Gamma-glutamyltranspeptidase to platelet ratio and albumin to gamma-glutamyltranspeptidase between degrees of the Barcelona clinic liver cancer on hepatocellular carcinoma patients in Haji Adam Malik general hospital Medan during 2015-2016

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Abstract. Hepatocellular carcinoma (HCC) is a primary malignancy of the liver and occurs predominantly in a patient with underlying chronic liver disease and cirrhosis. HCC presented at an advanced stage with right-upper-quadrant pain, weight loss, and signs of decompensated liver disease; it is now increasingly recognized at much measurements of the biomarker. Some of them are Gamma-glutamyltranspeptidase to platelet ratio (GPR) and Albumin to Gamma-glutamyltranspeptidase (AGR). This study aimed to know the difference between GPR and AGR between degrees of the Barcelona Clinic Liver cancer (BCLC) on HCC patients. A retrospective study was carried out in 166 outpatient and inpatient HCC in Haji Adam Malik General Hospital from January 2015–December 2016. Kruskal-Wallis test showed that there is no significant differentiation of GPR between degrees of BCLC (p=0.23), but there is a considerable differentiation of AGR between degrees of BCLC (p=0.032).

1. Introduction
Hepatocellular carcinoma (HCC) is the dominant form of primary liver cancer and is histologically and etiologically distinct from other forms of primary liver cancer. Approximately 70%-90% patients with HCC have an established background of chronic liver disease and cirrhosis, with major risk factors for developing cirrhosis including chronic infection with hepatitis B virus (HBV), hepatitis C virus (HCV), alcoholic liver disease and non-alcoholic steatohepatitis (NASH).[1,2,3]

The International Agency for Research and Cancer; a division in World Health Organization (WHO) reported a data of incidence liver cancer between male and female is 4:1, and the median age of presentation this cancer between 40 years old until 70 years old, and there is increasing incidence with increasing age.[4]

HCC is the third-leading cause of cancer death worldwide. Despite its enormous global impact, there is much disagreement about how best to stage and characterize this cancer. Like with any cancer, the goals of any tumor staging system in HCC are to estimate a patient’s prognosis, which allows for appropriate therapy to be selected. The identification of appropriate therapy, in turn, requires a staging...
paradigm that standardizes the platform for researchers to exchange data regarding treatments and outcomes.[5]

Nowadays, there is some staging system to characterize HCC including TNM system, Okuda system, The Barcelona Clinic Liver Cancer (BCLC), Cancer of Liver Italian Program (CLIP) scoring system, Japan Integrated Staging (JIS) scoring system, Chinese University Prognostic Index (CUPI), etc.[5,6]

The BCLC classification was first published in 1999 and is considered the standard HCC system by the American Association for the Study of Liver Disease (AASLD) and European Association for the Study of the Liver. BCLC was four groups; they are A, B, C and D.[5]

Gamma-glutamyltranspeptidase (GGT) is an enzyme located at the external surface of epithelial cells. GGT expression, highly sensitive to oxidative stress, is a part of the cell antioxidant defense mechanisms and an indicator of higher cancer risk. The highest expression is in liver disease. GGT survive longer in the blood than the other liver’s damage marker.[7,8,9,10]

Albumin is a stable molecule synthesized by the hepatocytes which maintain the intravascular colloid oncotic pressure and transports various substances.[10]

The gamma-glutamyltranspeptidase to platelet ratio (GPR) is a new simple laboratory index to predicts of liver fibrosis.[10]

Albumin to thegamma-glutamyltranspeptidase ratio (AGR) is a non-invasive marker, a combination of liver function parameters which reflect theprognostic prediction of cancer.[11]

This research aims to know the difference between GPR and AGR between degrees of BCLC on HCC patients in Haji Adam Malik General Hospital Medan was during 2015-2016.

2. Methods

2.1. Data Collection
This study was a retrospective study carried out at the installation of Outpatient and Inpatient General Hospital Center of Haji Adam Malik Medan from 1 January 2015 until 31 December 2016. All HCC who are from the anamnesis, physical examination, laboratory examination and imaging on the patient's medical record. The amount of data collected through the information systems of hospitals as much as 450 patients, but which have a value of the liver function, AFP. The results of the ultrasound and CT Scan Liver 3 phase totaled 166 patients who can further be into BCLC staging system A, B, C and D. HCC was diagnosed according to imaging result on CT scan liver 3 phase.[12]

2.2. Models Calculation
Calculation using this formula
GPR: (GGT/ULN*)/ platelet count (10^9/L) x 100 and AGR: albumin/ GGT
*ULN = Upper Limit Normal

2.3. Statistical Analysis
Data were analyzed by using the software of statistical SPSS 22. Demographic data is in numbers and percentages, then when the normal distribution of the data will be reported in the mean ± standard deviation while when data distribution is not normal will be reported with the median values (minimum-maximum). The difference of GPR between degrees of BCLC in HCC patients was analyzed using Kruskal-Wallis. The p-value < 0.05 indicates significant statistically.

