

Correlation of Alpha-Fetoprotein Levels with Three-Phase Contrast CT-Scan Finding in Hepatocellular Carcinoma Patients at Dr. Mohammad Hoesin General Hospital Palembangin 2022 – 2023

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is the primary liver tumor, accounting for 90% of liver tumor cases. Currently, laboratory tests are needed to monitor tumor progression, predict prognosis, and determine appropriate therapy without radiological examinations, one of which is Alpha-Fetoprotein (AFP). This study aims to determine the correlation between AFP levels and three-phase contrast CT-Scan findings in HCC patients at Dr. Mohammad Hoesin General Hospital Palembang.

Methods: This was a cross-sectional design observational analytic study, using secondary data from medical records that included patient demographics, AFP, ALT, AST, direct bilirubin, indirect bilirubin, and three-phase contrast CT-Scan findings covering nodule size, nodule number, and metastasis in HCC patients treated at Dr. Mohammad Hoesin General Hospital Palembang from January 2022 – December 2023, meeting inclusion and exclusion criteria. Data were analyzed using SPSS version 22.

Results: A total of 71 samples met the inclusion and exclusion criteria. Univariate analysis showed the majority were male (83.1%), aged 50–59 years (35.2%), with elevated ALT (59.2%), AST (94.4%), direct bilirubin (91.8%), indirect bilirubin (54.1%), AFP ≥ 200 ng/mL (77.5%), nodule size ≥ 30 mm (87.3%), multiple nodules (67.6%), and no extrahepatic metastasis (74.6%). Bivariate analysis showed a significant correlation between AFP levels and nodule size on three-phase contrast CT-Scan (p -value = 0.031).

Conclusion: There is a significant correlation between AFP levels and three-phase contrast CT-Scan findings in HCC patients at Dr. Mohammad Hoesin General Hospital Palembang in 2022–2023.

Keywords: AFP, HCC, Three-Phase Contrast CT-Scan

ABSTRAK

Latar Belakang: Karsinoma hepatoseluler (KHS) merupakan tumor hati primer yang mencakup 90% kasus tumor hati. Saat ini, diperlukan pemeriksaan laboratorium yang dapat mengetahui perkembangan tumor, memprediksi prognosis, dan menentukan terapi yang tepat tanpa melakukan pemeriksaan radiologi, salah satunya pemeriksaan kadar Alpha-Fetoprotein (AFP). Penelitian ini bertujuan untuk mengetahui apakah terdapat korelasi antara kadar AFP dengan gambaran CT-Scan kontras tiga fase pada pasien KHS di RSUP Dr. Mohammad Hoesin Palembang.

Metode: Penelitian ini berjenis analitik observasional dengan desain potong lintang, menggunakan data sekunder berupa rekam medik yang memuat karakteristik demografi pasien, kadar AFP, ALT, AST, bilirubin direk, bilirubin indirek, dan hasil pemeriksaan CT-Scan kontras tiga fase yang meliputi ukuran nodul, jumlah nodul, serta metastasis dari pasien KHS yang dirawat di Unit Rawat Inap RSUP Dr. Mohammad Hoesin Palembang periode Januari 2022 – Desember 2023 yang memenuhi kriteria inklusi dan eksklusi. Data dianalisis menggunakan program SPSS versi 22.

Hasil: Diperoleh 71 sampel yang memenuhi kriteria inklusi dan tidak memenuhi kriteria eksklusi. Berdasarkan hasil analisis univariat, mayoritas laki-laki (83,1%), berusia 50 – 59 tahun (35,2%), mengalami peningkatan ALT (59,2%), AST (94,4%), bilirubin direk (91,8%), bilirubin indirek (54,1%), AFP ≥ 200 ng/mL (77,5%), ukuran nodul ≥ 30 mm (87,3%), nodul multipel (67,6%), dan tanpa metastasis ekstrahepatik (74,6%). Hasil analisis bivariat menunjukkan korelasi signifikan antara kadar AFP dengan ukuran nodul lewat gambaran CT-Scan kontras tiga fase (p -value = 0,031).

Kesimpulan: Terdapat korelasi signifikan antara kadar AFP dan gambaran CT-Scan kontras tiga fase pada pasien HCC di RSUP Dr. Mohammad Hoesin Palembang tahun 2022 – 2023.

