**ORIGINAL ARTICLE**

# Diagnostic performance of triple-phase computed tomography in the evaluation of hepatocellular carcinoma

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**Abstract:**

The study aimed to evaluate the diagnostic performance of triple- phase CT imaging of liver for the evaluation of hepatocellular carcinoma (HCC) patients with cirrhosis and/or chronic liver disease. 39 radiological reports of patient who had undergone triple- phase contrast-enhanced CT liver study for suspected/known HCC from January 2016 to December 2018 were reviewed. The findings were validated with serum alpha-fetoprotein (AFP) levels concentration to confirm the malignancy of the HCC. The sensitivity, specificity, predictive values and diagnostic accuracy of the triple-phase CT were determined using ROC curve analysis. The HU cut-off value in triple-phase CT was further estimated for discrimination between benign (non-HCC nodule) and malignant (HCC nodule) hepatic lesion. Positive results of 20 HCC lesions and negative results of 19 non-HCC lesions were observed. Triple-phase CT imaging has a sensitivity and specificity of 85% and 94.7% ($p$ <0.001), respectively with 94.4% PPV and 85.7% NPV with the overall diagnostic accuracy of 89.7%. The optimal cut-off values of 43 HU at arterial phase, 50.5 HU at portal venous phase and 46 HU at delayed phase were proposed for discrimination between benign (non-HCC nodule) and malignant (HCC nodule) hepatic lesion. Triple-phase CT with high accuracy is helpful for the evaluation of hepatocellular carcinoma. It has indispensable role in characterizing and differentiating benign and malignant hepatic lesion, hence this protocol could further improve the clinical management of patients with cirrhosis and/or chronic liver disease.

**Keywords:** Diagnostic performance; hepatocellular carcinoma; triple-phase computed tomography

## 1. INTRODUCTION

Liver lesions are one of the most common cancer occurrences worldwide [1]. In Malaysia, with the well-known multiethnic country had recorded that liver cancer was one of the ten most occurrence cancers currently being diagnosed. The primary type of hepatic lesions that commonly encountered is hepatocellular carcinoma (HCC). HCC is an aggressive epithelial tumour arising from malignant hepatocytes in the liver [2]. Patients with the background of chronic liver disease and cirrhosis are highly contributed to the development of HCC. However, excessive alcohol consumption and spreading of viral hepatitis, including hepatitis B and C are the primary risk factor leading to the incidence of HCC [3]. An early stage diagnosis of HCC is essential to provide several possible curative treatments and improve the population survival rates [4].

The use of current radiological imaging techniques such as ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) and serological markers as well have essential roles in detecting early HCC lesions thus providing effective treatment options and surveillance [5]. Currently, ultrasonography has become a primary imaging technique essentially for early detection of HCC with the combination of serial alpha-fetoprotein (AFP) as a standard HCC biomarker, and it acts as basis surveillance for HCC [6]. However, advances well-defined dynamic imaging techniques, including contrast-enhanced CT and MR imaging are highly advocated for further evaluation of HCC when patients with elevated AFP and new suspicious lesions are reported in ultrasound study. Increased of serial AFP indicates a progressive tumour growth in the liver in which further imaging assessment is prompted for the confirmation of diagnosis. The enhancement of suspected tumour in

patients with cirrhotic liver by using these cross-sectional imaging studies is essential to provide information for the diagnosis and characterization of HCC [7]. Both CT and MRI are currently noninvasive imaging techniques used for detection features of HCC such as HCC nodules, non-HCC malignancy, and non-malignant entities [7]. Typical enhancement and patterns and quantitative method including CT number or Hounsfield unit (HU) in CT scanning parameter are calculated to differentiate the benign and malignant focal liver [8]. Multi-detector helical CT (MDCT) is valuable for early diagnosis of HCC and follow-up of patients with chronic cirrhosis or hepatitis [6]. This study aimed to evaluate the diagnostic performance of triple- phase CT imaging of liver for the evaluation of HCC patients with cirrhosis and/or chronic liver disease.

## 2. MATERIALS AND METHODS

### 2.1 Patients

This retrospective study was approved by institutional review board of the participating institution (NMRR-19-567-46986(IIR). Thirty-nine patients (n=39) radiological reports of patient who underwent triple-phase contrast-enhanced CT liver imaging for suspected/known HCC from January 2016 to December 2018 in the Department of Diagnostic Imaging of a government hospital and met the inclusion criteria were reviewed. Demographic data of patients including age and gender were recorded. The estimated sample size was in agreement with the proposed minimum sample size (n=34) for diagnostic accuracy study [9]. The CT images were retrieved from the Picture Archiving and Communicating System (PACS).

