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ORIGINAL ARTICLE

Correlation between Alpha Fetoprotein (AFP) Levels and Characteristics of Liver Lesions Using Computed Tomography (CT) scan in Hepatocellular Carcinoma: a Study at Dr. Hasan Sadikin Central General Hospital Bandung 2019

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Abstract

Introduction: Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver which is about 75% - 85%. The diagnosis of HCC is determined based on several factors, including the background of chronic liver disease, tumor markers, and imaging diagnosis. There are three main growth patterns of HCC that can be seen on computed tomography (CT) scan : massive, nodular, and diffuse infiltrative. HCC is locally invasive and tends to invade the portal vein, inferior vena cava and bile duct. Alpha fetoprotein (AFP) is one of the tumor markers used for early diagnosis of KSH and plays an important role in the development and progression of HCC.
Objective: To determine the correlation between alpha fetoprotein levels with characteristics of liver lesions using CT scan examination in HCC patients.
Method: This study was an observational analytic study with a cross-sectional design. Sampling was done retrospectively by collecting medical record data and the results of abdominal CT scan readings from January to December 2019. The study was conducted at the Department of Radiology, Department of Clinical Pathology and Instal-lation of Medical Records-SIRS Hospital Dr. Hasan Sadikin Bandung in February - April 2020. Univariable analysis was carried out to see the description of the proportion of each variable to be presented descriptively, which could be explained into descriptive analysis and hypothesis testing.
Results: There were 63 subjects, 48 men (76.2%), 15 women (23.8%), with the youngest age of 21 years, the oldest 86 years with an average age of 53.44 years. The highest average AFP levels were found in the group of patients with diffuse infiltrative growth patterns 93064.84± 177486,301 and the presence of a thrombus in the portal vein of 78770.98 ± 88358,791. The results of statistical tests using the Mann Whitney Test showed that there were significant differences between the levels of AFP and the growth pattern of liver lesions in HCC patientsbased on the results of the CT scan with a value of p = 0.040 (p≤0.05) and there were significant differences between the levels of AFP and portal vein thrombus in HCC patients based on the results of CT scan examination with a value of p = 0.040 (p≤0.05).
Conclusion : There is a significant correlation between AFP levels with the characteristics of liver lesions specifically the form of growth patterns and the presence of portal venous thrombus using CT scan examination of HCC patients in dr. Hasan Sadikin General Hospital.

Keywords: Hepatocellular carcinoma, Alpha fetoprotein, CT scan

1 | INTRODUCTION

Liver cancer is a malignancy in the liver, classified as primary and secondary (metastatic) liver cancer. (1, 2) Primary liver cancer ranks the sixth of most diagnoses and is the fourth leading cause of cancer deaths worldwide in 2018, with around 841,000 new cases and 782,000 deaths each year. The incidence and death rates are 2 to 3 times higher in men in most regions of the world, thus primary liver cancer ranks fifth most in men worldwide and second in the number of causes of death in men. (3)

The incidence of primary liver cancer in Indonesia ranks fifth after breast cancer, cervical cancer, lung cancer and colorectal cancer, and ranks third as the most common cancer in men. This is not surprising because the prevalence of chronic hepatitis B which is the most etiology of primary liver cancer which is hepatocellular carcinoma (HCC), is still quite high in Indonesia. (4)

Primary liver cancer is a malignancy with a very poor prognosis with a mortality ratio compared to an overall incidence of 0.95. (3)

Hepatocellular carcinoma is the most common primary liver malignancy around 75% -85%, the second is the intrahepatic cholangiocarcinoma in about 10% -15% of cases, and the remaining are the other types that are very rare. More than 80% of all HCC tumors worldwide occur when the underlying chronic liver disease has reached the cirrhotic stage. Carcinogenesis in liver cirrhosis is a complex multistep process characterized by the develop- ment of nonmalignant hepatocellular lesions that eventually progress into frank HCC. (5, 6)

The number of HCC patients hospitalized at Dr. Hasan Sadikin Central General Hospital in Bandung from January to December 2019 was 91 cases. The data does not include new cases from outpatient installations, old cases or follow ups.

