Correlation of Abdominal CT scan Score and Alpha-fetoprotein Levels in Hepatocellular Carcinoma

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Abstract

Objective: To assess the correlation between the Alpha-fetoprotein (AFP) level and characteristics of liver lesions listed in the abdominal computed tomography (CT) scan scores in hepatocellular carcinoma.

Methods: This was a retrospective analytic observational study with a cross-sectional design conducted at Sanglah Hospital in January 2017–January 2021. Subjects were patients diagnosed with hepatocellular carcinoma based on clinical and laboratory features. Samples were taken by consecutive sampling. The results of the abdominal CT scan were read by two radiologists with a predetermined abdominal CT scan scoring system. The AFP level data were taken at a maximum of 5 days before an abdominal CT scan was performed.

Results: A total of 64 subjects were included in this study. The mean serum AFP level was 1,000 IU/mL (range 0.54–61830 IU/mL). The mean abdominal CT scan score by examiner one was 10.093±5.59, while the examiner two provided a score of 10.281±5.45. The difference in mean CT scan scores between the two examiners was very low and insignificant (mean difference score -0.188; 95% CI -1.894–1.519). The rho Spearman value was 0.918 (p<0.001) between serum AFP levels and abdominal CT scan scores. In the partial correlation, the value of r=0.678 (p<0.001) was obtained after controlling for body mass index (BMI), age, and sex variables.

Conclusions: There is a strong positive correlation between serum AFP levels and abdominal CT scan scores in hepatocellular carcinoma patients. Further research is needed with a prospective design to reduce research bias.

Keywords: Abdominal computed tomography, alpha-fetoprotein, diffuse infiltrative, hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) or liver cancer is the type of cancer that causes the most deaths from cancer, which is estimated at 781,631 deaths (8.2% of the total number) in 2018.[1] HCC is the fifth most common cancer in men and the ninth in women with an estimated worldwide incidence ranging from 500,000 to 1,000,000 new cases per year. HCC is the most common type of liver cancer globally, accounted around 75% of all liver cancers.[2] Incidence rate of liver cancer per 100,000 person-years in 2018 was estimated at 9.3 whereas the corresponding mortality rate was 8.5.[1]

Hepatocellular carcinoma is also a major health problem in Asia with hepatitis B virus (HBV) infection as the main cause.[3] It was

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estimated that around 350 million individuals are chronically infected with HBV, and 170 million individuals were at risk for developing cirrhosis and hepatocellular carcinoma.[4] Hepatocellular carcinoma is a malignancy with a poor prognosis because it is often diagnosed at an advanced stage and usually cannot be treated.[5]

Radiological examination is one of the methods used for the diagnosis of HCC.[6] The sensitivity of computed tomography (CT) scan for diagnosing HCC ranges from 67.5% (55–80%) and specificity reaches 92.5% (89–96%), while magnetic resonance imaging (MRI) has a sensitivity of 81% and specificity 85%. The feature of HCC in CT radiology is an encapsulated hypervascular mass in the arterial phase.[7] HCC has 3 (three) main types of growth patterns that can be seen radiologically: massive solitary, multinodular, and diffuse infiltrative.[8] HCC with a solitary pattern shows a single mass image with or without satellite nodules. Multinodular HCC shows multiple nodules involving large areas of the liver.[9]

Alpha-fetoprotein (AFP) is the most frequently used tumor marker for diagnosing hepatocellular carcinoma.[9] Elevated AFP levels are found in about 60% of HCC patients, and only about 10–20% of early-stage HCC patients have abnormal AFP levels.[10,11] The AFP cut-off value of 20 ng/mL showed good sensitivity but low specificity, while the cut-off value of 200 ng/mL showed high specificity, but lost sensitivity.[9] Thus, AFP has poor sensitivity in detecting liver tumors that are small in size and non-specific in diagnosing HCC, especially in the early stages.[12] Also, AFP alone for screening HCC is controversial because elevated AFP levels can occur in other benign liver conditions.

