Updating AFP Level in Chronic Hepatitis B to Evaluate the Risk of Hepatocellular Carcinoma Occurrence

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ABSTRACT

***Background**: Hepatocellular carcinoma (HCC) is a cancer with poor prognosis. Indonesia is a country with high prevalence of chronic hepatitis B infection. The performance of alpha fetoprotein (AFP) as a tumor marker in HCC surveillance is primarily influenced by the etiology of the underlying liver disease.* ***Objective**: To determine the best cut-off value of AFP biomarker examination for HCC surveillance in patients with chronic hepatitis B infection.* ***Methods**: The study collected medical record data of the Hepatobiliary Division of Dr. Cipto Mangunkusumo Hospital from the period of 2017 to 2023. A total of 506 subjects with chronic hepatitis B of all spectrums (hepatitis B without cirrhosis, liver cirrhosis, and early-stage HCC, BCLC 0 and A) were included by total sampling that was performed from 26 July 2023 to 31 August 2023. Determination of the AFP cut-off value was carried out using the receiver operating characteristics (ROC) method.* ***Results**: For HCC surveillance caused by hepatitis B virus, ROC curve analysis resulted in an area under the curve (AUC) of 0.792 (95% CI, 0.719-0.866), and the cut-off value with the highest Youden index was 8.7 ng/ml, with 58% sensitivity, 94% specificity, positive predictive value (PPV) 56.14%, negative predictive value (NPV) 94.43%, positive likelihood ratio (LR+) 10.08, and negative likelihood ratio (LR-) 0.46.* ***Conclusion**: The cut-off value of AFP in HCC surveillance on hepatitis B specific etiology is lower than the cut-off value of AFP in previous HCC surveillance which was not etiologically specific. The cut-off value of 8.7 ng/ml produces the best sensitivity and specificity for the cut-off value for HCC surveillance with hepatitis B etiology.*

***Keywords**: AFP, hepatocellular carcinoma, chronic hepatitis B, surveillance, cut-off value.*

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide. About 78,200 new cases are found each year. The prognosis of liver cancer is very poor (overall mortality 0.95). Worldwide, 80% of the causes of HCC are hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infections, particularly in patients with advanced fibrosis or cirrhosis. The prevalence of chronic hepatitis B in Indonesia is approximately 7.1% (around 18 million people), and of these, an estimated 3.5 to 5.2 million patients will progress to cirrhosis and or liver cancer by 2030.[1,2]

The HCC surveillance program in Indonesia aims to do early detection of HCC, and hence, improving the survival of patients with HCC in Indonesia. The surveillance modalities used in Indonesia are abdominal ultrasound and AFP test every 6 months. However, in recent years the role of AFP measurement in HCC screening has been questioned. This is due to the low sensitivity and specificity of AFP in screening for HCC.[3–6] AFP levels are found to be elevated in non-malignant chronic liver diseases, such as chronic viral hepatitis and cirrhosis. Previous studies reported that AFP levels increase during liver cell regeneration, especially after massive necrosis of liver cells or liver resection.[7,8] On the other hand, 'normal' serum AFP levels (<10 ng/ml) are not uncommon in patients with HCC and small tumor masses. Low serum AFP levels in small size tumors may reflect the relatively small size of the tumor tissue or the tendency for better tumor differentiation at an early stage, resulting in less amount of protein.[9]

The performance of AFP test in HCC surveillance is less uniform. Some studies suggest this non-uniformity of results is mainly due to differences in ethnicity and underlying etiology of liver disease. The underlying viral etiology may modulate the diagnostic accuracy of AFP. Studies conducted by Chun in Korean population and Sanai in Egyptian population showed hepatitis B patients with HCC had lower cut-off point values compared to hepatitis C and non-viral patients with HCC.[3,4] In Indonesia, analysis has not been performed yet on the cut-off point of AFP in screening patients who are at risk of HCC based on hepatitis B etiology. This prompted researchers to conduct a study to determine the best cut-off value for AFP in HCC surveillance in Indonesian population with chronic hepatitis B infection.

