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Comparison of Platelet to Lymphocyte Ratio between Degrees of the Barcelona Clinic Liver Cancer on Hepatocellular Carcinoma Patients at Haji Adam Malik General Hospital

Gontar Alamsyah Siregar[1*], Dedi Irwansyah[2?]

[1]*Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia;* [2]*?*

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***Correspondence:** Gontar Alamsyah Siregar. Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia. E-mail: gontarsir@gmail.com

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Abstract

BACKGROUND: Hepatocellular carcinoma (HCC) is the fifth most common malignancy. The Barcelona Clinical Liver Cancer System (BCLC), guides the treatment of patients with HCC. Platelet to lymphocyte ratio (PLR) is an inflammatory marker used as a prognostic factor disease of HCC. An increase in PLR indicates higher host's inflammatory response and is associated with aggressive HCC behaviour, according to BCLC.

AIM: This study aims to determine the PLRs between among the degrees of BCLC (The Barcelona Clinic Liver Cancer) in HCC patients at Haji Adam Malik General Hospital in Medan during 2015-2016.

METHODS: This retrospective study involved 166 patients with HCC who were then classified by the BCLC guidelines. PLRs among the patient's degrees of BCLC were compared using Kruskal Wallis test.

RESULTS: A total of 166 HCC patients, 129 (77.7%) were men and 37 (22.3%) were women. The PLR value has a median value of 17841with the lowest value of 1776 and the highest value of 223684. There were differences in PLR levels with various BCLC stages in patients with HCC at Haji Adam Malik Hospital during 2015-2016 ($p = 0.026$).

CONCLUSION: There were differences in PLR levels with various BCLC stages in patients with HCC at Haji Adam Malik Hospital during 2015-2016.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy, with more than 30 cases per 100,000 people each year in Southeast and Central Asia. In the United States, the incidence has doubled over the past 20 years. The highest incidence of HCC was found in South East Asian Indonesia with a level of age standard (ASR) of 31.9 per 100,000 in men and 10.2 per 100,000 in women. HCC relates to some risk factors, including chronic hepatitis virus infection, Non-Alcoholic Fatty Liver Disease, alcoholism, and aflatoxin-contaminated food. The most common one is chronic Hepatitis B virus infection. Majority patients with chronic HBV infection have no typical symptoms, although the viruses are active and transmit into another person.

Guidelines for clinical practice is critical in directing and standardising the management of the disease. The Barcelona Clinical Liver Cancer System (BCLC), grades HCC and guides its. This staging system is complete and accurate since it does not only evaluate tumour characteristics, performance status and liver function but also connects disease staging to its treatment course [1]. Platelet and lymphocyte counts are basic haematological examinations that are very easy, fast to apply everyday and cheap. Platelet to lymphocyte ratio (PLR) is an inflammatory marker used as a prognostic

factor in various types of diseases. An increase in PLR indicates that the host's inflammatory response increased. This is associated with more aggressive tumour characteristics [2].

This study aims to determine the PLRs between among the degrees of BCLC (The Barcelona Clinic Liver Cancer) in HCC patients at Haji Adam Malik General Hospital in Medan during 2015-2016.

Material and Methods

Data collection

A retrospective study conducted at Internal Medicine Clinic Haji Adam Malik General Hospital in Medan from January 1, 2015, to December 31, 2016, in patients diagnosed with HCC. A total of 166 patients that had lymphocyte and platelet counts, liver function test, AFP, liver USG and 3-phase Liver CT Scans were recruited in this study and then grouped into BCLC A, B, C and D [2].

Statistics

All data were analysed using SPSS version 22. Demographic data were presented in numbers and percentages. Comparison of platelet to lymphocyte ratio between the degrees of BCLC of HCC patients was analysed using the Kruskal Wallis test.

