with extranodal locations (19.40%). Statistical analysis revealed an insignificant correlation between tumor location and microvessel density (p=0.08), with a tendency for high microvessel density in nodal locations. This result is in line with a study conducted on mantle cell lymphoma, which stated that there is no significant correlation between tumor location and microvessel density.[27]

The LRCHL subtype is the most common subtype of Hodgkin lymphoma in this study, which comprises 16 cases (51.60%). This is different from Konkay *et al*'s study in India, which found the MCCHL subtype as the most frequently found Hodgkin lymphoma subtype. The same also applies to a study in developing countries that found that MCCHL is the most common subtype of Hodgkin lymphoma.[28,29] High MCCHL subtype is related to HIV and is often related to a poor prognosis.[30] On the other hand, the LRCHL subtype is often related to a better prognosis compared to other subtypes.[31] Makboul *et al*. discovered a significant correlation between microvessel density and a high histological subtype of MCCHL.[24] However, statistical analysis in this study revealed an insignificant correlation between subtype and microvessel density (p=0.84). This is in line with Koh *et al*., who stated that there is no significant correlation between disease subtype and microvessel density (p=0.31).[18]

There is no study investigating the correlation between microvessel density and clinicopathological characteristics of Hodgkin lymphoma in Indonesia. To date, more studies are needed on the correlation between microvessel density and clinicopathological characteristics of Hodgkin lymphoma, including age, gender, tumor location, and subtype. Considering differences between this study and previous studies, especially the most frequently found subtype, microvessel density can be related to the patient's outcome, as with other cancer types such as non-Hodgkin lymphoma, colon cancer, cervical cancer, and prostate cancer.[32-35] Further studies with a more complete and larger sample of data are needed to prove the above possibility.

CONCLUSION

This study does not find any significant correlation between microvessel density and clinicopathological characteristics (age, gender, tumor location, and subtype) in Hodgkin lymphoma. Further studies are suggested to determine the role of microvessel density as a prognostic factor using patient outcome data such as progression-free survival and overall survival.

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