METHODS

This is a cross-sectional, retrospective diagnostic study. The study was conducted at the Hepatobiliary Division of Dr. Cipto Mangunkusumo Hospital by using medical record data from the period of 2017 to 2023. The sample size was calculated using the diagnostic research formula with sensitivity output, resulting in a minimum of 55 patients with HCC. The study subjects were obtained through total sampling until the minimum sample size of patients with HCC was obtained. Inclusion criteria were (1) male and female patients, above 40 and 50 years old, respectively, with non-cirrhotic chronic hepatitis B, (2) non-cirrhotic chronic hepatitis B patients aged ≥ 18 years who had a history of hepatocellular carcinoma in first degree family members, (3) hepatitis B patients with cirrhosis (Child Pugh A, B), (4) hepatitis B patients with cirrhosis, Child Pugh C, who have been planned to undergo liver transplantation. AFP level was checked maximum six months before or after attempted diagnosis of HCC, patients with HCC early stage BCLC 0 or A. Excluded patients were pregnant women, patients diagnosed with germ cell cancer or other cancers with liver metastases, patients with liver cirrhosis with hepatitis C virus, or non-viral etiology.

This study was approved by the Ethical Committee of Faculty of Medicine Universitas Indonesia (Protocol no. 23-06-0908).

Medical record data collection included demographics, AFP score, abdominal ultrasound, transient elastography, 3-phase abdominal CT scan or MRI, or liver biopsy, laboratory values to determine Child-Pugh score, AST to platelet ratio index (APRI), FIB-4, HCC diagnosis. The collected data were analyzed with descriptive statistics (median, range, and proportion) to describe qualitative variables and mean AFP score in HCC, cirrhosis, and chronic hepatitis B patients were calculated. Statistical differences of non-parametric and categorical data between subgroups were analyzed using the Mann-

Whitney U test. To analyze the accuracy of AFP diagnosis, data analysis by ROC curve with 95% confidence interval for area under the ROC curve (AUC) value was performed. Evaluation of the best cut-off point of AFP as a screening test was performed by assessing its sensitivity, specificity, PPV and NPV, which were calculated based on different cut-off points. Additional analysis was performed to improve the accuracy of cut-off point determination by calculating the highest Youden index. A result was considered statistically significant if the p value is <0.05. Statistical analysis was performed using SPSS version 26 and Microsoft Office Excel software. As the gold standard for the diagnosis of HCC in this study, a supporting examination of 3-phase CT scan or MRI of the abdomen was used. If the nodules found were not typical for the diagnosis of HCC, the examination was continued with Gd-EOB-DTPA MRI. In some cases where the image was atypical or inconclusive, HCC was confirmed by hepatic biopsy examination.

RESULTS

Total sampling was performed from 26 July 2023 to 31 August 2023. From medical record screening, 506 patients met the inclusion criteria, and 967 patients were excluded due to incomplete data, advanced stage, or did not fulfill the surveillance criteria. There were 56 patients with early-stage HCC, and 449 patients with non-HCC, consisting of 328 chronic hepatitis B patients with cirrhosis and 121 chronic hepatitis B patients without cirrhosis. Of the 56 patients with HCC who entered the study, 32 patients were captured through surveillance (**Table 1**).

Of the 56 patients with HCC, 38 patients had cirrhosis (67.8%). The median age at the time when diagnosis was confirmed in the group of HCC with cirrhosis patients is 60.5 years, HCC without cirrhosis is 60 years, while non-HCC patients, namely liver cirrhosis, is 55 years, patients with chronic hepatitis B without cirrhosis is 57 years. Male patients were dominant in the four groups. Median surveillance period in cirrhotic-HCC patients was 1058 (450-2238) days, while non-cirrhotic HCC was 2173 (1528-2977) days. Most HCC patients included in the analysis were in BCLC stage A (94%), Child-Pugh A (80.7%) (**Table 1**).

The distribution of AFP in patients with HCC and without HCC is shown in **Figure 1**. The highest percentage of cirrhotic HCC patients (50%) had serum AFP range of 10-200 ng/ml, followed by 42.1% with serum AFP <10 ng/ml. In non-cirrhotic patients, 52.6% of the patients had AFP levels < 10 ng/ml, followed by 31.6% with AFP levels of 10-200 ng/ml.

Table 1. Patient Characteristics.

