ORIGINAL ARTICLE

Diagnostic Performance of Triple-phase Contrast-enhanced Computed Tomography and Diffusion-weighted Magnetic Resonance Imaging for Evaluation of Hepatocellular Carcinoma

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ABSTRACT

Introduction: Ultrasonography has a primary role in detecting hepatocellular carcinoma (HCC). However, contrast-enhanced Computed Tomography (CECT) and Diffusion Weighted Magnetic Resonance Imaging (DW-MRI) are advocated for further evaluation of HCC when patients with elevated HCC biomarker and new suspicious lesions are depicted in ultrasonography. This study is aimed to evaluate the diagnostic performance of triple-phase CECT and DW-MRI for the evaluation of HCC in patients with chronic liver disease. **Methods:** Radiological reports of patients (n=39) who had undergone triple-phase CECT and DW-MRI of liver for suspected HCC were reviewed. The reports were validated with serum alpha-fetoprotein (AFP) analysis. Both imaging sensitivity and specificity were determined using ROC curve. The Hounsfield Unit (HU) and apparent diffusion coefficient (ADC) cut-off values were estimated for discrimination between HCC and non-HCC lesions. **Results**: AFP results showed 19 benign and 20 malignant HCC lesions. 85% sensitivity, 95% specificity and 90% accuracy were observed in triple-phase CECT (AUC 0.90, $p < 0.001$) while similar sensitivity, specificity and accuracy of 95% were observed in DW-MRI (AUC 0.95, $p < 0.001$). 43.0, 50.5 and 46.0 HU cut-off were observed in arterial, portal venous and delayed phases CECT, respectively while ADC cut-offs of $1.2405 \times 10^{-3} mm^2/s$ at b = 50 s/mm^2 and $1.2475 \times 10^{-3} mm^2/s$ at b= 1600 s/mm^2 were observed in DW-MRI. **Conclusion**: DW-MRI demonstrated more superior diagnostic performance than triple-phase CECT for the evaluation of HCC. The present findings could potentially facilitate the clinical management for improved accurate diagnosis of HCC in patients with chronic liver disease.

Keywords: : Contrast-enhanced CT, Diagnostic performance, Diffusion weighted-MRI, Hepatocellular carcinoma

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INTRODUCTION

Liver lesions are one of the most common cancer occurrences worldwide (1). In Malaysia, liver cancer is one of the ten most occurrence cancers currently being diagnosed. The primary type of hepatic lesions that commonly being encountered is hepatocellular carcinoma (HCC). HCC is an aggressive epithelial tumour arising from malignant hepatocytes in the liver (2). HCC is one of the most common malignant primary hepatic tumours worldwide and the third most likely cause of cancer-related deaths globally, after lung and stomach cancer (3). Patients with 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 (4).

There is also small population ranging from 5% to 20% of HCC patients with the history of negative of hepatitis B and hepatitis C infection known as non-B non-C hepatitis (NBNC-HCC) (5). An early-stage diagnosis of HCC is essential to provide several possible curative treatments and improve the population survival rates (6). The use of current radiological imaging techniques and serological markers have essential roles in detecting early HCC lesions, thus providing effective

treatment options and surveillance of HCC (7). Several routine non-invasive imaging studies are applicable for the diagnosis and prognosis assessments of HCC including ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI). Currently, ultrasonography has become a primary imaging technique essentially for early detection of HCC, and it acts as basis surveillance for HCC (8). This operator-dependent modality is performed for every six months follow up with the combination of serial alpha-fetoprotein (AFP) measurement as liver cancer biomarker to ensure long term patients' survival rates (9). However, advances well-defined dynamic imaging techniques including contrast enhanced CT (CECT) and MRI are highly advocated for further evaluation of HCC when patients with elevated AFP and new suspicious lesions are reported in ultrasonography. Increased of serial AFP indicates a progressive tumour growth in the liver in which the patients require further assessment for diagnosis. The enhancement of suspected tumour in patients with cirrhotic liver by using these cross-sectional imaging studies are essential to provide information for the diagnosis and characterization of HCC (9,10).