Results

The demographic data of 166 HCC patients, consisted of 129 male patients (77.7%) and 37 female patients (22.3%). The median age of HCC patients was 52.8 years (20-83). Hepatitis B virus infection was found in 84.9% of patients, while hepatitis C virus infection and other causes were in 4.8% and 10.2% patients, respectively.

Table 1: Demographic characteristics of subjects

Variable	n = 166
Gender	
Male	129 (77.7 %)[a]
Female	37 (22.3%)
Age	52.8 (20-83)[c]
Aetiology	
Hepatitis B	141 (84.9 %)[a]
Hepatitis C	8 (4.8 %)
Other	17 (10.2 %)
LIM	15.1 (1.9 – 60.8)[c]
PLR	17841 (1776 – 223684)[c]
PLT	280819 ± 138268[b]
BCLC	
A	12 (7.2 %)[a]
B	54 (32.5 %)
C	76 (45.8 %)
D	24 (14.5 %)

Lymphocytes have a median value of 15.10 U/L with the lowest value of 1.90 U/L and the highest value of 60.80 U/L, and the PLR had a median value of 17841.57 with the lowest value of 1776.32 and the highest value of 223684.21. The average platelet value was 280819.28 ± 138268.57 then for the BCLC staging system; the most was BCLC class C (45.8%), followed by BCLC B (32.5%), BCLC D (14.5%) and BCLC A (7.2%) (Table 1).

Table 2: Comparison of PLR levels of HCC patients on BCLC staging

BCLC	PLR	P
A	18534 (2509 -61267)	0,026
B	14069 (1776 - 223684)	
C	18469 (2536 – 119117)	
D	30007(3724 – 117500)	

There were differences in PLR levels with various BCLC stages in patients with HCC.

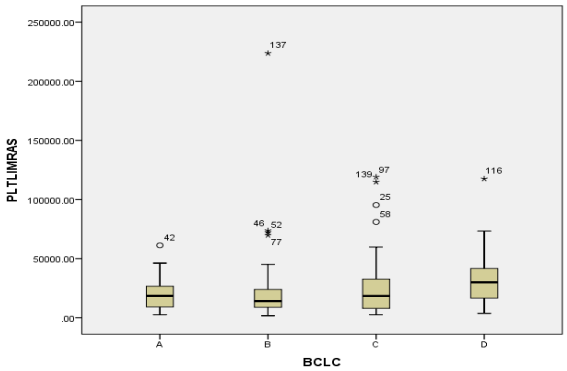

Figure 1: Comparison PLRs ratios between degrees of BCLC A, B, C and D

Discussion

In this study, it was found that the number of male HCC patient (77.7%) and female (22.3%) (Table 1). This is relevant with the research conducted by GLOBOCAN, cancer research (2012) which states that HCC patients are dominated with a male than a female with a ratio between 2: 1 to 4: 1. [3], the incidence of HCC in men was 40.0 and in women 15.3 per 100,000 population. Yuen et al., (2000) [4], and Cheung et al., (2006) [5], published that the percentage of male HCC patients compared to female 4: 1.

The median age of HCC patients in this study was 52.8 years (Table 1). Yuen et al., (2000) [4] and Cheung et al., (2006) [5] obtained that the median age of HCC patients in Hong Kong 61 and 63 years old. Park (2005) [6], studying HCC, with the highest incidence of HCC at the age of 55 years old. An analysis of subgroups in the United States examines Hispanic and African-American ethnicities, the highest

incidence of HCC at the age of 45-65 years.

The most common aetiology of the incidence of HCC, according to this study, is hepatitis B infection (Table 1). This is also relevant to other studies. Chronic HBV infection has been known to be closely related to the incidence of HCC. HBV infection contributes greatly to the incidence of HCC and its mortality rate, around 63.9% of the incidence of HCC is caused by HBV infection [7], [8].

