Comparison of Alpha-Fetoprotein Level in Varying Severity Degree of Hepatocellular Carcinoma Assesed with the Barcelona Clinic of Liver Cancer During 2015-2016 in Haji Adam Malik General Hospital Medan

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ABSTRACT

Background: *Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related deaths worldwide. Presently, the reference staging system to evaluate the prognosis of HCC is The Barcelona Clinic Liver Cancer (BCLC) system. The aim of the study was to identify the comparison of alpha-fetoprotein (AFP) level in varying severity degree of HCC patient assessed with BCLC.*

Method: *This retrospective observational study used patients' medical record hospitalized for HCC between January 1st 2015 until December 31st 2016 in Adam Malik Hospital. From 166 HCC patients with AFP, liver function test (LFT), home sleep test (HST), ultrasonography (USG), and computerized tomography (CT) scan liver 3 phase were included in this study. The comparison of AFP in severity of HCC based on BCLC system was analyzed.*

Results: *About 77.7% HCC patients were male. The mean age was 52 ± 13.63 years. The most cause of HCC was hepatitis B infection. Median AFP was 574.97 ng/mL. According to the BCLC staging system, 12 patients were classified as stage A (7.2%), 54 patients stage B (32.5%), 76 patients stage C (45.8%) and 24 patients stage D (14.5%). There's significance difference value of AFP in varying stage of BCLC for HCC, which the highest value in BCLC stage D, followed by C, B and A (p = 0,001)*

Conclusion: *There's significance difference value of AFP in varying stage of BCLC for HCC patients.*

Keywords: *hepatocellular carcinoma, alpha-fetoprotein, The Barcelona Clinic Liver Cancer (BCLC) system*

ABSTRAK

Pendahuluan: *Karsinoma hepatoseluler (KHS) merupakan penyebab kematian oleh karena kanker ketiga terbanyak di seluruh dunia. Saat ini, sistem stase yang direkomendasikan untuk KHS adalah The Barcelona Clinic Liver Cancer (BCLC). Tujuan penelitian ini adalah untuk mengetahui perbandingan kadar alfa feto protein pada berbagai derajat keparahan pasien KHS yang diukur dengan sistem BCLC.*

Metode: *Penelitian ini merupakan studi retrospektif pasien KHS di Rumah Sakit Adam Malik dari tanggal 1 Januari 2015 hingga 31 Desember 2016. Dari 166 pasien dengan data AFP, fungsi hati, HST, USG dan CT scan liver 3 fase diklasifikasikan ke dalam sistem BCLC dan dianalisis dalam penelitian ini.*

Hasil: *77,7% pasien KHS di Adam Malik adalah laki-laki dengan rerata usia berkisar 52,8 ± 13,63 tahun. Etiologi KHS terbanyak adalah hepatitis B (84,9%) dengan rerata kadar AFP pasien 574,97 ng/mL. Sistem*

BCLC terbanyak adalah BCLC kelas C (45,8%), diikuti BCLC B (32,5%), BCLC D (14,5%), dan BCLC A (7,2%). Terdapat perbedaan kadar AFP yang signifikan antara berbagai stadium BCLC pada pasien KHS, dimana kadar AFP signifikan lebih tinggi pada BCLC kelas D, diikuti BCLC C, B dan A (p = 0,001)

***Simpulan:** Terdapat perbedaan kadar AFP yang signifikan antara berbagai stadium BCLC pada pasien KHS, dimana kadar AFP lebih tinggi signifikan pada BCLC kelas D, diikuti oleh BCLC C, B dan A.*

***Kata kunci:** karsinoma hepatoseluler, alfa fetoprotein, sistem The Barcelona Clinic Liver Cancer (BCLC)*

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth-leading cause of cancer in men and seventh in women, and also representing 7% of all cancer in human.[1,2] Globally, HCC is the third-leading cause of cancer-related death after lung and stomach cancer. The annual incidence of HCC is similar with its deaths every year that represent aggressiveness of the disease.[1,3,4] Incidence of HCC increases progressively along with advancing age and more common in men with male to female ratio 3.7:1.[1,5,6] The increasing incidence is also related to hepatitis B, C virus infection, and alcohol intake as the most frequently risk factors of HCC in Europe and United States, while in Asia, hepatitis B virus infection is the main one.[1,2,7,8] Overall 54% cases of HCC is related to chronic hepatitis B infection, 31% to hepatitis C infection, and 15% to other factors.[1] The differences in the geographical distribution of HCC reflects the differences in exposure to the hepatitis viruses and different environmental pathogens, so the incidence is highest in East Asia, Sub-Saharan Africa and Melanesia, with 85% of the total number of cases, while in industrialized countries, the incidence is lower except in South Europe.[1,7,9]