Both CT and MRI are non-invasive imaging techniques used for detection of HCC features such as HCC nodules, non-HCC malignancy, and non-malignant entities (10). Typical enhancement and attenuation values including CT number or Hounsfield unit (HU) in CT scanning parameter are quantified to differentiate the benign and malignant HCC (11). Prompt MRI is required when there is a presence of suspicious features of liver lesion, more than 1 cm in CT findings (12). In MRI technique, apparent diffusion coefficient (ADC) is a quantitative imaging parameter in diffusion-weighted MRI (DW-MRI) technique for the evaluation of benign and malignant liver lesion (1). Multi-detector CT (MDCT) has been reported as a valuable imaging tool for early diagnosis of HCC and follow up of patients with chronic cirrhosis or hepatitis (8). However, patient dose from CT procedure may exceed the radiation levels identified to increase the probability of health effects (13). Negative and inconclusive findings in CT have served MRI as an alternative non-ionizing modality for further evaluation and diagnosing the liver lesion (8). Due to the lack of obvious clinical features in early stage of HCC, most patients miss the best treatment time by the time of diagnosis, leading to a poor prognosis because of the high degree of malignancy and metastasis caused by HCC (14). It is of great importance to select appropriate imaging examination techniques to improve the early diagnosis of HCC and patients' survival. The diagnostic performance of CT and MRI in characterizing HCC lesions have been reported in the literatures elsewhere (10,15). However, such study on the Malaysian HCC patients was not well reported. The aim of this study was to investigate the diagnostic performance of triple-phase CECT and DW-MRI imaging protocols for the evaluation of HCC in patients with chronic liver disease.

MATERIALS AND METHODS

Sample and Population

The ethics approval for the study was granted from Ministry of Health of Malaysia (NMRR-19-567-46984 (IIR)). This retrospective study retrieved the patients' radiological reports with age over 18 years who had undergone both triple-phase CECT and DW-MRI liver examinations for suspected HCC between January 2016 to March 2019 in the Department of Diagnostic Imaging, Hospital Selayang, Selangor, Malaysia. The reports were retrieved from the CT and MRI Picture Archiving and Communicating System (PACS). Patient reports from either triple-phase CECT or DW-MRI liver examination only and those with non-interpretable DW-MRI sequence due to artefacts were excluded from the study. A total of 39 radiological reports was estimated by using Raosoft Sample Size Calculator software with margin of error of 5% and a confidence interval of 95%. A sample size of 34 has been recommended as the minimum sample size for diagnostic accuracy study (6).

Imaging Protocol

CT liver examination was performed on a SIEMENS SOMATOM Sensation 64 MDCT Scanner. The multiphasic protocol consisted of unenhanced, hepatic arterial, venous arterial and delayed phases with slice reconstruction thickness of 5 mm. Iohexol (Omnipaque) was administered via a power injector at the rate of 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 or a bolus tracking algorithm (Care Bolus, Siemens). For MRI liver procedure, the images were acquired on a SIEMENS MAGNETOM Aera 1.5T MRI Scanner with dynamic contrast-enhanced MRI protocol using Gadoxetate disodium (Gd-EOB-DTPA; Primovist) and gadobenate dimeglumine (Gd-BOPTA/Dimeg, Multihance). The protocols included late hepatic arterial, portal venous and delayed phase. Localizer, pre-contrast T1 and T2, HASTE, VIBE, post-contrast T1 and T2 weighted, and DWI sequences with two b values (b=500 s/mm^2 and b=1600 s/mm2) and ADC maps were performed in the MRI protocol.

Quantification of CT and DW-MRI imaging parameters

For CT liver, mean Hounsfield Unit (HU) values of HCC lesions as image attenuation data were calculated during the arterial, portal venous and delayed phases. A circular region of interest (ROIs) ranged 1 - 2 mm^2 were drawn on the clearly demonstrated portion of liver lesions on the CT images using PACS workstation (Fig. 1). For MRI liver, ADC values of HCC lesions was measured on the ADC map images by referring the enhancing MRI sequence images including T1, T2 weighted and DWI images. For each DWI image, the ADC values were automatically calculated by the MR system and displayed on the ADC

maps. The mean ADC measurements of each lesion were recorded at ADC maps images of b=500 s/mm^2 and b=1600 s/mm^2. The quantifications of HU and ADC on the selected primary lesions were based on the radiological reports and validated by a radiologist.

Validation of radiological findings with serum AFP

The radiological findings of triple-phase CECT and DW-MRI were validated against HCC biomarker of AFP results. Patients with increased AFP serum levels than normal at baseline (8ng/ml) were correlated with the presence of liver lesions. AFP serum levels in patients who are more than 400ng/ml are highly indicated as a diagnostic value associated with HCC (17). Further laboratory examinations and radiological imaging tests are essentials to combine the result of AFP to make a definite diagnosis of HCC (18).

