Factors associated with tumor size of hepatocellular carcinoma

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Abstract. Determining the association of age and laboratory parameters with tumor size of hepatocellular carcinoma (HCC). The study was at Adam Malik Hospital Medan from June-December 2016. 100 HCC patients were enrolled; those with excluding liver metastatic. Baseline characteristics of gender, age, obtaining etiology of HCC. Liver function tests, viral marker, and INR were done. Based on tumor size from abdomen CT, patients were three groups: tumor size below 3 cm, 3-5 cm, and above 5 cm size. Patients were also divided based on Child-Pugh class. Correlation of age and laboratory results with tumor size of HCC patients were analyzed. Age have negative correlation with tumor size in HCC patients (r=-0.297, p=0.032) while AFP have positive correlation with tumor size (r=0.446, p<0.001). Total bilirubin, AST, and ALT have negative correlation but non-significant (r=-0.045, -0.078, -0.126 respectively). Albumin and INR have positive correlation but non-significant (r=0.021, 0.112 respectively). Our study suggests that older age correlates with smaller tumor size, while AFP level has a significant correlation with tumor size in HCC patients. AFP level may be a useful marker for determining the prognosis of HCC patients.

1. Introduction
Hepatocellular carcinoma (HCC) is the second common cause of death from cancer worldwide. It is estimated to be responsible for nearly 746,000 deaths in 2012 (9.1% of the total). The prognosis for liver cancer is very low (overall ratio of mortality to the incidence of 0.95), and as such the geographical patterns in incidence and mortality are similar. HCC is largely a matter of the less developed regions where 83% of the estimated 782,000 new cancer cases worldwide occurred in 2012. It is the fifth most common cancer in men and the ninth in women. In men, the regions of high incidence are Eastern and South-Eastern Asia, that is, including Indonesia,[1]

Infection of Hepatitis B and C virus were still the leading cause of HCC. Several meta-analyseshave demonstrated that risk of HCC is 15-20 times greater among Hepatitis B Virus (HBV) infected individuals as compared to uninfected population,[2–4] while individuals positive for anti-Hepatitis-C-Virus (anti-HCV) had 17 times the risk of HCC as compared to anti-HCV negative.[4,5] Other causes that can develop HCC were non-alcoholic fatty liver disease, aflatoxin, alcohol and genetic factors.
Alpha-fetoprotein (AFP) is a protein of fetal component produced during the embryonic period by the visceral endoderm of the gestational sac and, later by the liver.[6] Some studies have demonstrated that the presence of elevated of alpha-fetoprotein in patients with liver cancer is a risk factor for the development of HCC. In cirrhotic patients with nodules >2 cm, coincidental findings by two imaging techniques were considered diagnostic of HCC, or alternatively, one imaging technique along with AFP levels above 400 ng/ml (EASL guideline 2001). Unfortunately, in 2005 EASL guideline dropped AFP levels from the diagnostic scheme.[7,8]

Nevertheless, increasing AFP production in patients with liver cancer might reflect, largely & abnormal or altered liver cell generation,[9] Bilirubin, albumin and the international normalized ratio (INR) are some of the parameters in the Child-Pugh score to determine the prognosis of patients with the chronic liver disease, mainly cirrhosis. Abnormal liver enzyme levels such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) may signal liver damage.[10] Thus, we hypothesize that there are relationships between AFP levels and other laboratory parameters mentioned with tumor size in HCC.

Therefore, the purpose of this study was to determine associations of age and different laboratory parameters with the size of tumors of HCC patients at Haji Adam Malik Hospital, Medan.

2. Methods

2.1. Data Collection

By using cross-sectional analytical study, the study was at tertiary care hospital, Adam Malik General Hospital in Medan, Sumatera Utara, Indonesia from June to December 2016. Outpatients and inpatients aged over 18 years who were with HCC as evidenced by abdominal ultrasound and CT-scan were included in the study. Patients having primary tumor elsewhere with liver metastatic were excluded. There are a recording of demographic data such as gender, age, and address. All patients were tested for liver function tests, viral marker (HBsAg, Anti HCV), and INR. Based on clinical examination and laboratory tests, patients were classified into 3 categories: Child-Pugh class A, B, and C. Based on tumor size measured by abdomen CT, patients were also divided into 3 groups: Tumor size is below 3 cm (group A). Tumor size is 3-5 cm (group B). Tumor size is above 5 cm size (group C). Correlation of age and laboratory results with tumor size of HCC patients were analyzed.

2.2. Statistical Analysis

All data were analyzed using statistical package SPSS (version 17.0; SPSS, Chicago, IL, USA). Baseline characteristics were described as number and percentage for categorical data and as mean and standard deviation for numerical data. The link between quantitative variables (age, laboratory parameters) with tumor size came from the Pearson correlation coefficient. A p <0.05 was considered to indicate statistical significance.

3. Results

Baseline characteristics of hepatocellular carcinoma patients in Haji Adam Malik Hospital Medan from June to December 2016 are in Table 1. Out of 100 HCC patients, most were male (81%) compared to female (19%) with mean age 57.2 years ± 14.74. Etiology of HCC was mostly caused by Hepatitis B(84%), followed by other cause (11%) and Hepatitis C(5%). In tumor size groups, the 19 (19%) patients were in group A. 48 (48%) patients were in group B. 33 (33%) patients were in group C. In Child-Pugh class, the 12 (12%) patients were in class A, 56 (56%) in class B, and 32 (32%) in class C.