### 2.2 Imaging Protocol

CT liver study was performed by using a SIEMENS SOMATOM Sensation 64 CT Scanner. Contrast-enhanced CT protocol employed iohexol (Omnipaque) or iodixanol (Visipaque) contrast media administration via a power injector at 2–3 mL/s for total of 100–120 mL (rate and volume depending on intravenous access, patient weight and renal function) by using either a fixed time interval (until 2000) or a bolus tracking algorithm (2000 –present: Care Bolus, Siemens or Smart Prep, GE). Non-enhanced, hepatic arterial phase, portal venous phase and delayed phase CT images were acquired in all patients.

### 2.3 CT Image Analysis

CT attenuation values (marked as mean Hounsfield Unit ($HU_{mean}$) were quantified for the selected lesions. A circular region of interest (ROIs) ranging from 1-2 $mm^2$ were drawn on the sites of lesion from the CT images in the three phases contrasted CT study including arterial phase, portal venous phase and delayed phase using PACS workstation (Figure 1). The HU quantification was performed based on the radiological reports in the PACS workstation.

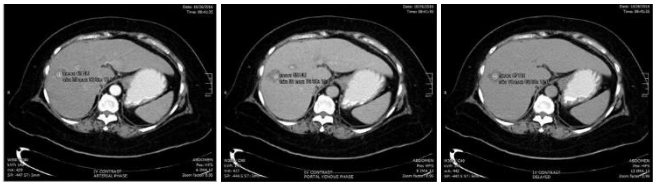

Figure 1: Quantification of region of interest in arterial, portal venous and delayed phases

### 2.4 Validation of Radiological Reports with Reference Standard

The radiological findings were validated with serum AFP levels concentration of the patients as a reference standard to confirm the malignancy of the HCC. Patients with increased AFP serum levels more than baseline value (8ng/ml) were correlated with the presence of liver lesions. AFP serum levels above 400ng/ml are highly indicated as a diagnostic value associated with HCC [10]. However, further review on follow-up imaging study or treatments is attempted in the case of patients presented with low AFP level to confirm the diagnosis of HCC [11]. Positive result (HCC) was recorded based on the radiological report of a suggestive or suspicious HCC lesion with increasing AFP serum levels, including additional imaging study; short-term follow-up imaging and / or treatment. In contrast, negative result (non-HCC) was recorded based on the radiological report in which no lesion was detected, or a visualized lesion was characterized as benign [12].

### 2.5 Statistical analysis

Diagnostic accuracy of triple-phase CT liver in detecting and characterizing HCC) was calculated by using diagnostic accuracy test (Bayesian Theorem) comparing with the concentration of AFP serum levels as a reference standard. The sensitivity, specificity, positive predictive value and negative predictive value of each phase were calculated. Receiver operating characteristic (ROC) curve was generated using IBM SPSS version 21 (SPSS Inc., Chicago, IL, USA) to determine the cut-off value of CT value from each phase of contrasted CT study for differentiating between non- HCC nodules (benign) and HCC nodules (malignant) liver lesion.

## 3. RESULTS AND DISCUSSION

### 3.1 Diagnostic Performances of Triple-phase CT Imaging in Diagnosing HCC

Out of 39 patients radiological report, 24 (61.5%) males and 15 (38.5%) female patients radiological reports involved in this study with the mean age of 60 ± 11.9 (ranging from 36 to 80) years old. The mean $HU_{mean}$ of non-HCC nodules (benign) ranges from 37.89 ± 13.51 to 41.00 ± 12.71 and the mean $HU_{mean}$ of HCC nodules (malignant) ranges from 50.50 ± 8.42 to 55.10 ± 11.01 in the three CT phases. Out of 39 cases, 17 cases (43.6%) were true positive, 3 cases (7.7%) were false negative, 18 cases (46.2%) were true negative and 1 case (2.6%) was false positive. Diagnostic performance of triple-phase CT in diagnosing HCC is presented in Table 1.

Table 1: Diagnostic performance of triple-phase CT in diagnosing hepatocellular carcinoma

| Sensitivity | Specificity | PPV | NPV | Diagnostic accuracy |
|---|---|---|---|---|
| 85.0% | 94.7% | 94.4% | 85.7% | 89.7% |

The result showed CT imaging can detect accurately 17 malignant lesions (HCC nodules) among 39 focal liver lesions. CT technique has become a routine liver evaluation as it can acquire image at peak enhancement of the liver parenchyma [13]. High specificity of CT (94.74%) indicated that CT imaging was good for excluding 18 non-HCC nodules among 39 liver lesions. High specificity of CT imaging in diagnosing patients with non-HCC nodules is essential to diagnose the presence non-HCC nodules to avoid misdiagnosed and further unnecessary curative treatments in the healthy patients [4].