Given the performance, AFP alone is not sufficient for diagnosing HCC. Therefore, contemporary imaging techniques, such as CT scans, are needed for additional screening. Research shows a significant correlation in HCC patients between AFP levels and the characteristics of liver lesions, especially in growth patterns and the presence of portal vein thrombus using a CT scan.[13,14] Therefore, this study aims to assess the correlation between AFP levels and the characteristics of liver lesions through a CT scan in HCC at Sanglah Hospital.

Methods

This study is an analytic observational study with a retrospective cross-sectional design that assessed the abdominal CT scan of hepatocellular carcinoma patients and at the same time examined serum AFP. Based on the assessment of the two variables, an analysis was carried out to assess the relationship. The research location was at the Radiology Installation of Sanglah Hospital Denpasar in January 2017–January 2021 with the ethical clearance protocol number 2021.02.1.0260. The subjects of this study were patients diagnosed with hepatocellular carcinoma who met the inclusion and exclusion criteria, then taken consecutively until completed the number of samples was.

Inclusion criteria were all patients with hepatocellular carcinoma diagnosed through physical examination, liver function tests, and serum AFP levels were checked. Serum AFP was conducted before the abdomen CT scan examination. In addition, exclusion criteria were incomplete medical records, pregnancy, and history of other malignancies, chronic heart disease, or chronic kidney disease.

In this study, the type I error was set at 5%, the one-way hypothesis, so that $Z\alpha$ = 1.96. The type II error is set at 10%, then $Z\beta$=1.28. This study refers to previous research, where a significant correlation of 0.40 was obtained.[13] The sample size for correlative analysis refers to the sample determination formula as follows:

$$\left[\frac{Z_\alpha + Z_\beta}{0{,}5 * \ln\left[\frac{1+r}{1-r}\right]}\right]^2 + 3$$

The minimum sample size required in this study is 64 people. The tools used in this study were patient medical records, data collection sheets (numbers, patient initials, AFP serum level data from medical records), and the Picture Archiving and Communication System (PACS) at Sanglah Hospital to view the results of abdominal CT-Scans in patients. Abdominal CT scans taken with coronal and sagittal reformat axial slices by a Philips Brilliance 64 CT Scan are taken precontrast phase, the arterial phase at 35–37 seconds after contrast injection, venous phase 80–95 seconds after injection and phase delay 120 seconds after injection. Also, with the CT scan tool, Siemens Somatom Go-Top 128 slices were taken precontrast phase, the arterial phase at 23-27 seconds after contrast injection, the venous phase at 60-75 seconds after injection, and the delay phase at 80–95 seconds after injection. Abdominal CT scan scoring of the

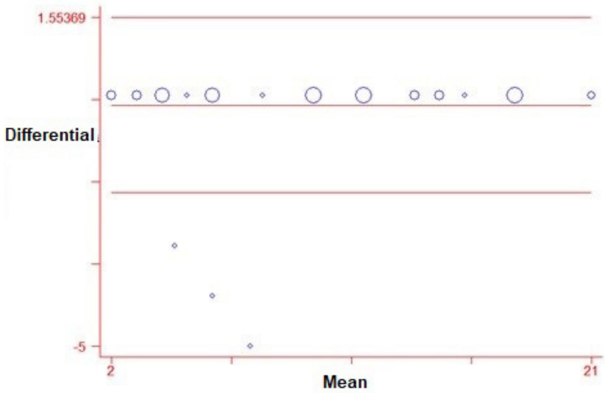

Fig. 1 Scatter Plot of the Bland-Altman Test on HCC with Abdominal CT scan

HCC was distinguished as growth type and main characteristic. HCC growth type consists of multinodular with uniform nodule size (score=1), a large massive nodule that fills one lobe of the liver (score=2), and diffuse infiltrative as small nodules (score=3). Main characteristics (score=1) were divided into arterial enhancement, disrupted capsule, thrombus tumor, irregular shape, satellite nodules, extrahepatic metastases, tumor diameter (≤2 cm = 0, >2 cm = 1), and number ≤3 pieces = 0, >3 pieces = 1). Data analysis in this study consisted of descriptive statistical analysis, Kolmogorov-Smirnov normality test, correlation test and Bland Almant limit of agreement test for the consistency test of examiner one and examiner 2, Pearson correlation test to assess the direction and strength of the correlation between AFP levels and the picture score. Abdominal CT scan in HCC, and multiple linear regression test to determine the relationship between AFP levels and abdominal CT scan scores in HCC by considering the variables of age, sex, and BMI. All of the above analysis stages use the help of IBM Statistical Package for the Social Science (SPSS) statistics 24.0.