Nowadays, the recommended staging system of HCC is Barcelona Clinic Liver Cancer (BCLC). The system is able to relate the stage of HCC with treatment modalities and survival rate estimation based on response of each treatment. The treatment strategies in BCLC are liver resection, percutaneous ethanol injection (PEI), radiofrequency ablation (RF), liver transplantation, transarterial chemo-embolization (TACE), sorafenib, and symptomatic treatment. However, if clinically indicated, combination therapy is also able to be applied.[3,10,11]

Alpha-fetoprotein (AFP) is one of inadequate screening or diagnostic tests for HCC because of its low sensitivity and specificity. However, a few studies found that AFP is attributed to patient survival rate and could help to identify the increasing risk of HCC, number of recurrence, and bad prognosis after hepatectomy and liver transplantation.[3,12] The aim of the study is to identify the comparison of AFP level in varying severity degree of HCC patient assessed with The Barcelona Clinic Liver Cancer (BCLC) during 2015-2016 in Haji Adam Malik General Hospital Medan.

METHOD

This is a restrospective study which took place in the outpatient and inpatient care facility of Haji Adam Malik General Hospital Medan from 1st January 2015 until 31st December 2016 on HCC-diagnosed patient based on medical record, including anamnesis, physical diagnostic, laboratory and imaging with ICD X C22.0 coding. There are 450 collected data from hospital information system, however, only 166 data have AFP, liver function, USG, 3-phase liver CT scan results. Then, appropriate data is classified to A, B, C, and D BCLC staging sytem.

All appropriate data were analyzed with SPSS software. Data on demography were described in number and percentages, afterwards data will be reported with mean ± standard deviation if normally distributed and with mean (minimal-maximal) if not normally distributed. The comparison of alpha-fetoprotein in varying severity degree of HCC patient assessed with BCLC were analyzed with Kruskal Wallis test, with $p < 0.05$ shows statistically significant.

RESULTS

Table 1 shows data on demography of 166 HCC patient since 1st January 2015 to 31st December 2016, with 129 men (77.7%) and 37 women (22.3%). The mean age of HCC patient in Haji Adam Malik General Hospital is 52.8 ± 13,63 years old. The most common HCC etiology is hepatitis B virus infection (84.9%), while percentage of hepatitis C virus infection-related HCC is 4.8% and other causes is 10.2%. The most common stage is BCLC class C (45.8%), followed by BCLC class B (32.5%), BCLC class D (14.5%), and BCLC class A (7.2%).

Table 1. Characteristic of HCC patient demography in Haji Adam Malik General Hospital 2015-2016 (n = 166)

Variable	n (%)
Gender	
Male	129 (77,7)[a]
Female	37 (22,3)
Age	52,8 ± 13,63[b]
Etiology	
Hepatitis B	141 (84,9)[a]
Hepatitis C	8 (4,8)
Others	17 (10,2)
Alpha-fetoprotein	574, 97 (0,73-675700)[c]
Barcelona Clinic Liver Cancer	
A	12 (7,2)[a]
B	54 (32,5)
C	76 (45,8)
D	24 (14,5)

[a] categorical data: n (%); [b] numerical data, normal distribution: mean ± SD; [c] numerical data, abnormal distribution: median (min-max)