Variables	HCC (n=56)		Non-HCC (n=449)	
	Cirrhosis (n=38)	Non-cirrhosis (n=18)	Cirrhosis (n=328)	Non-cirrhosis (121)
Sex				
Male	29 (76.3%)	16 (84.2%)	247 (75.3%)	76 (62.8%)
Female	9 (23.7%)	2 (11.1%)	81 (24.7%)	45 (37.2%)
Age (years)	60.5 (54.8-65.2)	60 (46-63)	55 (48-60)	57 (49-64)
Male	60 (53.5-65)	60 (47.3-63.8)	54 (47-60)	55 (44.5-64)
Female	63 (59.5-71)	54.5 (SD = 3.5)	56 (50-61.5)	59 (53.5-64.5)
Surveillance				
Yes	22 (57.9%)	10 (55.6%)		
No	16 (42.1%)	8 (44.4%)		
Median length of surveillance (days)	1058 (450-2238)	2173 (1528-2977)		
BCLC stage				
0	1 (2.6%)	1 (5.6%)		
A	37 (97.4%)	17 (94.4%)		
Child Pugh				
A	27 (71.1%)	18 (100%)	254 (77.4%)	
B	11 (28.9%)	-	70 (21.3%)	
C	-	-	4 (1.2%)	

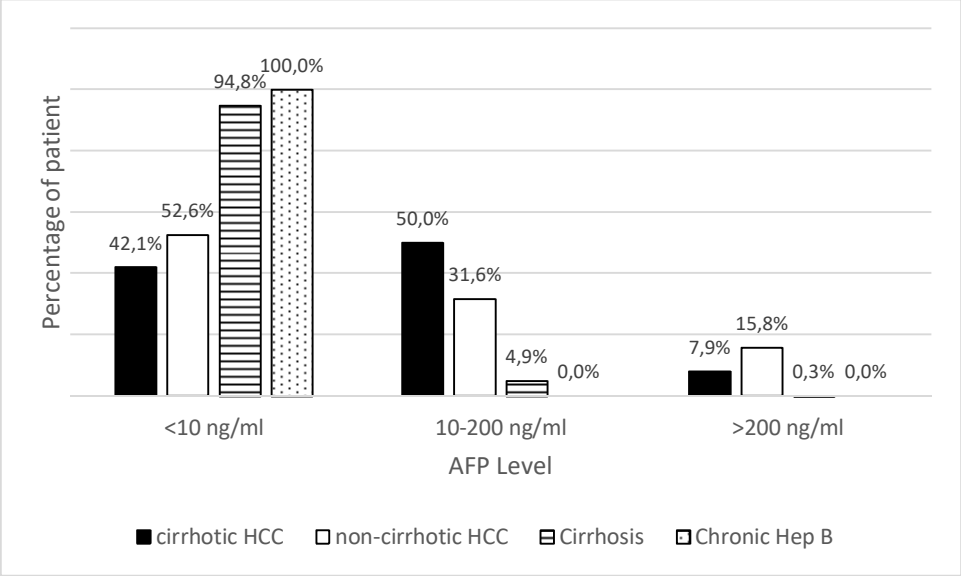

Figure 1. Distribution of AFP in HCC with cirrhosis, HCC without cirrhosis, cirrhosis, and chronic hepatitis B patients.

The results of the normality test of AFP did not show a Gaussian distribution. The results of the Kolmogorov-Smirnov test indicated skewed data distribution. **Table 2** shows the median AFP value. Cirrhotic HCC patients have the highest median AFP, i.e., 11 ng/ml, followed by non-cirrhotic HCC patients with 8.97 ng/ml, cirrhosis patients with 3.17 ng/ml, and patients with chronic hepatitis B without cirrhosis, have the lowest median of AFP, i.e., 2.63 ng/ml.

Kuskal-Wallis test. Post-hoc Mann-Whitney test: HCC with cirrhosis vs HCC without cirrhosis p=0.866, HCC with cirrhosis vs cirrhosis p<0.001, HCC with cirrhosis vs chronic hepatitis B p<0.001, HCC without cirrhosis vs cirrhosis p=0.002, HCC without cirrhosis vs chronic hepatitis B p<0.001, cirrhosis vs chronic hepatitis B p<0.001.