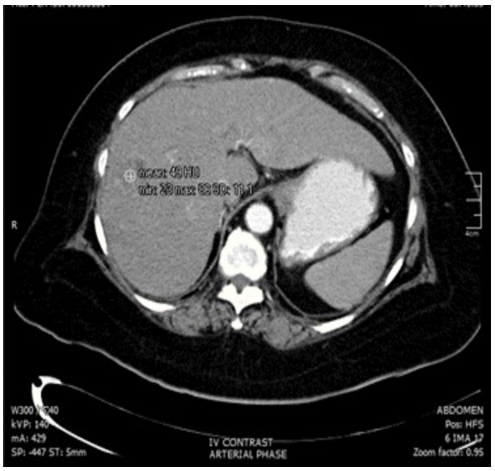

Fig. 1: Region of interest (ROI) was drawn on the clearly demonstrated portion of the liver lesion in the CT image

Statistical Analysis

The diagnostic performance of triple-phase CECT and DW-MRI liver in detecting and characterizing HCC were performed by using diagnostic accuracy test (Bayesian Theorem) comparing with AFP serum levels as a reference standard. The results are presented as true positive, true negative, false positive and false negative. The positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity of both protocols were calculated. Receiver operating characteristic (ROC) curve was generated to determine the performance of CECT and DW-MRI for discriminating HCC and non-HCC lesions. Then the ROC curve was further executed to determine the cut-off value of HU and ADC values for discriminating HCC and non-HCC lesions. The analysis was performed using Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, version 23) (IBM Corp. N.Y. USA).

RESULT

A total of 39 radiological reports with chronic liver disease which consist of 24 (61.5%) male and 15 (38.5%) female patients were included in this study. The subjects were within the mean age of 58.0 ± 24.5 years with ranged of 36 to 80 years old. Distribution of CT HU in arterial, venous and delayed phases of triple phase CECT and ADC maps of b=500 s/mm^2 and b=1600 s/mm^2 in DW-MRI are shown in Fig. 2 and Fig. 3, respectively. Higher HU was observed in non-HCC lesions than HCC lesions in the triple phase CECT while lower ADC was observed in that HCC lesions than non-HCC lesions in DW-MRI.

The area under curve (AUC) of CT HU at arterial, venous and delayed phases are 0.833 (p = 0.014), 0.767 (p = 0.040) and 0.789 (p = 0.034), respectively which are within the good range of diagnostic accuracy to characterize the HCC and non-HCC liver lesion. From the analysis, the HU cut-off to differentiate between

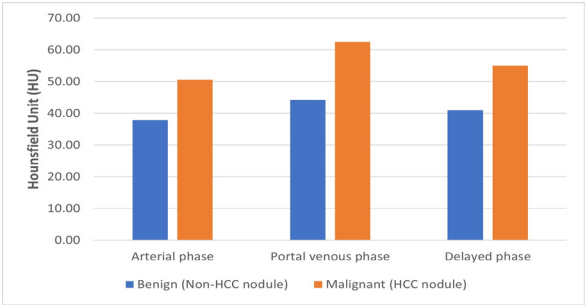

Fig. 2: Distribution of HU in arterial, venous and delayed phases of triple-phase CECT

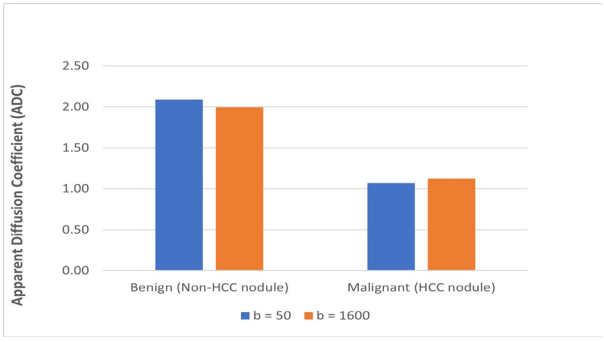

Fig. 3: Distribution of ADC maps of b=500 s/mm^2 and b=1600 s/mm^2 in DW-MRI

HCC and non-HCC lesions are 43.00 HU at the arterial phase, 50.50 HU at the portal venous phase and 46.00 HU at the delayed phase.

Furthermore, the AUC of DWI at b value = 50 is 0.860 (p = 0.027) and AUC at b value = 1600 is 0.940 (p = 0.010) which are within the range of excellent diagnostic accuracy to differentiate between the HCC and non-HCC liver lesions. The ADC cut-off to differentiate between HCC and non-HCC lesions are 1.2405 x 10 -3 mm^2/s at b value = 50 and 1.2475 x 10 -3 mm^2/s at b value = 1600.