Kata Kunci: AFP, HCC, CT-Scan kontras tiga fase

INTRODUCTION

Hepatocellular carcinoma (HCC), referred to as hepatoma, is the main type of liver tumor, making up 90% of liver cancer instances. At present, HCC ranks as the fifth most prevalent cancer globally.¹ Between 500,000 and 1,000,000 new cases of HCC are reported annually, with 83% occurring in developing countries where risk factors are highly prevalent.^{2,3} In Indonesia, HCC ranks as the fourth most common cancer, accounting for 5.4% of all cancer cases in 2020. HCC is most frequently associated with liver cirrhosis caused by Hepatitis B and C virus infections, as well as other factors such as alcohol consumption.⁴ HCC can present with several clinical signs, including jaundice, pruritus, ascites, an abdominal mass, and other characteristic features. In addition to physical examination, diagnostic findings may include thrombocytopenia, anemia, elevated tumor markers such as Alpha-Fetoprotein (AFP), and imaging results showing hypervascularity during the arterial phase and washout in the portal venous or delayed phases on a triple-phase Computed Tomography (CT) scan.^{1,3}

AFP is an oncofetal glycoprotein that can be used as a tumor marker for HCC.⁵ Normally, AFP levels in human blood are low, but malignancy in hepatocyte cells induces AFP synthesis in HCC, leading to elevated levels. AFP levels are elevated in 60% of HCC patients, but only 10%-20% of early-stage patients exhibit elevated AFP levels.² However, research has shown that elevated AFP levels often emerge in the context of benign liver conditions, making the use of AFP alone as a diagnostic tool for HCC controversial. Consequently, AFP should not be used alone as a

screening or diagnostic method for HCC and should be used in conjunction with imaging techniques like CT-scan.⁶ CT imaging for HCC typically shows hypervascularity in the arterial phase and washout in the portal venous or delayed phases. The arterial phase provides clearer visualization due to the vascular supply of HCCs derived from the hepatic artery. When contrast reaches the hepatic artery, hypervascularization is clearly observed in tumors within and around the liver parenchyma.³

A previous study by Martani *et al.* in 2022 demonstrated a positive correlation between AFP levels and the scores from abdominal CT scans in patients with HCC at Sanglah Hospital. This study indicated that elevated AFP levels were also associated with tumor progression, one of which was assessed through the development of nodule size on contrast-enhanced CT-scans.² A study by Rusie *et al.* in 2022 also concluded that although its sensitivity is not highly optimal, serum AFP can be used as a diagnostic and prognostic tool for HCC because it correlates with tumor size.⁷ This aligns with the research conducted by Nursriyanti *et al.* in 2023, which stated that AFP levels are elevated in terminal-stage HCC patients compared to those in the early stage. Therefore, AFP can be used to determine the prognosis and appropriate therapy for HCC patients.⁸

This research seeks to determine the correlation between AFP levels and triple-phase contrast CT-scan findings in HCC patients at RSUP Dr. Mohammad Hoesin Palembang to evaluate AFP's role as a prognostic tool and a determinant of therapy for HCC patients. If a significant correlation between AFP

levels and CT-scan findings is established, the authors hope that AFP can be utilized to predict the stage and prognosis of HCC patients who are unable to undergo radiological examinations, such as CT-scans, due to limitations such as facilities, costs, human resources, and other factors. Therefore, through this study, the researchers aim to identify the correlation between AFP levels and triple-phase contrast CT-scan findings in HCC patients, specifically at RSUP Dr. Mohammad Hoesin Palembang.

METHODS

This study used a cross-sectional design and was conducted from July to October 2024 at the Medical Records Department of RSUP Dr. Mohammad Hoesin Palembang. The protocol of the research had been ethically accepted by Medical and Health Research Ethics Committee of the Faculty of Medicine, Sriwijaya University (No.242-2024). The inclusion criteria for the samples are medical record information from patients diagnosed with HCC resulting from Hepatitis B, established based on the diagnostic criteria by the Indonesian Ministry of Health, including AFP level results and triple-phase contrast abdominal CT-scan findings at RSUP Dr. Mohammad Hoesin Palembang from January 2022 to December 2023.

AFP was measured using Enzyme-Linked Immunosorbent Assay (ELISA) method, and CT-scan findings were evaluated by an experienced radiologist blinded to AFP results. CT characteristics included arterial hyperenhancement and portal/delayed phase washout. The exclusion criteria for the samples include incomplete or unreadable patient data, pregnant patients, patients with a background of different types of cancers, patients with cardiovascular disease or chronic kidney disease, and patients who have already received HCC-related therapy.