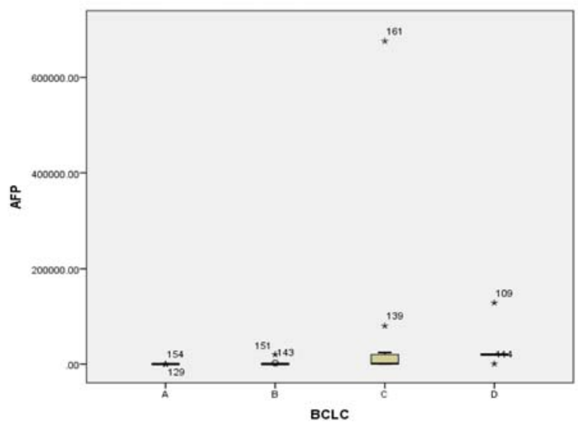

Figure 1. Boxplot of comparison of AFP level with BCLC A, B, C, D staging system

There is a significant difference of AFP level among all BCLC stage in HCC patient, where significant level of AFP is higher in BCLC class D, followed by BCLC C, B, and A based on Kruskal Wallis test (p = 0.001). The white blood cells, total bilirubin, direct bilirubin, AST, and albumin also showed significant differences among all BCLC stage in HCC patients.

DISCUSSION

As the development of science, diagnostic utilities have developed (chemical biomarker and imaging), and current holistic therapy for HCC, those will improve patient overall survival. One year survival rate and three years survival rate of HCC patient vary between 44.3-67% and 24-45% with median survival between 8 and 37 months.[3]

The Barcelona Clinic Liver Cancer (BCLC) is a staging system which recommended in assessing HCC lesion, as the system includes prognostic variable based on tumor status, liver function, and patient clinical appearance. The system has been validated and used globally. BCLC classified HCC patient into 5 classes, those are A, B, C, D: (1) BCLC stage 0 (very early) is defined as single tumor sized < 2 cm, without vascular invasion with good performance status eastern cooperative oncology group (ECOG), that is ECOG 0. With good liver function (Child Pugh A). The recommended therapy for patient in this class is tumor mass resection; (2) BCLC class A (early HCC) is defined as single tumor sized > 2 cm or 3 nodules sized < 3 cm, ECOG0, Child Pugh A or B. The recommended therapies for patient in this class are liver transplantation, Percutaneous Ethanol Injection (PEI), and Radiofrequency Ablation (RF). A few studies show that 5 years survival rate is 40-70%; (3) BCLC class B (Intermediate HCC) is defined as untreated asymptomatic multinodules, without vascular invasion. The recommended therapy is transarterial chemo-embolization (TACE); (4) BCLC class C is defined as HCC patient with tumor symptoms (symptomatic tumor) and ECOG 1-2, macrovascular invasion (segmental or portal invasion) or extrahepatic metastase. The recommended therapy for patient in

Table 2. Comparison of AFP, routine blood test and liver function in hepatocellular carcinoma (HCC) patient with Barcelona Clinic Liver Cancer (BCLC) staging

	BCLC A	BCLC B	BCLC C	BCLC D	p
AFP (ng/ dL)	2,72 (1,08 – 58)	140 (1,11 – 20000)	1134,56 (0,73 – 675700)	20000 (485-128000)	0,001
Hb (gr/dL)	12,03 ± 2,24	13,2 ± 4,05	11,2 ± 2,56	10,4 ± 3,2	0,143
WBC (/µL)	9756,43 ± 4567,8	9772,63 ± 5496,8	9810,39 ± 4001,3	16278,3 ± 9021,7	0,004
HCT (%)	36,1 ± 6,49	34,5 ± 6,57	32,8 ± 7,7	30,9 ± 9,6	0,058
PLT (/µL)	297583,3 ± 132890,5	270000 ± 137485,09	289486,8 ± 142191,7	269333,3 ± 135690,3	0,514
Total bilirubin (mg/dL)	0,52 (0,39 - 1,3)	0,94 (0,3 - 3,38)	1,37 (0,29 - 28,3)	2,78 (0,31 - 29,8)	0,004
Direct bilirubin (mg/dL)	0,21 (0,1 - 1,1)	0,5 (0,1 - 27,3)	0,7 (0,1 - 22,5)	2,2 (0,1 - 21)	0,022
ALP (U/L)	119,5 (69 - 637)	153,5 (67 - 761)	172,5 (34 - 1252)	215,5 (87 - 700)	0,108
AST (U/L)	33,75 ± 20,21	162,24 ± 268,32	270,86 ± 674,14	377,42 ± 460,08	0,003
ALT (U/L)	29,58 ± 16,18	65,59 ± 107,57	70,72 ± 77,5	102,17 ± 99,1	0,282
Gamma GT (U/L)	154,33 ± 83,74	223,31 ± 196,69	256,37 ± 188,36	309,17 ± 211,45	0,571
Albumin (g/dL)	3,1 ± 0,36	2,9 ± 0,49	2,8 ± 0,5	2,5 ± 0,6	0,002