The correlation of age and laboratory results with tumor size of HCC patients was described in Pearson’s correlation in table 2. Mean total bilirubin, albumin, INR, AST, ALT and AFP were 2.44 ± 14.74 mg/dl, 3.39 ± 0.96 g/dl, 1.41 ± 0.28, 72.31 ± 22.31 U/L, 56.10 ± 28.32 U/L, and 660.82 ± 229.61 ng/ml respectively. Pearson’s correlation test revealed a negative correlation between age and size of tumor (r = -0.297, p-value = 0.032), suggesting that, older age have smaller tumor size (figure
Meanwhile, AFP levels have positive correlation with the size of tumor (r=0.446, p value = <0.001). It was highly significant, suggesting that, as tumor size increases the AFP levels also increase (figure 2). Total bilirubin, AST, and ALT levels had negative correlation but non-significant (r=-0.045, -0.078, -0.126 respectively). There was also weak correlation between serum albumin (r = 0.021) and INR (r = 0.112) with tumor size, but both data were non-significant (p-value > 0.05).

Table 1. Baseline characteristics of hepatocellular carcinoma patients.

| Variable       | n = 100 |
|----------------|---------|
| Gender         |         |
| Male           | 81 (81%)a |
| Female         | 19 (19%)b |
| Age (years)    | 57.2± 14.74b |
| Etiology       |         |
| Hepatitis B    | 84 (84%)a |
| Hepatitis C    | 8 (5%) |
| Others         | 11 (11%) |
| Tumour size (cm) |     |
| <3             | 19 (19%)a |
| 3-5            | 48 (48%) |
| >5             | 33 (33%) |
| Child-Pugh class |  |
| A              | 12 (12%)a |
| B              | 56 (56%) |
| C              | 32 (32%) |

*a*categorical data: n (%)
*b*numerical data, normal distribution: mean ± SD

Table 2. It is a correlation of age and laboratory results with tumor size of HCC patients.

| Variable       | Mean ± SD | R     | p-value |
|----------------|-----------|-------|---------|
| Age (years)    | 57.2 ± 14.74 | -0.297 | 0.032a |
| Total Bilirubin (mg/dl) | 2.44 ± 0.35 | -0.045 | 0.693 |
| Albumin (g/dl)  | 3.39 ± 0.96  | 0.021  | 0.778 |
| INR            | 1.41 ± 0.28  | 0.112  | 0.341 |
| AST (U/L)      | 72.31 ± 22.31| -0.078 | 0.546 |
| ALT (U/L)      | 56.10 ± 28.32| -0.126 | 0.195 |
| AFP (ng/ml)    | 660.82 ± 229.61| 0.446  | <0.001a |

*r* = Pearson’s correlation coefficient

*a*p<0.05

**Figure 1.** Pearson’s correlation of age vs tumor size.

**Figure 2.** Pearson’s correlation of AFP vs tumor size.
4. Discussion

Our research shows that the most common cause of HCC in our population is viral infection by Hepatitis B. Southeast Asia (other than East Asia and Central Africa) is known to be a region with a high prevalence of viral hepatitis. Basic health research in Indonesia found that prevalence of hepatitis is about 1.2% in 2013, which was twice as much as in 2007, where Hepatitis B infection was the most prevalent.[11]

HBV is responsible for 50%-80% of HCC cases worldwide, whereas 10%-25% of cases are thought to be a result of HCV infection. Among eight HBV genotypes (A to H) that have been classified, patients with HBV genotype C have a higher risk of developing HCC. Genetic mutations have been in some of these patients that may contribute to this greater risk.[12–14] It’s unknown whether genotype C-HBV were more common in our population. More research in genotyping is needed to confirm the cause of hepatitis B as the leading cause of HCC in this population. This also indicates that the hepatitis B prevention program might still not effective.

HCC is rarely diagnosed at a young age, so our study focused on patients over the age of 18. This was in line with the study results in which the average patient age was 57 years old ± 14.74. Our study showed there was a negative correlation between age and tumor size. It was comparable to a study conducted by Xin-Sen Xu, et al. which reported average tumor size of HCC patients was smaller in older patients than younger patients (6.8 ± 0.3 cm vs 7.0 ± 0.3 cm, p-value 0.46). Their study found that age associated with less aggressive tumor (lower AFP level). On the other hand, the survival rate of aged patients was significantly worse than younger patients. It was speculated that regardless of the higher cancer aggressiveness of younger patients, the better health conditions and stronger tolerance to curative treatment might both contribute to the better overall prognosis in younger patients.[15]

There was a significant relationship between serum AFP level with tumor size. This result was in line with the prior study by Abbasi A, et al. which reported a relation between serum AFP level and size of the tumor (r=0.472) with a p-value of < 0.0001.[16] Some other studies have shown that the presence of elevated levels of AFP in patients with liver cancer might reflect, largely an abnormal or altered liver cell regeneration. Although EASL guideline does not include AFP levels anymore as a diagnostic criterion for HCC, AFP still plays an important role in determining progression and one of the prognostic factors of HCC patients.

The limitation of this study was the period of investigation which was only 6-month of time. Diagnosis of HCC was based on non-invasive criteria and not by pathology evidence (immunostaining for GPC3, HSP70, and glutamine synthetase and/or gene expression profiles). Nevertheless, this study is important to confirm that AFP marker is still useful for determining the prognosis of HCC patients.

5. Conclusion

Our study showed that serum AFP and age had a significant correlation with the size of tumor of HCC patients. AFP level serves as a useful marker for influencing the prognosis of hepatocellular carcinoma patients. Older age may have had smaller tumor size, although overall prognosis must be evaluated from each case. Based on these findings, there must be a plan for the better treatment strategy including hepatitis prevention program and cancer surveillance.

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