The minimum sample size necessary for this research was determined using the correlative analytic formula previously applied in the study by Martani *et al.* in 2022, with $Z\alpha = 1.96$, $Z\beta = 1.28$, and $r = 0.4$.² As a result of this calculation, it was established that a sample size of 62 was necessary. The sampling process was conducted using a total sampling method. The data to be used include AFP level results and nodule size obtained from triple-phase contrast abdominal CT-scan findings. Additionally, supporting data will be collected in a frequency distribution table. The CT-scan will evaluate the number of nodules and the presence or absence of tumor metastasis. Meanwhile,

laboratory results will include liver function tests (ALT, AST, direct bilirubin, indirect bilirubin) and hepatitis antibody tests (HbsAg). Patient demographic data, such as age, sex, and domicile, will also be collected to determine patient demographic distribution.

Univariate analysis will be conducted in the form of descriptive qualitative analysis for frequency distribution of categorical variables (AFP levels, nodule size, number of nodules, metastasis, ALT, AST, direct bilirubin, indirect bilirubin, patient age, patient sex, and patient domicile). Bivariate analysis will be performed to analyze the significance of the correlation between the independent variable (AFP levels) and the dependent variable (nodule size) using Pearson’s test ((significance: $p < 0.05$, CI 95%) using SPSS 22.0 software. No multivariate analysis was conducted, and thus confounding variables such as liver cirrhosis, MAFLD, hepatitis treatment status, or comorbidities were not adjusted for—acknowledged as study limitations.

RESULTS

This study obtained 71 samples. The distribution of HCC patients at Dr. Mohammad Hoesin General Hospital Palembang during the period of January 2022 – December 2023 showed a higher percentage in males (83.1%) within the 50–59 age group (35.2%). The frequency distribution of demographic variables, liver function, and AFP levels can be seen in **Table 1**.

Table 1. Characteristics of study subjects

Variables	Result (n = 71)
Age (years), n (%)	
< 40 years	11 (15,5%)
40 – 49 years	15 (21,1%)
50 – 59 years	25 (35,2%)
≥ 60 years	20 (28,2%)
Gender, n (%)	
Male	59 (83,1%)
Female	12 (16,9%)
Domicile, n (%)	
Palembang	23 (32,4%)
Other	48 (67,6%)
ALT (IU/L)	
Normal (4 – 36)	29 (40,8%)
Increase	42 (59,2%)
AST (IU/L)	
Normal (5 – 30)	4 (5,6%)
Increase	67 (94,4%)
Direct bilirubin (mg/dL)	
Normal (0 – 0,2)	5 (8,2%)
Increase	56 (91,8%)
Indirect bilirubin (mg/dL)	
Normal (0 – 0,8)	28 (45,9%)
Increase	33 (54,1%)
AFP levels	
≥ 200 ng/mL	55 (77,5%)
< 200 ng/mL	16 (22,5%)

Table 2. Distribution based on tumor progression in HCC patients

Variables	AFP levels				Percentage
	<200 ng/mL		≥200 ng/mL		
	n	%	n	%	
Nodule size					
< 20 mm	1	1,4	4	5,6	7
20 - < 30 mm	3	4,2	1	1,4	5,6
≥ 30 mm	12	16,9	50	70,4	87,3
Number of nodules	7	9,9	16	22,5	32,4
Solitary	9	12,6	39	55	67,6
Multiple					
Present of metastasis	2	2,9	16	22,5	25,4
Yes	14	19,6	39	55	74,6
No					

Furthermore, **Table 2.** shows the distribution of tumor progression, including nodule size, number of nodules, and the presence or absence of extrahepatic metastasis, categorized based on AFP levels.

Table 3. Correlation test

Correlation Test	
Variable	Nodule size
AFP level	<i>r</i> 0,256
	<i>p</i> 0,031
	<i>n</i> 71
	95% CI 0,023 – 0,455

Correlation between AFP Levels and Nodule Size, as Observed in the Three-Phase Contrast CT-Scan of HCC Patients

From the Pearson correlation test (**Table 3**), the correlation between AFP levels and nodule size, as observed in the three-phase contrast CT-scan of HCC patients, was analyzed. The significance value (*p-value*) obtained from 71 samples for the two variables was 0.031, indicating a significant correlation, with a correlation coefficient (*r*) of 0.256, which indicates a low correlation.