The Kruskal-Wallis test showed p<0.001, which means there were differences in AFP values between the four groups; post-hoc analysis was continued using the Mann-Whitney test which showed that there was no difference in AFP values between the HCC with cirrhosis group compared to the HCC without cirrhosis group (p=0.866). In the comparison of HCC with non-HCC in all groups, there were significant differences (p <0.001).

AFP levels were then analyzed in ROC curve. The resulted AUC value was 0.792 (95% CI, 0.719-0.866), as shown in **Figure 2**. The cut-off point value of AFP indicating the highest Youden index was 8.7 ng/ml with sensitivity value of 58%, specificity 94%, PPV 56.14%, NPV 94.43%, PLR 10.08, and NLR 0.46.

Researchers then divided the subjects into two groups, i.e., cirrhotic HCC and non-cirrhotic HCC, to assess whether there were differences in the cut-off point value and the significance

Table 2. Summary of AFP levels (ng/ml) of the study subjects in median and 1st and 3rd quartile.

Group	Subject (n)	1st quartile	Median	3rd quartile	p value
HCC with cirrhosis	38	3.92	11	45.6	<0.001
HCC without cirrhosis	18	2.8	8.97	69.67	
Cirrhosis	328	2.23	3.17	4.57	
Chronic hepatitis B	121	1.83	2.63	3.72	

Kuskal-Wallis test. Post-hoc Mann-Whitney test: HCC with cirrhosis vs HCC without cirrhosis p=0.866, HCC with cirrhosis vs cirrhosis p<0.001, HCC with cirrhosis vs chronic hepatitis B p<0.001, HCC without cirrhosis vs cirrhosis p=0.002, HCC without cirrhosis vs chronic hepatitis B p<0.001, cirrhosis vs chronic hepatitis B p<0.001.

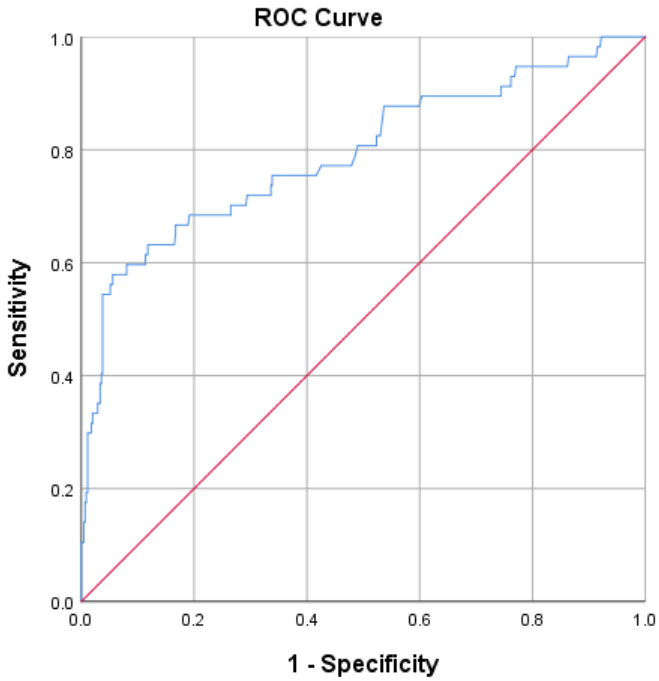

Figure 2. ROC curve of AFP examination in cirrhotic and non-cirrhotic HCC

of the AFP diagnostic value between the two groups. ROC curve analysis in the cirrhotic HCC vs cirrhosis, showed AUC of 0.803 (95% CI, 0.722-0.884) as shown in **Figure 3.**

The best cut-off point value of the Youden index in cirrhotic HCC vs cirrhosis was 8.6 ng/ml, with sensitivity, specificity, PPV, NPV, and LR+ of 60.5%, 92.4%, 45.10%, 95.24%, and 7.09, respectively.