3. Result
Demographic data of 166 HCC patients since January 1, 2015 – December 31, 2016, consisting of 129 patients were men (77.7%) and 37 female patients (22.3%). The median age of HCC was 52.8 years, with the lowest period of 20 years and the highest age 83 years. Most HCC etiology caused by hepatitis B virus infection (84.94%), while the viral infections hepatitis C totaled 4.82% and other causes as much as 10.24%. The median value GGT was 184.5 U/L with the lowest value 17U/L and
the highest value 985 U/L; the median value GPR was 1.29 with the lowest cost and the highest value respectively were 0.06 9.8. The average of platelet 280.82 ± 138.269 (103/L) then to the staging system BCLC is highest, class C (45.8%), followed by BCLC B (32.5%), BCLC D (14.5%) and BCLC A (7.2%).

Table 1. Baseline demographic and clinical characteristic of HCC patients in Haji Adam Malik Medan General Hospital 2015-2016.

| Variables   | n = 166 patients |
|-------------|------------------|
| Gender      |                  |
| Male        | 129 (77.7%)a     |
| Female      | 37 (22.3%)a      |
| Age         | 52.8 (20-83)c    |
| Etiology    |                  |
| Hepatitis B | 141 (84.94%)a    |
| Hepatitis C | 8 (4.82%)a       |
| Others      | 17 (10.24%)a     |
| GGT         | 184.5 (17-985)c  |
| Albumin     | 2.9 (1.1-4.2)c   |
| PLT         | 280.82±138.269b  |
| GPR         | 1.29 (0.06-9.8)c |
| AGR         | 0.1486 (0.003-0.176)c |
| BCLC        |                  |
| A           | 12 (7.2%)a       |
| B           | 54 (32.5%)a      |
| C           | 76 (45.8%)a      |
| D           | 24 (14.5%)a      |

a categorical data: n (%)
a numeric data, normal distribution: mean ± SD
a numeric data, abnormal distribution: median (min - max)

Table 2. Difference of GPR value in HCC patients on staging BCLC.

| BCLC | GPR        | P       |
|------|------------|---------|
| A    | 0.71 (0.13-4.02) |        |
| B    | 1.22 (0.06-9.80)  |        |
| C    | 1.29 (0.10-8.50)  | 0.23a   |
| D    | 1.98 (0.15-5.620) |        |

aSignificant p<0.05

Based on the Kruskal-Wallis Test, there is no difference GPR value between degrees of BCLC in HCC patients in Haji Adam Malik General Hospital Medan during 2015-2016.
Figure 1. Boxplot difference of GPR value in HCC patients on degree BCLC staging system.

Table 3. The difference of AGR value in HCC patients on staging BCLC.

| BCLC | AGR         | P     |
|------|-------------|-------|
| A    | 0.1946 (0.003–0.130) |       |
| B    | 0.1950 (0.003–0.159) |       |
| C    | 0.1354 (0.004–0.176) | 0.032*|
| D    | 0.0093 (0.003–0.820) |       |

*a significant p<0.05

Based on the Kruskal-Wallis Test, there is significant difference AGR value between degrees of BCLC in HCC patients in Haji Adam Malik General Hospital Medan during 2015-2016.

Figure 2. Boxplot difference value of AGR on BCLC staging system.

4. Discussion
BCLC is a staging system for HCC patient that is for prognostic prediction and treatment plan.[6]
Figure 3. The BCLC staging system (INASL consensus on HCC, Kumar et al.).

GPR is a non-invasive marker that is currently considered to be accurate in assessing liver fibrosis. In this study there is no difference between the various stadium BCLC GPR on HCC patient in Haji Adam Malik General Hospital Medan for the year was 2015-2016, meaning that there is no difference in liver fibrosis that occurs in these patients. This study disagrees with Lemoine M et al. in their study in Gambia, West Africa that showed GPR has a significant correlation with liver fibrosis and cirrhosis in patients with chronic HBV infection in West Africa.[10] The differentiation of result because of the distinction of the population the study. The previous study was on chronic HBV infection patient who does not have fibrosis or is undergoing liver fibrosis, whereas this study was in HCC patient who has mostly liver fibrosis or cirrhosis.[12] The BCLC staging system does not compare the liver fibrosis.[6]

There is a significant difference between the various levels of AGR in patients BCLC stage of HCC in Haji Adam Malik Medan general hospital in 2015-2016. This study agrees with a study from Jing C et al. in China.[11]

5. Conclusion
There are two conclusions from this study. First, no difference GPR value between degrees of BCLC in HCC patients in Haji Adam Malik General Hospital Medan during 2015-2016. The second, there is significant difference AGR value between degrees of BCLC in HCC patients in Haji Adam Malik General Hospital Medan during 2015-2016.

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