ORIGINAL RESEARCH

Serum AFP (Alpha Fetoprotein) levels profile of hepatocellular carcinoma patients in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

Dyeneka Rustanti Indreswara [1], Ummi Maimunah[2*], Endang Retnowati[3]
[1]Medical Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
[2] Department of Internal Medicine, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.
[3] Department of Clinical Pathology, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

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***Corresponding author**
Ummi Maimunah
ummi.maimunah@fk.unair.ac.id

ABSTRACT

Background: Hepatocellular carcinoma (HCC) accounts for more than 90% of liver cancer which is the second most common cause of cancer-related death worldwide. The incidence of HCC was 626.000 cases every year worldwide. Early detection and therapy can prevent metastasis, progressivity, and recurrence. AFP level ≥ 400 ng/ml and USG results can be used as a diagnosis parameter of hepatocellular carcinoma. **Objective**: To analyze the AFP level's profile in hepatocellular carcinoma. **Materials and Methods**: Descriptive methods used in this study with data collected from medical records on patients that fulfilled the inclusion criteria in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia during the periods of 1st January 2013 - December 31st 2015. This study used various variables such as age, gender, etiology and size of the tumor, number of a nodule, hepatic function with child classification, staging BCLC, and AFP level. **Results**: This study found that the 98 patients with hepatocellular carcinoma with high AFP level or >400 ng/ml were dominated by younger patients with average age of 49.91 years, the most common etiology was hepatitis B (56.8%), poor results of laboratory tests (SGOT, SGPT), patients with all level of hepatic function based on Child-Pugh classification and staging B of the tumor (70.5%). Patients with normal AFP ≤20 ng/ml were dominated by female patients, with the most common etiology of fatty liver and others, and with BCLC A and C staging. Descriptively, there was no difference in AFP level based on the number of nodules and size of tumor. **Conclusion**: The most common patients with high AFP level are those who have hepatitis B as etiology, younger age, male gender, high SGOT level and BCLC B staging. Meanwhile, patients with normal AFP level dominated with female and non-hepatitis patients. In this research, we found no differences of AFP level based on number and size of tumor descriptively.

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BACKGROUND

Hepatocellular carcinoma or hepatoma is a malignancy of the liver and has become the sixth most common malignancy in the world and with incidence of approximately 626,000 cases per year (Sareo, et al., 2014). Hepatocellular carcinoma accounts for more than 90% of liver cancer which is currently the second most common cause of cancer-related death worldwide. Hepatoma related annual death rates during the past two decades have increased, and the majority of all cases of hepatoma worldwide found in Asia Pacific region thus represents a major public health problem (European Association For The Study of the Liver, 2012).

Hepatocellular carcinoma has a wide range of risk factors but the closely linked and suspected etiology is Hepatitis B and Hepatitis C viral infection, alcoholic liver disease, non-alcoholic steatohepatitis, the consumption of food contaminated with aflatoxin, diabetes, and obesity. The largest risk factor for the development of HCC is cirrhosis of any etiology so other liver diseases that notably cause cirrhosis can increase the risk of HCC (Omata, et al., 2017). Early detection and treatment of hepatocellular carcinoma can prevent the progression of the disease and prevent metastasis of cancer. One example of early detection of hepatocellular carcinoma is the examination of AFP levels (Omata et al., 2017). However, the AFP level > 400 ng/ml and ultrasound results that support the HCC could be the diagnosis parameters though sometimes still needs other investigations, such as CT scan and MRI (Wong, et al., 2014).

AFP or alpha-fetoprotein is a glycoprotein with a molecular weight of 70,000. AFP is synthesized by the liver, intestines, and fetal yolk sac. AFP levels increase in hepatocellular carcinoma because liver cells undergo differentiation like the fetal liver cells. However, the usefulness of AFP as a diagnostic test in small HCCs is limited to those smaller than 5 cm in diameter. AFP has low specificity among the high-risk population, which are people with active hepatitis or cirrhosis, because in that condition AFP levels also increased reflecting the necroinflammation and regeneration process (Minami, et al., 2015).

OBJECTIVE

The objective of this study was to determine the profile of AFP levels before therapy in patients with hepatocellular carcinoma.