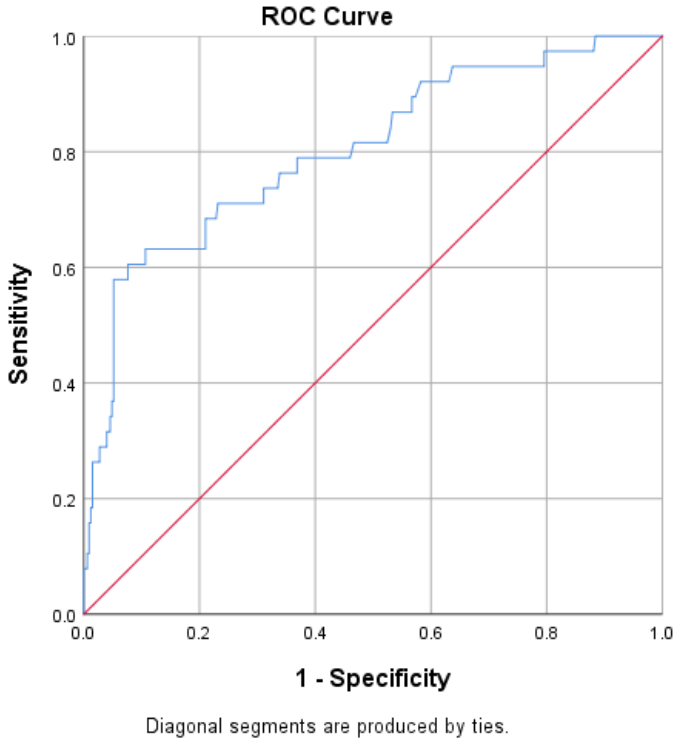

Figure 3. ROC curve of AFP examination in cirrhotic HCC.

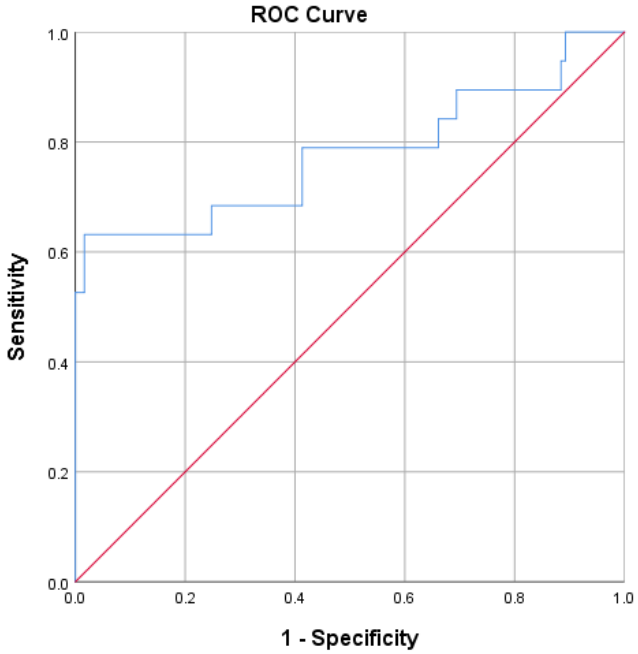

Figure 4. ROC curve of AFP examination in non-cirrhotic HCC.

ROC curve analysis (**Figure 4**) in the non-cirrhotic HCC vs chronic hepatitis B without cirrhosis, produced an AUC of 0.777 (95% CI, 0.631-0.923) with the cut-off point value obtained from the Youden index was 6.6 ng/ml with sensitivity, specificity, PPV, NPV, and LR+ of 63.16%, 98.35%, 85.71%, 94.44%, and 38.21, respectively.

DISCUSSION

The AFP cut-off point of HCC surveillance used in Indonesia is > 10 ng/ml. This cut-off point is used for HCC surveillance without distinguishing the specific etiologies, whether viral or non-viral.[10] Studies conducted abroad found that the underlying etiology of HCC can modulate the diagnostic accuracy of AFP. Research conducted by Chun in the Korean population found that the AFP cut-off point for etiologic hepatitis B of 8.4 ng/ml, lower than hepatitis C 9.2 ng/ml and non-viral 14.6 ng/ml.[3] Research conducted by Sanai on the Egyptian population to determine whether there are differences in AFP cut-off points based on etiology, to establish diagnosis of HCC, found the cut-off point for hepatitis B of 102 ng/ml, hepatitis C 200 ng/ml, and non-viral 400 ng/ml.[4]