Diagnostic accuracy test (Bayesian Theorem) of triple

Table I: Diagnostic accuracy test (Bayesian Theorem) of triple-phase CECT and DW-MRI liver in detecting and characterizing HCC against AFP results

Characteristics	Triple phase CECT	DW-MRI
True Positive (TP)	17 (43.6%)	19 (48.7%)
False Negative (FN)	3 (7.7%)	1 (2.6%)
True Negative TN)	18 (46.2%)	18 (46.2%)
False Positive (FP)	1 (2.6%)	1 (2.6%)
Total (N)	39 (100%)	39 (100%)

Table II: Diagnostic performances of CT and MRI in diagnosing HCC

Imaging Protocol	Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy
Triple-phase CECT	85.0%	95.0%	94.0%	86.0%	90.0%
DW-MRI	95.0%	95.0%	95.0%	95.0%	95.0%

phase CECT and DW-MRI liver in detecting and characterizing HCC against AFP results is shown in Table I. Diagnostic performance analysis of triple-phase CECT and DW-MRI is shown in Table II. DW-MRI showed higher sensitivity than CECT (95% vs 85%,

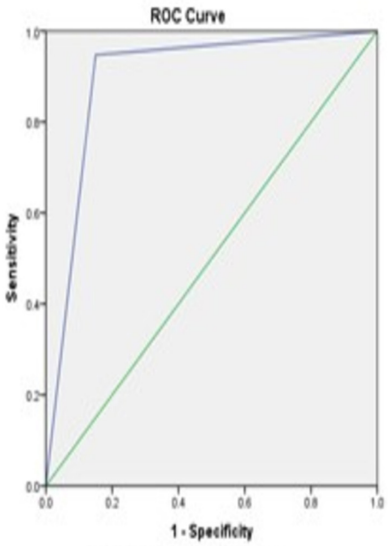

Fig. 4: ROC curve analysis of (a) CECT and (b) DW-MRI in discriminating HCC and non-HCC lesions. CECT and DW-MRI shows AUC of 0.90 and 0.95, respectively (< 0.001)

respectively), and similar specificity of 95%. DW-MRI showed higher overall diagnostic accuracy of 95% (AUC 0.95) as compared to that of CECT of 90% (AUC 0.90) as shown in Fig. 4.

DISCUSSION

In this study, a total of 39 patients' data radiological reports with suspected HCC that underwent triple-phase CECT and contrast-enhanced DW-MRI were evaluated. The HU of CECT and ADC of DW-MRI were quantified among the true positive results (HCC lesions) and true negative results (non-HCC lesions). Three CT scanning phases of arterial, portal venous and delayed phase have been considered as the primary approach for the diagnosis of liver carcinomas (19). However, four phases-CT including non-contrast CT and triple-phase CT are essential to detect the features of HCC lesions especially in cirrhotic liver patients with the presence of fibrotic and inflammatory changes (20). However, liver lesion is not visible on a non-contrast CT due to the inherent contrast that is too low between the lesion tissue and surrounding liver parenchyma (8). On the other hand, non-contrast CT are useful for tumour follow-up after chemoembolization or after tumour ablation (21).

Our findings show that for the non-HCC lesions , the attenuation values varied in each phase due to the different lesion characteristics of non-HCC lesions. However, the HCC liver lesions were observed to have higher attenuation value in all CT scanning phases as compared to the benign lesions. The hypervascular HCC received most of their blood supply from the hepatic artery and as their grade of malignancy increased, the contribution of portal venous in supplying blood decreased (11).

From the ROC curve analysis, the AUCs were observed to be within the good range of diagnostic test to differentiate between HCC and non-HCC liver lesions. In the arterial phase, the HU cut-off of 43 was determined to differentiate between non-HCC and HCC lesions. The HCC was hypervascular and had high contrast accumulation during the arterial phase. Hence, the arterial phase is useful to diagnose the HCC lesions. More importantly, the enhancement of HCC lesions has been recommended to be visualized at the late arterial phase (8). In the portal venous phase, 50.50 HU was determined to differentiate between the HCC and non-HCC liver lesions. In the delayed phase, HU cut-off CT of 46.00 is being proposed to distinguish between the HCC and non-HCC lesions. The application of delayed phase in CT liver scan has improved the differentiation of HCC from non-HCC lesions by enhancement of malignant HCC capsule lesions (19). Hence, the determination of HU cut-off in three-phase CT liver scan is essential for discrimination of HCC and non-HCC liver lesions.