BCLC: Barcelona Clinic Liver Cancer; AFP: alpha-fetoprotein; WBC: white blood count; HCT: hematocrit; PLT: primary liver transplantation; ALP: alkaline phospatase; ALT: alanine aminotransferase this class is Sorafenib, a tyrosine kinase inhibitor. Five years survival rate for patient in class B and C is 50%; (5) BCLC class D (endstage HCC) is defined as HCC patient with bad performance status (ECOG 3-4), as a result of tumor-related disabilities. The recommended therapy for patient in this class is symptomatic therapy with 5 years survival rate 20%.[7,8,10]

AFP is a commonly used biomarker in diagnosing HCC, however in some hospitals in developed country, combination with des-gamma-carboxy-protrombin test is used to increase the accuracy in diagnosing HCC.[5] The elevation of AFP level in serum can also be found during pregnancy, gonadal tumor, and other type of malignancies like Ca gaster. Hamed et al reported that elevation of AFP also be found in acute and chronic hepatitis patient without HCC. Sensitivity of AFP is only 60-80%, while the specificity is 70-90% in diagnosing HCC. AFP level $\geq$ 400 ng/mL usually confirmed a HCC diagnosed.[5]

The result of this study shows that there is a significant difference of AFP level in various BCLC stages in HCC patient in Haji Adam Malik General Hospital Medan, where AFP level is significantly higher in BCLC class D that shows end state of HCC. HCC patient in this class also shows bad performance status (ECOG 3-4) as a result of tumor-related disability with low 5 year survival rate, which is 20% followed by BCLC class C, B, and A with $p = 0.001$.

The same result is also reported from previous study by Rafael Gomez et al and Umberto Cillo et al that elevation of AFP is related to high metastatic incidence and tumor progressiveness and become an important significant prognostic factor for HCC patient. HCC patient with high AFP level > 200 ng/mL shows bad prognosis, high vascular invasion, and more progressively increasing of tumor size, and also significantly more serious class of BCLC.

Burnett NP et al reported that HCC patient with AFP level > 500 ng/mL is significantly related to worse BCLC scoring compared to HCC patient with AFP level < 10 ng/mL, 10-150 ng/mL and 150-500 ng/mL with $p < 0.001$.

Other parameters were analyzed in this study and showed that leucocyte, total billirubin, direct bilirubin and AST are higher in HCC patient with BCLC class D, followed by BCLC class C, B, and A. Whereas albumin level in HCC patient BCLC class D (2,5 $\pm$ 0,6 mg/dL) is significantly lower, followed by BCLC class C (2,8 $\pm$ 0,5 mg/dL), BCLC class B (2,9 $\pm$ 0,49 mg/dL), and BCLC class A (3,1 $\pm$ 0,36 mg/dL) with $p < 0.05$. Moscanen JC et al explained that HCC derives from a chronic inflammatory process in liver parenchyma, which preceded by hepatitis B, C virus infection, alcohol ingestion and hepatotoxic drugs so there will be a significantly increasing of leucocyte in HCC patient.[14] Carr BI et al reported that patient with high level of bilirubin have high risk of portal vein thrombosis and faster progressiveness of tumor size as so it is a worse prognostic factor in HCC development because it will damage liver function.[15]

Junfei Jin et al reported that elevation of SGOT reflects liver cell, membrane, and parenchyma damage in HCC patient. The more severe of HCC stage (BCLC D), liver damage will be more serious and increase serum AST significantly.[16] Nojiri S et al reported that albumin can suppress proliferation and tumor cell cycle in HCC patient so becoming a goof prognostic indicator for patient.[17] This study also shows that HCC patient with BCLC class D has low albumin level, followed by BCLC clas C, B, and A with $p < 0.05$.

CONCLUSION

There is significant difference in level of AFP among varying BCLC stage in HCC patient on Haji Adam Malik General Hospital 2015-2016, which AFP level is significantly higher in BCLC class D, followed by BCLC class C, B and A.

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