Another study in the Caucasian population using an AFP surveillance cut-off point >20 ng/ml, found that 38% of HCC cases did not show an increase in AFP levels.[11] Meanwhile another study in America using the cut-off point of 10 ng/ml found HCC with hepatitis C etiology, 43% of the African-American population, and 18% of a mixed group of Asians, Hispanics, and Caucasians did not show elevated AFP levels.[12] Another study in an Asian population with the cut-off point of 20 ng/ml showed that 16% of HCC patients with hepatitis C etiology did not showed increased AFP levels.[13] In populations in the Middle East, 20% of HCC patients had normal serum AFP levels < 10 ng/ml.[4]

The above studies showed that the ethnic group and etiologic of HCC influence the secretory value of AFP. Specific research looking for AFP cut points based on etiology in Indonesia has not been carried out. Because the prevalence of hepatitis B in Indonesia is higher than hepatitis C and non-viral hepatitis, this study focuses on finding the AFP cut-off value for HCC surveillance in patients with etiologic hepatitis B.

HCC surveillance program in Indonesia is using an AFP cut-off point of 10 ng/ml or an increase in AFP levels compared to the previous examination or the discovery of liver nodules on abdominal ultrasound. The value of 10 ng/mL

was determined based on the results of diagnostic studies conducted by Marrero et al and Biselli et al. [5,6] In this study, the ROC curve produced an AUC of 79.2% (95% CI, 71.9%-86.6%), which is not much different from the previous research by Marrero et al that also obtained an AUC of 78% (95% CI: 74%-83%). The cut-off point of 8.7 ng/ml was obtained from the Youden index and still resulted in low sensitivity, but with high specificity. These results are in line with the study conducted by Marrero et al and Biselli et al that also obtained a sensitivity of 66%, with specificity of 82%.[5,6] Research conducted by Jasirwan et al in Indonesia showed different results which stated that the AFP surveillance with cut-off point of 10 ng/ml was still good to be used in Indonesia with sensitivity of 82.6%, specificity 71.2%, PPV 65.6%, NPV 85.9%, and LR+ of 2.87.[14] These different results are due to differences in the study population, where the HCC patients analyzed in Jasirwan et al's study involved all stages of HCC with the majority of subjects had advanced stage HCC. In addition, Jasirwan et al's study did not specifically assess the cut-off point for AFP caused by hepatitis B virus.

In screening or surveillance, the cut-off point should ideally have higher sensitivity than specificity. However, considering that the sensitivity of AFP in most studies is poor, and increasing the sensitivity will increase the false positive rate, which then increases the use of advanced imaging examinations, then the cut-off point value of 8.7 ng/ml is a good choice for HCC surveillance with hepatitis B etiology in Indonesia with good PPV (56.14%), LR + (10.08), and LR - (0.46).

Sub-analysis of the ROC curve in cirrhosis HCC vs cirrhosis subjects produced AFP cut-off point from the Youden index of 8.6 ng/ml. This value is not much different from the HCC cut-off value without considering the presence or absence of cirrhosis. For non-cirrhotic HCC vs chronic hepatitis B subjects, the best cut-off point obtained from the Youden index is 6.6 ng/ml. From these results, the AFP cut-off point value in non-cirrhotic HCC is lower. As far as we know, there have been no studies yet that analyzed the AFP cut-off point by dividing HCC subjects based on their cirrhosis status. These results are in line with the research of Jasirwan et al which showed that HCC patients without cirrhosis tend to have lower AFP levels than HCC patients with liver cirrhosis.[14]

HCC is more common in men with an incidence two to four times higher than in women.[15] In this study, male-to-female ratio (M:F ratio) was 3.75. These results are also similar to research conducted by Zhu et al, which stated that in the Asia-Pacific region (especially North Korea, South Korea, Indonesia, and Vietnam), the HCC rate in men was 4 times higher than in women. Globally, the M:F ratio ranges from 2:1 to 4:1, with higher differences found in higher risk regions.[16,17]

Men are known to have a higher risk of progressing to HCC than women. This is because men are more likely to consume cigarettes and alcohol, and also have more visceral fat, which is a risk factor for HCC.[18] In addition, the protective role of estrogen in women is thought to be a cause of sexual dimorphism. Higher estrogen concentration in women plays a role in reducing liver inflammation and protective against malignant transformation of hepatocytes and the negative impact of risk factors.[19–22]