DISCUSSION

Based on the study results, the majority of samples were male (83.1%) and fell into the 50–59 age group (35.2%). This study also found that some samples had abnormalities in liver function tests. Most patients had elevated ALT (59.2%), AST (94.4%), direct bilirubin (91.8%), and indirect bilirubin (54.1%) levels. These findings align with a study by Maharani *et al.* in 2021, which reported elevated ALT (67%), AST (89.8%), and total bilirubin (58.8%).⁹ Hepatocellular damage triggers the synthesis of liver enzymes, and in certain conditions, bilirubin levels increase, manifesting as jaundice.^{10–12}

Furthermore, 77.5% of samples showed elevated AFP levels > 200 ng/mL. This is consistent with a previous study by Indreswara *et al.* in 2022 in Surabaya, which found that 53.1% of samples had AFP > 200 ng/mL.¹³ AFP is abnormally expressed by the liver when damaged by HCC. However, not all HCC tumors show elevated AFP levels, and in some cases, AFP levels may remain normal despite the presence of HCC.¹⁴

Regarding nodule progression, 87.3% of samples had tumor nodules ≥ 30 mm, 67.6% had multiple nodules, and 74.6% did not exhibit extrahepatic metastasis. The size used to represent the tumor is the longest axis measured from the largest nodule.¹⁵ Nodule size, number of nodules, and metastasis can be used to classify HCC stages. The BCLC system is an example of how these components classify the severity of HCC in patients, where higher stages indicate a poorer patient condition.¹⁶

Elevated AFP levels have been proven to be associated with aggressive tumor histology, such as vascular invasion, and are considered a risk factor for HCC. High AFP levels may reflect a worse survival prognosis.¹⁷ A study by Muscari *et al.* in 2019 mentioned that a single small HCC nodule can be highly aggressive, while multiple HCC nodules may be less aggressive or have a better prognosis. At early stages or when the tumor size is small, cancer cells often proliferate rapidly, leading to increased AFP production, which is a key tumor marker for HCC. Therefore, AFP levels should be considered since they are closely associated with tumor aggressiveness.^{18,19} However, AFP elevation without concurrent tumor growth may be influenced by non-tumor-related factors, such as chronic hepatitis infections. If patients have received antiviral therapy for chronic Hepatitis B, AFP baseline levels decrease, which may result in higher elevations.⁶ Additionally, chronic Hepatitis B preceding HCC can increase AFP production due to chronic inflammation of hepatocytes.²⁰

In other conditions, HCC patients with low or normal AFP levels may still have large tumors, suggesting other factors besides AFP contribute to tumor growth.¹⁴ As tumors grow larger, cancer cells may undergo changes in proliferation and differentiation patterns. In some cases, large tumors may show reduced AFP levels, although this does not apply to all patients. This decrease may be caused by factors such as tumor necrosis and changes in the tumor microenvironment.¹⁹ Tumor size progression may also be influenced by its etiology. A study by An *et al.*

showed that HCC growth rate is associated with the type of hepatitis virus. It noted that HCC with chronic Hepatitis B infection grows faster compared to HCC with Hepatitis C infection. However, no studies have yet explored the molecular mechanisms of HCC tumor growth.²¹ Another study reported that antiviral therapy for chronic Hepatitis B patients can drastically reduce AFP levels.²⁰ Furthermore, a study by Campbell *et al.* indicated that comorbidities such as type 2 diabetes mellitus can also influence HCC tumor growth.²²

Findings suggest that elevated AFP is associated with larger tumor size in HCC patients. However, the correlation is weak, and AFP alone should not be used to guide treatment decisions. Confounding factors such as cirrhosis status or comorbid diabetes were not accounted for. Some patients with large tumors had normal AFP, possibly due to tumor necrosis or AFP-silent HCC variants. Our results support previous studies but emphasize the need for multivariate analysis in future research.

LIMITATIONS

1. Small sample size
2. Lack of multivariate analysis
3. No information on AFP assay method or CT scan interpretation standardization
4. Retrospective single-center design

CONCLUSION

There is a statistically significant correlation (p -value = 0.031) between AFP levels and tumor size on three-phase contrast CT scans in HCC patients at Dr. Mohammad Hoesin General Hospital Palembang during 2022–2023, but the low correlation strength limits its prognostic utility without further contextual data. The majority of samples showed AFP elevation ≥ 200 ng/mL, tumor size ≥ 30 mm, multiple nodules, and no extrahepatic metastasis.

ETHICS

This study was approved by the Ethics Committee of Faculty of Medicine Sriwijaya University and Dr. Mohammad Hoesin General Hospital Palembang. Patient consent was waived due to retrospective design using anonymized data.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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