The percentage of diagnostic accuracy of CT imaging was 89.74%. This result showed that the CT imaging was effective to differentiate correctly between the HCC and non-HCC nodules among all the patients with known/suspected HCC. High PPV of CT (94.4%) indicates that CT has high probability of patients with the presence of malignant (HCC) lesions that have positive test results and truly have the HCC lesion confirmed by serum AFP findings. In contrast, high NPV in CT (85.7%) in specifies that CT has a high probability of patients with the absence of HCC lesions that have negative test results and truly does not have the HCC lesion as confirmed by serum AFP findings.

Triple-phase CT including hepatic arterial phase, portal venous phase and delayed phase has been considered as the primary approach for liver carcinomas diagnosis [14]. On the other hand, there was a guideline recommended four-phase CT including non-contrast enhanced CT and triple-phase CT as a good imaging technique to detect the features of HCC lesions especially in patients with cirrhotic livers in which the presence of fibrotic and inflammatory changes [15]. However, the diagnostic value of four-phase CT liver study is still debatable. In a particular condition, liver lesion is not visible in a non-contrast enhanced CT due to the inherent contrast that is too low between the lesion tissue and surrounding liver parenchyma [6]. Additionally, four-phase CT would contribute extra radiation dose to the patients without diagnostic value for the diagnosis of liver lesion.

### 3.2 Optimal HU Cut-off Values

From the ROC curve analysis, the areas under the curve (AUCs) in all three phases were observed to be within the good range of diagnostic test to differentiate between benign and malignant liver lesions. Triple-phase CT showed optimal HU cut-off values for discriminating benign and malignant HCC lesion in arterial, portal venous and delayed phases were 43.0, 50.5 and 46, respectively (Table 2).

Table 2: Optimal HU cut-off values in arterial, portal venous and delayed phases in discriminating benign and malignant HCC lesions

| | Arterial phase | Portal venous phase | Delayed phase |
|---|---|---|---|
| AUC | 0.83 | 0.77 | 0.79 |
| p-value | 0.01 | 0.05 | 0.03 |
| Sensitivity | 80.0% | 70.0% | 70.0% |
| Specificity | 78.0% | 67.0% | 67.0% |
| Optimal HU cut-off | 43.0 | 50.5 | 46.0 |

Increased HU values in HCC lesions are due to the hypervascular appearance of the lesions [13]. Increased CT attenuation value in portal venous phase signifies its important role as an imaging biomarker for the evaluation of malignancy of HCC. The portal venous had proven to provide a better demonstration of hypervascular HCC lesion and hypovascular benign lesion hyperplasia [16]. Well-differentiated HCC often receives preferential portal venous blood, whereas moderately and poorly differentiated tumors are supplied with arterial blood [17]. This vascular pattern characterization indicates the valuable diagnostic value of triple-phase CT as HCC radiological hallmarks [18]. The previous study [13] pointed out that the addition of delayed phase in CT scanning had improved the differentiation of HCC from benign lesions by enhancement of malignant capsule lesions. Hence, the determination of cut-off HU values in all scanning phases is essential to provide a cut-off point for discriminating the malignancy of focal liver lesions.

### 3.3 Current gold standard and imaging modalities in clinical practices

In this study, AFP was used as the reference standard for tumor biomarker that currently referred by clinicians in diagnosing HCC. AFP is considered as a gold standard to correlate HCC with radiological findings [11]. Chou et al. [12] further explained that the reference standards in diagnosing HCC could be histopathologic examination based on the explanted liver or non-explant histologic specimens, imaging plus clinical follow up, or a combination of these. Our findings reported the range of serum AFP value to predict the presence of focal liver lesions was more than 8ng/ml. However, not all patients with the presence of HCC lesions were recorded to have an increased level of AFP serum. Our findings are consistent with the previous literature affirming that some patients with the cases of HCC were reported not to have significant elevations of AFP level [11]. In this particular circumstance, we recorded the serum AFP levels with the combination of the follow-up imaging study or treatments to confirm the diagnosis of the liver lesion as suggested by the previous study [11]. Furthermore, Health

Technology Assessment Report from the Ministry of Health Malaysia has provided substantial evidence that the combination of AFP within six-month intervals and the US within 12-month intervals have high sensitivity and specificity at 92.2% and 95.0% in HCC screening [19].

## 4. CONCLUSION

Triple-phase CT with high diagnostic performance is helpful for the evaluation of HCC. It has indispensable role in characterizing the vascular property of the lesion. CT attenuation value is an important imaging marker as signified by the optimal HU cut-off values in arterial, portal venous and delayed phases for differentiating benign and malignant hepatic lesion. Hence this protocol could further improve the clinical management of HCC patients with cirrhosis and/or chronic liver disease.

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