MATERIALS AND METHODS

This research was a descriptive study using secondary data from the medical records of hepatocellular carcinoma patients in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia in the period of 2013-2015. The exclusion criteria in this study were post-treatment patients' data including resection, ablation, transplantation, or TACE and data that did not completely consist of the variables studied. The variables analyzed in this study were age, gender, etiology, laboratory data (SGOT, SGPT, albumin, bilirubin, tumor size, number of nodules, AFP levels), liver function based on the classification of Child-Pugh and BCLC staging. The collected data were processed with SPSS version 17, and the quantitative data were displayed as mean and standard deviation (X ± SD), while qualitative data were displayed in in numbers and percentages. Tumor size in this study was defined as the diameter of the largest tumor.

RESULTS

This study was able to collect 250 data. After being analyzed with the inclusion and exclusion criteria, we obtained 98 data and used these data as sample. Demographic characteristics of the patients with hepatocellular carcinoma showed that they had average age of 52.13 ± 11:41 years old with the youngest 21 years old and the oldest 87 years of age. HCC patients consisted of 78 male patients and 20 female patients. The distribution of the patients' demographics is shown in Table 1.

Table 1. Distribution of HCC patients based on demography

Age (years old, mean ± SD)	52.13±11.41
Gender: Male	78 (79.6 %)
Female	20 (20.4 %)

Furthermore, based on etiology, the most common etiology was hepatitis B with 46 patients (46.9%) as shown in Figure 1.

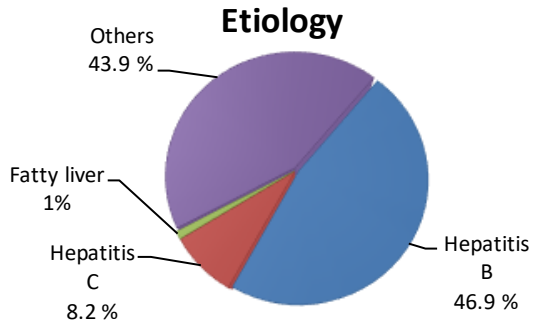

Figure 1. Distribution of HCC patients based on etiology

Reviewing from liver function laboratory tests and based on Child-Pugh classification, it was found that the majority of the patients had high levels of AST and ALT, low levels of albumin and bilirubin, with the most liver function was Child B as shown in Table 2.

Table 2. Distribution of HCC patients based on Liver Function

SGOT (U/L, mean±SD)	237.703±246.273
≤40	8 (8.2%)
>40	90 (91.8 %)
SGPT (U/L, mean±SD)	74.739±71.0094
≤40	34 (34.7 %)
>40	64 (65.3 %)
Albumin (g/L, mean±SD)	2.9±6.5082
>3.5	15 (15.3 %)
3-3.5	29 (29.6 %)
<3	54 (55.1 %)
Bilirubin total (mg/dl, mean±SD)	4.822±7.199
<2	51 (52 %)
2-3	11 (11.2 %)
>3	36 (36.7 %)
Child Score	
A	32 (32.7 %)
B	45 (45.9 %)
C	21 (21.4 %)

The distribution of patients with HCC by AFP levels was known that majority of the HCC patients as many as 44 people (44.9%) have very high AFP levels that were >400 ng/ml. As shown in Figure 2.

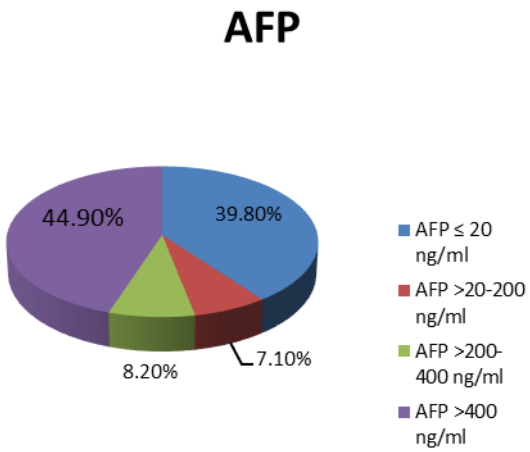

Figure 2. Distribution of HCC patients based on AFP levels

The profile of HCC patients by AFP levels showed that patients with AFP levels >400 ng/ml had younger age's average, mostly males, while the most commons etiology was hepatitis B and C, with high average of SGOT level, and generally had BCLC B staging. Meanwhile, normal AFP level of ≤20 ng/ml was found mostly in females, those with fatty liver and other etiology as well as BCLC A and C staging. Those with AFP level > 20-200 ng/ml had the highest bilirubin average and biggest tumor size, as shown in Table 3.