The determination of HCC management ideally requires the involvement of various scientific disciplines, such as hepatology, digestive surgery, interventional radiology, diagnostic radiology, radiation oncology, and anatomic pathology, which are incorporated in a team. (7)

The diagnosis of HCC is determined based on several factors, including the background of chronic liver disease, tumor markers, and imaging diagnosis. (7, 8) Approximately 70-90% of HCC patients have risk factors in the form of chronic liver disease and liver cirrhosis, with the most preva-lent risk factors being hepatitis B virus, hepatitis C virus, alcoholic liver disease, and non-alcoholic steatohepatitis (NASH), and others. (9, 10)

Tumor markers that are criteria for diagnosis of HCC are alpha fetoprotein (AFP) and Protein Induced by Vitamin K Absence or Antagonist-II (PIVKA-II). However, the most commonly used is AFP. (7, 8) If there is chronic hepatitis B or chronic hepatitis C associated with liver cirrhosis, elevated levels of tumor markers and typical features of imaging, a definitive diagnosis of HCC can be established. (7, 8)

Radiological examination is one of the determining factors for establishing the diagnosis of HCC. The sensitivity of computed tomography (CT) scans in diagnosing HCC ranges from 67.5% (55-80%) and specificity of 92.5% (89-96%), while magnentic resonance imaging (MRI) has 81% sensitivity and 85% specificity.(11) The typical features of HCC on radiology are encapsulated hypervascular mass in the arterial phase and washout in the portal vein phase or delayed phase on CT scan or 3-phase MRI examination. If a hypervascular appearance is obtained in the arterial phase without a washout in the venous or delayed phase, or a hypovascular appearance in the arterial phase, further investigation is needed. HCC is locally invasive and tends to invade the portal vein, inferior vena cava and bile duct. (7, 11, 12, 13)

Hepatocellular carcinoma is known to have three main growth patterns that affect the form of radiolog-

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ical imaging, namely: massive solitary, multinodular, and diffuse infiltrative. Massive solitary HCC is a large single mass with or without satellite nodules. Multinodular HCC appears as a number of discrete nodules involving large areas of the liver. Manifestations of diffuse HCC are small nodules with innumerable indistinct borders that distort the parenchyma but do not cause discrete mass. (14)

Alpha fetoprotein is a glycoprotein consisting of 591 amino acids. AFP is the main protein component that is synthesized by the visceral yolk sac endoderm of the fetus in early fetal life which is subsequently synthesized by the fetal liver. Immediately after birth, the levels drop dramatically or even almost undetectable and will increase again when certain pathological conditions occur. Since the 1970s, AFP has been used as a tumor marker for HCC diagnosis. (15, 16)

Increased levels of AFP consistently occur in most patients with HCC, and on this basis AFP is one of the useful tumor markers for early diagnosis of HCC. However, normal AFP values can be found in approximately less than 40% of initial HCC and approximately 15 - 40% of advanced HCC. Smaller tumors more often show low AFP levels. However, the correlation between AFP levels and tumor size remains unclear because the capacity to synthesize AFP can differ between tumors. It has been reported that large numbers of HCC cells that produce AFP show poor tumor differentiation, high tumor burden, and risk of recurrence after tumor resection. Serum levels of AFP in almost 75% of cases of HCC are found to be more than 10 ng / ml. AFP serum levels according to HCC diagnosis criteria by the National Consensus on Management of HCC are said to be significant if > 200 ng / ml and tend to increase. (7, 15, 17, 18)

Serum levels of AFP not only have a diagnostic value but also have a predictive value for the prognosis of HCC. Serum AFP examination has been considered an important indicator of the assessment of postoperative recurrence and metastatic HCC. (19)