In this study, the DWI in the contrast-enhanced MRI sequences has provided an advance technique in improving the signal contrast between the tumours and background liver parenchyma by restricted the movement of water molecules in the tumour. Exploitation of different tissue characteristics by DWI over conventional MRI sequences leads to enhance HCC detection, characterization and post-treatment evaluation (21). The different b values in the DWI (b = 50 s/mm^2 and b = 1600 s/mm^2) are essential in

clinical application to access the changes in tissue signal intensity and calculations of ADC maps (22). The measurement of ADC is considered as a diagnostic tool in DWI technique in which it calculated the area of water molecules could cover per second (22). The results showed the mean ADC at b = 50 s/mm^2 and b = 1600 s/mm^2 were higher in non-HCC lesions as compared to the HCC lesions. The variation of measured ADC value is highly associated with tumour cellularity (23).

Based on the ROC analysis of ADC values, the AUCs of b = 50 s/mm^2 and b = 1600 s/mm^2 were 0.860 and 0.920, respectively which indicate these sequences were within the excellent range of the diagnostic test to discriminate between the HCC and non-HCC liver lesions. The ADC cut-off at b = 50 s/mm^2 and b = 1600 s/mm^2 were determined at 1. 2405 x 10^{-3}mm^2/s and 1. 2475 x 10^{-3}mm^2/s, respectively to differentiate between the HCC and non-HCC lesions. DWI images have been reported to be more sensitive to diffusion resulting in greater lesion to liver contrast at the larger b value (22). Hence, the determination of ADC values in DWI sequence are valuable in MRI sequences for discrimination of HCC and non-HCC lesions.

From diagnostic performance analysis, DW-MRI has shown sensitivity of 95.0% in diagnosing the patients with HCC lesions. This result indicates DW-MRI is able to detect 19 malignant lesions over the total of 39 focal liver lesions. This result is consistent with the previous study which proposed MRI as a preferable imaging modality for the diagnosis of HCC as MRI showed higher per lesion sensitivity than CT imaging (3). On the other hand, DW-MRI has specificity of 95%, indicating its good performance to exclude 18 non-HCC lesions over the total of 39 focal liver lesions. High specificity of DW-MRI in diagnosing patients with non-HCC lesions is essential to avoid misdiagnosed and further unnecessary curative treatments in the healthy patients.

High diagnostic accuracy of DW-MRI (95%) indicated that the DW-MRI is an effective MRI protocol to differentiate between the HCC and non-HCC lesions among the patients with suspected HCC. With the PPV of 95%, DW-MRI can detect high probability of patients with the presence of HCC lesions that have positive test results and truly have the HCC lesion as confirmed by the serum AFP result. On the other hand, 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 the serum AFP results.

In this study, serum AFP was used as a tumour biomarker for diagnosing HCC. 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 procedures (24). In our study, the range of serum AFP value to predict the presence of focal liver lesions was more than 8ng/ml. However, not all the patients with the presence of HCC lesions were recorded to have an increased level of AFP serum. It has been claimed in some patients with the cases of HCC were reported not to have significant elevations of AFP level (17). Thus, in the present study the serum AFP levels were recorded with the combination of the follow-up imaging study or treatments received by the patients to confirm the diagnosis of HCC lesions. The combination of AFP within six-month intervals and ultrasonography reports within 12-month intervals have high sensitivity and specificity at 92.2% and 95.0%, respectively in HCC screening (25). The incorporation of AFP and ultrasonography has been reported to increase the sensitivity of HCC detection in HCC screening (26, 27).

Currently, ultrasonography, contrast-enhanced CT and MR imaging are the current imaging tests being performed in Hospital Selayang for detection, diagnosing and characterizing HCC. Ultrasonography is considered as the initial test to detect any presence of solid liver lesions in the liver (25). Ultrasonography for every six months follows up with the combination of serial AFP measurement are used as screening tool of HCC. When there is a new suspicious lesion was recorded in ultrasonography with an elevated AFP, CECT is indicated for further evaluation. CT imaging is being used as a reference diagnostic imaging test for HCC detection and characterization. However, when the CT results shown negative or inconclusive findings of liver lesions of patients with suspected HCC, contrast-enhanced MR imaging technique is indicated for further evaluation of liver HCC. Thus, MR imaging is considered as a complement diagnostic imaging tool in diagnosing and characterizing HCC.

CONCLUSION

In conclusion, DW-MRI has superior diagnostic performance (sensitivity 95%, specificity 95%, diagnostic accuracy 95%) than triple-phase CECT (sensitivity 85%, specificity 95%, diagnostic accuracy 90%) in characterizing the HCC and non-HCC lesions in patients with chronic liver disease.

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