Table 3. Profile of HCC patients based on AFP level

Variables	AFP ≤20	AFP >20-200	AFP >200-400	AFP >400
Age (years, mean±SD)	51.82±9.101	55.29±11.557	63.13±16.19	49.91±11.397
Gender:				
Male	27 (69.2 %)	7 (100 %)	6 (75 %)	38 (86.4 %)
Female	12 (30.8 %)	0 (0 %)	2 (25 %)	6 (13.6 %)
Etioloy:				
Hepatitis B	11 (28.2 %)	5 (71.4 %)	5 (62.5 %)	25 (56.8%)
Hepatitis C	1 (2.6 %)	1 (14.3%)	1 (12.5 %)	5 (11.4 %)
Fatty liver	1 (2.6 %)	0 (0%)	0 (0 %)	0 (0%)
Others	26 (66.7 %)	1 (14.3%)	2 (25 %)	14 (31.8 %)
Laboratory:				
SGOT (U/L, mean±SD)	173.64±225.7	242.57±278.85	207.12±157.07	299.27±262.98
SGPT (U/L mean±SD)	67.23±62.22	68.86±27.93	84.12±67.81	80.62±83.59
Albumin (g/L, mean±SD)	2.78±0.69	3±0.49	2.74±0.46	3.02±0.66
Total Bilirubin (mg/dl, mean±SD)	3.97±5.16	6.27±13.84	1.785±1.22	5.9±7.9
Child Score:				
Child A	12 (30.8%)	2 (28.6 %)	2 (25 %)	16 (36.4 %)
Child B	18 (46.2%)	4 (57.1%)	4 (50 %)	19 (43.2 %)
Child C	9 (23.1%)	1 (14.3%)	2 (25 %)	9 (20.5 %)
Size of tumor (cm, mean ±SD)	10.90±5.94	14.75±7.85	10.38±6.76	10.92±5.68
Number of nodule:				
Solitary	21 (53.8%)	4 (57.1%)	4 (50 %)	22 (50 %)
Multiple	18 (46.2%)	3 (42.9 %)	4 (50 %)	22 (50 %)

Variables	AFP ≤20	AFP >20-200	AFP >200-400	AFP >400
Staging BCLC				
BCLC A	2 (5.1%)	0 (0%)	0 (0 %)	1 (2.3 %)
BCLC B	23 (59%)	5 (71.4%)	4 (50 %)	31 (70.5%)
BCLC C	5 (12.8%)	1 (14.3 %)	2 (25 %)	3 (6.8%)
BCLC D	9 (23.1%)	1 (14.3%)	2 (25%)	9 (20.5 %)

DISCUSSION

Hepatocellular carcinoma patients generally were 40-70 years old (El-Serag & Hashem, 2011). It was compatible with the results of this research that the average age of patients with HCC was 52 years old. The finding that most of HCC patients were elderly was associated with increased expression of *AR* and *PI3KR1* in the elderly that was an oncogenic regulator (Katsuka, et al., 2014). In addition, it was also because of hepatocellular carcinoma disease pathogenesis can take many years and the lack of early symptoms of the disease (Omata, et al., 2017). HCC generally affects males with an epidemiological ratio of 2.4 : 1 (Sareo, et al., 2014). This trend was due to the androgen receptor in males which was suspected to have an active path to the occurrence of HCC, immune response and epigenetics, which has higher rates among males (Omata et al., 2017). In addition, HCC patients were dominated by males because they tend to consume alcohol and smoking as well as having more visceral fat, which is a risk factor of HCC (Oemanti, et al., 2011).

Among the HCC patients it was found that the most common etiology was hepatitis B. Several meta-analyses also demonstrated that the risk of HCC was 15-20 times greater among HBV-infected individuals compared to uninfected population. Therefore, prolonged duration of HBeAg positivity or high HBV-DNA levels may be associated with an increased risk of HCC.

Hepatitis B becomes the primary etiology of HCC because the virus can encode oncogenic processes by the double mutations in the basal core, furthermore leads to hepatocarcinogenesis (Tseng, et al., 2012). The second common etiology was other diseases which include diabetes mellitus, alcohol addiction, and obesity that can develop steatohepatitis and produce proinflammatory agents, leading to carcinogenesis (Mittal, et al., 2015).