Increased levels of AFP can also be seen in adult patients with any type of hepatitis or liver cirrhosis. Increased AFP is usually between 10 to 500 ng / ml and sometimes found up to 1000 ng / ml. This increase seems to occur when there is a high level of inflammatory activity in the liver or towards the final phase of acute hepatitis when liver function begins to recover. AFP levels between 10 ng / ml and 1000 ng / ml represent gray areas, because in conditions such as chronic hepatitis and cirrhosis and small HCC are also whitin this range. (15, 20)

Serum AFP levels might also increase in malignancies other than HCC. This increase in AFP is often associated with non-seminomatous germ cell tumors, where AFP is an important tumor marker associated with clinical symptoms. Increased AFP can occur in gastric malignancies, bile ducts and pancreas, but levels that exceed 1,000 ng / ml are found only in <1% of. (21)

Research by Tangkijvanich et al in 2000 found a positive correlation between tumor size and an increase in serum AFP in HCC, besides that an increase in AFP tended to correlate with more aggressive types of cancer, including diffuse or massive types, bilobar tumor involvement, and the presence of portal venous thrombosis. (17)

Research conducted by Farinati et al in 2006 states that there is a significant relationship between increased levels of AFP with the presence of portal thrombosis in KSH patients.[22]

2 | RESEARCH DESIGN AND METHODOLOGY

This study was an observational analytic study with a cross-sectional design by selecting retrospective data from the medical records of HCC patients who came for examination and met the inclusion criteria at the Central General Hospital Dr. Hasan Sadikin Bandung from January 2019 to December 2019. The inclusion criteria in this study were to have AFP laboratory results from the Clinical Pathology Laboratory Dr. Hasan Sadikin Bandung and having the results of a CT scan of the abdomen-pelvis with contrast from the Radiology Installation Dr. Hasan Sadikin Bandung and was diagnosed with HCC. Exclusion criteria are having had curative surgery, chemotherapy or radiotherapy, as well as having ma-

lignancy in other body parts such as gastric cancer, bile duct cancer, pancreatic cancer, and others.

Abdominal-pelvic CT scan readings are done by 2 radiologists. The normality test for numerical data analysis is tested using the One Way Anova test and using the unpaired T test if the data is normally distributed and the alternative is the Kruskal Wallis and Mann Whitney tests if the data is not normally distributed.

3 | RESULTS

This study included 63 subjects with characteristics based on age and sex is shown in Table 1. The mean age of HCC patients in Dr. Hasan Sadikin Bandung General Hospital is 53.44 years, standard deviation is 14,190, median is 52.00 years with the youngest patient age is 21 years and the oldest is 86 years. Based on gender, HCC patients are predominantly male gender of 48 people (76.2%) while female patients are 15 people (23.8%).

In table 2 shows that the average AFP levels of HCC patients is 46267.66, the standard deviation is 117381.29, the median is 1047.60 with the lowest AFP content is 1.90 and the highest is 820860.00. On abdominal-pelvic CT scan, HCC patients with characteristics of massive liver lesions were 28 people (44.4%), diffuse infiltrative 23 people (36.5%) and multinodular 12 people (19.0%). HCC patients with the presence of portal venous thrombus were 13 people (20.65) and patients without portal venous thrombus were as many as 50 people (79.4%).

Table 3 explains the average comparison or relationship between AFP levels and the characteristics shape of the growth pattern. In the massive category form group, the average AFP level was 19461.64 ± 41171,527. In the multinodular group, the mean AFP level was 19120.43 ± 57309.186. In the diffuse infiltrative form group, the average AFP level was 93064.84 ± 177486,301. Statistical test results in the above study group obtained information on the P value on the AFP content level smaller than 0.05 (P value <0.05), which means significant or statistically significant in the patient group in the form of massive, multinodular and diffuse infiltrative.