Results

This study was conducted using medical record data at Sanglah Hospital Denpasar from January 2017–January 2021, with a total number of samples that met the inclusion criteria of 64 subjects (Table 1).

To determine the results consistency of CT scan scores, a reliability test was conducted between examiner one and examiner two using the Bland–Altman test and obtained a rho value of 0.987 (Fig.1). The result indicates a very high concordance between examiner one and two. The mean difference in CT scan scores between examiner one and examiner two was -0.188 (95% CI -1.894–1.519) (10.093±5.59 vs. 10.281±5.45), which indicates a very low and insignificant difference in mean scores between the two examiners (Fig.1).

In Fig. 1, generally, there is a very high concordance between the two examiners, i.e., most of the patients had the same score from the examinations by both examiners. Meanwhile, three samples have a fairly large difference in scores (3, 4, and 5 points). However, statistically, this difference was not significant. The correlation test for abdominal CT scan scores and AFP levels used the Spearman test because the AFP levels were not normally distributed. The Spearman test found that r=0.843, which indicates a high correlation between CT scan scores and AFP levels (Fig. 2). Furthermore, the p-value <0.001 indicates that this correlation is statistically significant.

Table 1 Basic Characteristics of Research Subjects

Characteristics	n=64
Gender	
Male, n (%)	51 (79.7)
Female, n (%)	13 (20.3)
Age (years), mean ± SB	56±11
BMI	
Underweight, n (%)	58 (90.6)
Normal, n (%)	4 (6.3)
Obese, n (%)	2 (3.1)
Serum AFP level (IU/mL), median (min-max)	1000 (0.54–61830)

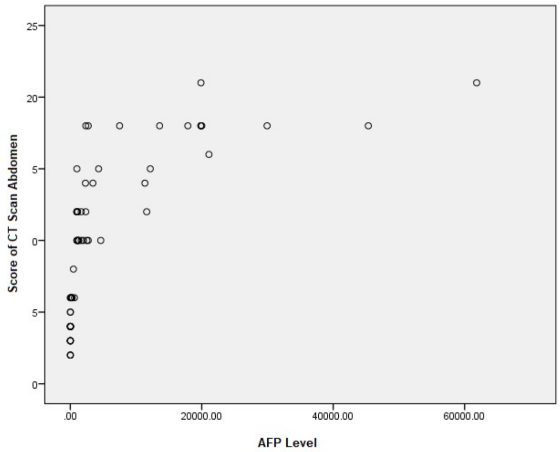

Fig. 2 Spearman Correlation Graph between AFP Levels and Abdominal CT scan Scores

A partial correlation regression test was performed to assess the relationship between abdominal CT scan scores and AFP levels by taking into account confounding variables (age, sex, and BMI) and obtained p<0.001 (r=0.460) for abdominal CT scan scores (Table 2). Meanwhile, no confounding variable was significantly correlated with increasing AFP levels (p>0.05).