HBV carcinogenicity to the liver occurs through a chronic inflammatory process, increased hepatocyte proliferation, integration of HBV DNA into host cell DNA and HBV specific protein activity interacting with liver cells. Changes in hepatocytes from inactive conditions to replicate active cells determine the level of liver carcinogenesis. The coincidence of HBV infection with exposure to other oncogenic agents such as aflatoxin can cause HCC without going through liver cirrhosis condition. The amount of HBV and its genotypic factors affect the pathogenesis of HCC.

Other causes of HCC development are because HBV DNA can integrate with human genes, which can interfere with endogenous tumour suppressor and various other gene regulators or can also facilitate the emergence of proto-oncogenic activity. This imbalance between pro-oncogenic factors and tumour suppressor signals support the growth of HCC [10].

The effect of fat metabolic disorders, inflammation also contributes to insulin resistance. Proinflammatory cytokines and transcription factors are overexpressed in fatty tissue and liver. Obesity, which is mild chronic inflammation, is a risk factor for insulin resistance and NAFLD. There are induced by excessive intake, which is an early cause of decreasing insulin sensitivity. Obesity makes fat accumulation and activates the signalling flow of c-JunN-terminal kinase (JNK) and NF-κB) which results in increased production of proinflammatory cytokines such as TNF-α and IL-6. In addition to various proteins in fatty tissue such as adiponectin and leptin, it is considered the main link between obesity, insulin resistance and related inflammatory diseases. This series of inflammation is a risk factor for the development of HCC [11].

Inflammation is a protective immune response to dangerous stimuli such as pathogens and dead cells, which are regulated by the host. Inflammation is the stimulation of tumour progression. Tissue biomarkers reflect SIRS conditions that show prognostic value. Some haematological parameters include modified Glasgow Prognostic Score (mGPS), C-reactive protein (CRP), neutrophil to lymphocyte ratio (NLR), inflammation-based index (IBI) and platelet to lymphocyte ratio (PLR) [12].

Virchow suggested the relationship between inflammation and cancer through the theory of leukocyte infiltration in tumours, which generally characterise cancer cells. Since then, more evidence and research have suggested that the inflammatory response correlates with tumour progressions such as angiogenesis and tumour invasion. Invasion and migration of tumour cells are related to inflammatory cells, including lymphocytes, neutrophils and platelets. Platelets are important effector cells in hemostasis, recently have a role in the inflammatory response. Platelets recognise and kill pathogens and release various immune mediators and endothelial cell responses [13].

PLR is the result of calculating the ratio of platelet counts to lymphocytes. As an important component of the host's defence system, lymphocytes play an important role in various types of neoplasms. Tumour-infiltrating lymphocytes affect the outcome of patients with malignancy. High platelet counts indicate a poor prognosis, where lymphocyte infiltration around the tumour is associated with a better prognosis [14].

In this study, there were significant differences in PLRs to various BCLC stages in HCC patients (Table 2) and (Figure 1). Therefore PLR can be used to determine the progressiveness of HCC. The use of BCLC as a staging tool has been used universally. BCLC staging includes radiological assessment, while PLR is simpler, using routine blood tests [15]. Zheng et al. (2017) [16] stated that increasing NLR and PLR indicates a poor prognostic in HCC patients. NLR and PLR were reliable and cheap biomarkers in clinical decisions to the treatment of HCC.

Lee et al. (2015) [17], published that HCC patients with higher platelet counts had a greater risk of extrahepatic metastasis. With a large platelet count, it can secrete large amounts of VEGF (vascular endothelial growth factor) and PDGF (platelet-derived growth factor). This is an important factor for angiogenesis, cell proliferation and tumour metastatic. Ma W. et al. (2016) [15] found that increasing PLR indicated a poor prognostic in HCC patients. Wang H. et al., (2017) [18] stated that high PLR values are associated with the presence of HBV infection, tumour size, age over 60 years, and higher levels of BCLC. PLR indicates a poor prognostic in HCC patients. Likewise, in a similar study by Lin WF et al., (2018) [19], the same results were found where high PLR had worse prognostics.

In conclusion, there is a significant difference in PLR in BCLC degrees.

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