The incidence of HCC is also found to be higher with the increase of the age. In the population in the United States, the median age of HCC diagnosis in men ranges from 60-64 years, while in women ranges from 65-69 years.[23] In China and Taiwan, the median age of HCC diagnosis is 63 years; in South Korea, most women are diagnosed with HCC at the age of 70-79 years, while men are aged 50-59 years.[24] This study divides HCC into 2 subgroups, i.e., HCC with cirrhosis and HCC without cirrhosis. The median age of diagnosis of HCC with cirrhosis in men is 60 (53.5-65) years, which is younger than women whose median is 63 (59.5-71) years. This result is in line with research by Zhang et al which stated that men are generally diagnosed with HCC at a younger age than women.[24] In the non-cirrhotic HCC subgroup, the opposite happened, the median age of diagnosis in men is 60 (47.3-63.8) years, which is older than women whose median is 54.5 ± 3.5 years. However, this value cannot represent the population because

there were only 2 HCC female patients without cirrhosis, and each was 52 and 57 years old, so this result cannot represent the HCC M:F ratio in the population.

The median age of HCC diagnosis in this study was relatively younger compared to other countries. This is probably because this study only included subjects from surveillance programs and non-surveillance patients who presented with early-stage HCC. In addition, the diversity of age-specific patterns is associated with differences in the predominance of hepatitis viruses in the population, age at the time of viral infection, and low neonatal immunization coverage in developing countries, where vertical transmission is the main route of transmission.[17,25]

Most HCC patients are older adults, possibly related to the accumulation of somatic mutations, deactivation of the immune system, chronic exposure to risk factors, and increased expression of oncogene regulators AR and PIK3R1 in older adults.[24,26] In addition, this is also due to the pathogenesis of chronic liver disease which takes years to develop HCC and minimal symptoms in early stage HCC patients.[1] Hepatitis B virus (HBV) infection requires two to three decades to become HCC.[27]

This study included 33 early-stage HCC subjects and excluded 17 intermediate and 3 advanced stage HCC subjects. By looking at this data, it seems that the surveillance program in Indonesia is still showing its benefits in capturing HCC patients at an early stage. Median surveillance period for HCC patients with cirrhosis was 1058 (450-2238) days, 2 times shorter than 2173 (1528-2977) days for HCC patients without cirrhosis. This shows that patients with cirrhosis need a shorter time to develop HCC compared to non-cirrhotic patients. Research by Yi et al conducted an analysis with adjustments for gender and age, finding that cirrhosis increased the incidence of HCC 42 folds, followed by hepatitis B infection (21 folds), and hepatitis C infection (19 folds). Long-term studies showed that HCC develops approximately one to eight percent per year in patients with cirrhosis.[19,28] This study found that in HCC patients, 67.86% HCC patients had liver cirrhosis, two folds than patients without underlying liver cirrhosis (32.14 %).

The strength of this study is that total sampling was carried out on the entire spectrum of the chronic hepatitis B population that underwent HCC surveillance, and non-surveillance patients with early-stage HCC (BCLC 0 and A), and therefore, resulting in an AFP cut-off point that is suitable for use for HCC surveillance.

The weakness of this study is that some data are not available for several variables because this study uses secondary data, and hence, a lot of medical record data were excluded. Most patients in this study were male, which limits the generalizability of the study results to the female population. The study was conducted at a national referral hospital, so the prevalence of HCC will be higher compared to primary or secondary hospitals, and therefore, it could cause differences in positive and negative predictive value.

CONCLUSION

This study found that the cut-off point for HCC surveillance with a hepatitis B specific etiology was lower compared to the AFP cut-off point for non-etiology specific. The cut-off point value of 8.7 ng/ml produces the best sensitivity and specificity for the cut-off point for HCC surveillance with hepatitis B etiology. This cut-off point value was selected by considering sensitivity to optimize early detection of HCC, and specificity to be cost-effective.

Since this study found that there were differences in the cut-off points for HCC surveillance based on etiology, it is recommended that further research to be conducted to assess the best cut-off points for HCC surveillance for hepatitis C and non-viral etiologies. In chronic hepatitis B patients without liver cirrhosis, awareness of HCC needs to be increased because the AFP cut-off point is lower compared to HCC patients with liver cirrhosis.

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