HCC patients generally had higher levels of SGOT, SGPT and bilirubin and low albumin levels that are associated with liver damage. SGOT and SGPT in HCC patients in this study were generally high and correlated with the parenchymal inflammatory process from the result of carcinogenesis (Okajima, et al., 2015), while most patients had Child B liver function with bad liver damage.

Reviewing the characteristics of the tumor, it was known that the majority of the patients had tumor size >5 cm, solitary nodule and BCLC B staging. Minimum numbers of HCC patients with small nodule size were due to the limited examination for diagnosis (Kumar, et al., 2014). Profile of serum AFP level in HCC patients obtained a very high level. AFP or> 400 ng ml had the youngest average age. Research by Minami, et al., (2015) also showed the similar finding, and this was because the young patients more often had positive HbsAg (Minami, et al., 2015). From a gender perspective, AFP levels above 400 ng/ml belonged to male patients, and normal AFP levels below 20 ng/ml belonged to the majority of female patients. This was contradictory to the research from Shata *et al.*, (2014) who found that there was no difference in AFP levels between men and women (Shata, et al., 2014).

AFP levels profile based on etiology was showed that the AFP level> 400 ng/ml had common etiology of hepatitis B and hepatitis C. High AFP levels in patients with hepatitis infection reflect necroinflammation and regeneration process. High AFP levels in hepatitis B virus infection is associated with mutations in tumor suppressor gene p53 and β-catenin (Minami, et al., 2015). In terms liver of function, AFP levels above 400 ng/ml belonged to patients with high SGOT average and descriptively, there was a tendency to elevated levels of SGOT, SGPT, albumin to AFP. This was consistent with a studies of Pramudya, et al., (2015) who found a significant difference between the levels of SGPT and albumin with increasing levels of AFP (Pramudya, et al., 2015). When the liver function was with assessed by the Child-Pugh classification, it was found that AFP >400 ng/ml was in almost all patients with various liver functions.

Profiles of AFP level based on characteristics of the tumor showed that the AFP levels >400 ng/ml was dominated with BCLC B staging. Descriptively, there was no difference in AFP levels based on the number of nodules because patients with solitary or multiple nodules had AFP levels >400 ng/ml. AFP levels >20-200 ng/ml had the largest average tumor size. This was contrasted with the results of Abbasi's study which showed a significant correlation between AFP levels and tumor size (Abbasi, et al., 2011). The relationship between tumor size and AFP was caused by the high expression of HMGA1 which was a protein that supports oncogenic transformation and progression of cancer that leads to massive liver damage. Increasingly massive liver damage further increased AFP levels (Andreozzi, et al., 2016). The limitation of this study was the small number of samples, so it was necessary to do periodic studies for a longer time to obtain a larger sample to have more representative and meaningful results.

CONCLUSION

Profiles of AFP levels in HCC patients indicated that those with very high AFP levels had the youngest average age, with the most common etiologies of hepatitis B, male gender, high SGOT mean, and BCLC-B staging. On the other hand, the patients of AFP levels >20-200 had the largest average tumor size. In addition, most female patients and patients with fatty liver and other etiology had normal AFP levels or ≤20 ng/ml.

REFERENCES

Abbasi, A., Bhutto, A., Butt, N., Munir, S., 2011. Correlation of serum alfa feto protein and tumor size in hepatocellular carcinoma. Journal of Pakistan MA, 62: 33–36. doi: 10.17957/TPMJ/16.3178.

Andreozzi, M., Quintavalle, C., Benz, D., Quagliata, L., Matter, M., Calabrese, D., Tosti, N., Ruiz, C., Tomillo, L., Fusco, A., Heim, MH., Ng, KY., Pallante, P., Terracciano, L., Piscuoglio, S., 2016. HMGA1 expression in human hepatocellular carcinoma correlates with poor prognosis and promotes tumor growth and migration in In Vitro models. Neoplasia Journal, 18(12): 724–731. doi: 10.1016/j.neo.2016.10.002.

El-Serag and Hashem., 2011. Hepatocellular carcinoma. The New England Journal of Medicine, 365: 1118–1127. doi: 10.1056/NEJMra1001683.

European Association For The Study of the Liver., 2012. Clinical practice guidelines: Management of hepatocellular carcinoma. J Hepatol, 56: 908–943. doi: 10.1016/j.jhep.2011.12.001.