Table 3 explains the relationship between AFP levels and portal venous thrombus. In the portal venous thrombus group in the category of thrombus, the average AFP level was 78770.98 ± 88358.791. In the category of absence of thrombus group, the average AFP level was 37816.79 ± 123161.292. Statistical test results in the above study group obtained information on the value of P on the AFP content level smaller than 0.05 (P value <0.05), which means significant or statistically significant in the patient group with portal venous thrombus and absence of thrombus

4 | DISCUSSION

Characteristics of the subjects in this study showed that the most prevalent gender of patients with HCC was male, namely 48 people (76.2%) while female patients were fewer, namely 15 people (23.8%). Thus a male-female ratio of 3.2 : 1 can be obtained for the prevalence of women and men. This is consistent with data from The Global Cancer Observatory, Globocan which states that the prevalence of HCC in men is higher than women with a male-female ratio usually averaging between 2:1 and 4:1. These results are also in accordance with some literature, such as research conducted by Abbasi et al who stated that the prevalence of KSH in men is more than women by a ratio of 70.4%: 29.6% or 2.38: 1. Research by Tangkijvanich et al even mentioning the ratio of men and women reaching a ratio of 7:1. (10, 22, 23)

The characteristics of the subjects of this study are based on age, showing that the average age of HCC patients in Dr. Hasan Sadikin General Hospital Bandung is 53.44 years, standard deviation is 14,190 and median is 52.00 years. This is similar from some studies which state the average age of diagnosed KSH is 53 years according to Abbasi et al, while according to Tangkijvanich the average is around 51 years. (23)

Based on the characteristics of the liver lesion CT scan examination research subjects showed that HCC patients in Dr. Hasan Sadikin General Hospital Bandung with the characteristics of massive liver

TABLE 1: Characteristic Description of HCC Patients Basedon Age and Gender

Variable	N=63
Age	
Mean±Std	53,44±14,190
Median	52,00
Range (min-max)	21,00-86,00
Gender	
Male	48(76,2%)
Female	15(23,8%)

TABLE 2: Overview of AFP levels and characteristics of liver lesions (shape and presence of portal venous thrombus) on CT scan of patients with HCC

Variable	N=63
AFP levels	
Mean±Std	46267,66±117381.29
Median	1047,60
Range (min-max)	1,90-820860,00
Characteristic	
Massive	28(44,4%)
Multinodular	12(19,0%)
Diffuse Infiltrative	23(36,5%)
Portal vein thrombus	
Yes	13(20,6%)
No	50(79,4%)

TABLE 3: AFP level description of hepatic cell carcinoma patients based on CT scan results

Variable	AFP levels				value*)
	Mean	SD	Median	Min-Max	
Characteristics					0,040**)
Massive	19461,64	41171,527	25,40	1,90-200000,00	
Diffuse Infiltrative	93064,84	177486,301	36598,80	2,40-820860,00	
Multinodular	19120,43	57309,186	93,40	2,60-200000,00	
Portal vein thrombus					0,040*)
Yes	78770,98	88358,792	45883,00	2,40-20000,00	
No	37816,79	123161,292	124,85	1,90-820860,00	

*) Mann Whitney Test **) Kruskall Wallist Test

lesions were 28 people (44.4%), diffuse infiltrative were 23 people (36.5%) and multinodular were 12 people (19.0%). HCC patients with the presence of portal venous thrombus were 13 people (20.65) and patients without portal venous thrombus were 50 people (79.4%).

The highest average AFP levels were found in the group of patients with diffuse infiltrative growth patterns 93064.84 ± 177486,301 and the presence of a thrombus in the portal vein of 78770.98 ± 88358,791. This is in accordance with research conducted by Tangkijvanich et al in 2000 which stated that increased AFP tended to correlate with more aggressive types of cancer, including diffuse type and the presence of portal venous thrombosis. The results of this study also support the statement of Farinati et al. stating that there is a significant relationship between elevated levels of AFP and the presence of portal venous thrombus. (17)

5 | CONCLUSIONS

There is a significant correlation between AFP levels with the characteristics of liver lesions specifically the form of growth patterns and the presence of portal venous thrombus using CT scan examination of HCC patients in dr. Hasan Sadikin General Hospital with p value =0,040 (p≤0,05).

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