Discussion

This study involved 64 subjects of patients with hepatocellular carcinoma (HCC). There were more male subjects (79.69%) in this study, almost four times more than female subjects (20.3%) (Table 1). This is by the epidemiology of HCC in general, where the incidence of HCC in men is 2–4 times the incidence in women.[2]

In most populations, the incidence of HCC is directly correlated with age up to 75 years of age. The median age at diagnosis in males is 60–64 years, while the median age in females is 65–69 years.[15] However, the median age at diagnosis is lower in Africa, i.e., 58 years in Egypt and 46 years in other African countries.[16]

Table 2 Partial Correlation between AFP Levels and Abdominal CT scan Scores in HCC

Variable	r-partial	P
AFP level	0.460*	<0.001*
Age	0.024	0.223
Gender	0.0004	0.879
BMI	0.005	0.566

*controlled for age, gender, and BMI

In this study, the mean age of the subjects was 56 years. In this study, most of the patients had a BMI classified as underweight (90.6%) compared to a normal or obese BMI. Meanwhile, according to the literature, obesity is an independent risk factor for HCC in the general population. Obesity is also a risk factor for the development of HCC from chronic viral hepatitis.[15] However, weight loss is also a common problem in cancer patients, including HCC, in 54% of cancer patients and 80% of cancer patients. patients with advanced cancer.[1] Therefore, the high number of patients with underweight BMI in this study can be explained by the weight loss commonly experienced by these cancer patients.

Hepatocellular carcinoma can produce AFP values ranging from normal to >100,000 ng/mL, approximately 30% of patients have normal AFP levels at diagnosis and can remain low, even into advanced stages. AFP >400-500 ng/mL is considered a diagnostic threshold for HCC.[15,17] In this study, median AFP levels were 1000 IU/mL, or 1210 ng/mL, with AFP levels ranging from 0.54–61830 IU/mL (0.6534 – 74814.3 ng/mL), which corresponds to the range of AFP levels found in HCC patients in the literature.

In this study, two examiners read the results of the abdominal CT scan and determined the abdominal CT scan score for HCC. The concordance between examiners in this study was very good. Most of the study subjects got the same score for abdominal CT scan results. The three subjects with significant differences in scores on the Bland-Altman Graph (Fig. 1) were due to differences of opinion in classifying HCC as massive or multilobulated.

CT with contrast is an imaging modality for screening and surveillance in high-risk populations. Hepatocellular carcinoma is a unique tumor among other malignancies because imaging can establish a definite diagnosis without a tissue diagnosis. In this case, a CT scan plays a role in establishing the diagnosis, determining the appropriate therapy, and monitoring the therapeutic response. In general, histological confirmation of malignancy is required only when imaging studies are uncertain.[18]

There have not been many studies examining the reliability of abdominal CT scan images in HCC. In a multicenter study involving 382 radiologists, the reliability of the 2014 LI-RADS (Liver Imaging Reporting and Data System) in HCC patients was also found to be quite good. In addition, the reliability of LI-RADS abdominal CT scan in hepatocellular carcinoma is not affected by familiarity with LI-RADS or the duration of post-residency practice.[19] This shows that the appearance of abdominal CT scans in the diagnosis and monitoring of HCC has high reliability even in radiologists who have no abdominal expertise.

There is a high correlation between abdominal CT scores and AFP levels in hepatocellular carcinoma. From the correlation graph, it can be seen that there is a positive correlation between abdominal CT scores and AFP levels. This shows that an increase in abdominal CT scores also represents an increase in AFP levels in HCC patients. This is appropriate because AFP levels generally increase with the progression of HCC, while higher abdominal CT scan scores in this study also indicate more disease progression.[12] From the partial correlation test results, only AFP levels were known to be significantly correlated with abdominal CT scan scores after controlling for variables of age, sex, and BMI. Meanwhile, the variables of age, sex, and BMI were not significantly correlated with abdominal CT scan scores in HCC patients.

This study concludes that there is a positive correlation between AFP levels and a CT scan of the abdomen in patients with hepatocellular carcinoma. There are still weaknesses in this study, including using a retrospective cross-sectional approach by taking data based on available medical records at a particular time so that clinical data and the course of the disease cannot be obtained entirely. The study was difficult to determine whether each abnormality contributes independently or together with tumor size on AFP levels in HCC due to the abdominal CT scan scoring in general. Therefore, improvement of research methodology using prospective study design is needed to avoid selection bias. CT scan results and AFP levels can also be measured under structured conditions to avoid confounding factors. Validating the scoring system in this study to be used in further research, both for diagnostic and prognostic purposes.

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