Katsuka, E., Tanaka, S., Mogushi, K., Matsumura, S., Ban, D., Ochiai, T., Irie, T., Kudo, A., Nakamura, N., Tanaka, H., Tanabe, M., Arie, S., 2014. Age-related clinicopathologic and molecular features of patients receiving curative hepatectomy for hepatocellular carcinoma. The American Journal of Surgery, 208: 450–456. doi: 10.1016/j.amjsurg.2014.01.015.

Kumar, A., Acharya, S.K., Singh, S.P., Saraswati, VA., Arora, A., Duseja, A., Goenka, M.K., Jain, D., Kar, P., Kumar, M., Kumaran, V., Mohandas, K.M., Panda, D., Paul, S.B., Ramachandran, J., Ramesh, H., Rao, P.N., Shah, S.R., Sharma, H., Thandassery, RB., 2014. The Indian National Association for study of the liver (INASL) consensus on prevention, diagnosis, and management of hepatocellular carcinoma in India: The Puri Recommendation. Journal of Clinical and Experimental Hepatology, 4: 3–26. doi: 10.1016/j/jceh.2014.04.003.

Minami, T., Tateishi, R., Kondo, M., Nakagomi, R., Fujiwara, N., Sato, M., 2015. Serum alpha-fetoprotein has high specificity for the early detection of hepatocellular carcinoma after hepatitis C virus eradication in patients. Medicine (Baltimore) Journal,94. doi: 10.1097/MD.0000000000000901.

Mittal, S., Sada, YH., El-Serag, HB., Kanwal, F., Duan, Z., Temple S., 2015. Temporal trends of non-alcoholic fatty liver disease-related hepatocellular carcinoma in the veteran affairs population. Clinical Gastroenterology Hepatology Journal, 13: 594–601. doi: 10.1016/j.cgh.2014.08.013.

Oemanti, R., Rahajeng, E., Kristanto, A.Y., 2011. Prevalensi tumor dan beberapa faktor yang mempengaruhinya di Indonesia. Balai Penelitian dan Pengembangan Kesehatan: 190–204.

Okajima, C., Arij, S., Tanaka, S., Matsumura, S., Ban, D., Ochial T., Irie, T., Kudo, A., Nakamura, N., Tanabe, M., 2015. Prognostic role of child-pugh score 5 and 6 in hepatocellular carcinoma patients who underwent curative hepatic resection. The American Journal of Surgery, 209: 99–205. doi: 10.1016/j.amjsurg.2014.03.009.

Omata, M., Cheng, AL., Kokudo, N., Kudo, M., Lee, JM., Jia, J., Tateishi, R., Han, K., Chawla, YK., Shiina, S., Jafri, W., Payawal, DA., Ohki, T., Ogasawara, S., Chen, PJ., Lesmana, CRA., Lesmana, LA., Gani, RA., Obi, S., Dokmeci, AK., Sarin, SK., 2017. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: A 2017 Update. Hepatology International Journal, 11: 317–370. doi: 10.1007/s12072-017-9799-9.

Pramudya, D., Kholili, U., Nusi, I.A. 2015. Korelasi kadar alfa feto protein dan ukuran tumor pada karsinoma hepatoseluler. Fakultas Kedokteran Universitas Airlangga.

Sareo, T., Devi, Y., Singh, L., 2014. Hepatocellular carcinoma in situs inversus totalis- A case report, Med J Indonesia, 23(1): 48. doi: 10.13181/mji.v23i1.690.

Shata, Y., Mudawi, S., Fedail, S., Hassan, BA., Ismaeil, AM., Ahmed, MA., 2014. Assessment of lens culinaris agglutinin- reactive fraction of alpha feto protein as an early diagnosis marker for hepatocellular carcinoma among sudanese patients with chronic liver disease. Cancer and Oncology Research, 2(1): 1–6. doi: 10.13189/cor.2014.020101.

Tseng, TC., Liu CJ., Chen, CL., Wang, CC., Su, TH., Kuo, SF., 2012. Serum hepatitis B virus-DNA levels correlate with long-term adverse outcomes in spontaneous hepatitis B e antigen seroconverters. Journal Infectious Disease, 205: 54–63. doi: 10.1093/infdis/jir687.

Wong, GL., Chan, HL., Tse, YK., Chan, HY., Tse, CH., Lo, AO., Wong, VW., 2014. On-treatment alpha-fetoprotein is a specific tumor marker for hepatocellular carcinoma in patients with chronic hepatitis B receiving entecavir. Hepatology Journal, 59: 986–995. doi: 10.1002/hep.26739.