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Could ADC values be a promising diagnostic criterion for differentiating malignant and benign hepatic lesions in Asian populations

A meta-analysis

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Abstract

Background: Liver cancer exhibits geographic and ethnic differences in its prevalence and biology, which implies that it is impractical to develop universal guidelines for all patients. Thus, a meta-analysis was conducted to identify the accuracy of apparent diffusion coefficients (ADCs) for discriminating malignant from benign liver lesions in Asians.

Methods: Eligible studies published in PubMed, Ovid, and Embase/Medline were updated onto October 2014. STATA 12.0 and Meta-Disc 1.4 were used to perform this meta-analysis.

Results: Eight studies comprising 661 benign liver lesions and 598 malignant liver lesions fulfilled all the inclusion criteria. The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were 0.88 (95% confidence interval [CI] 0.75–0.95), 0.93 (95% CI 0.86–0.97), 12.42 (95% CI 6.09–25.31), 0.13 (95% CI 0.06–0.29), and 95.58 (95% CI 35.29–258.89), respectively. Overall, the area under the summary receiver-operating characteristic curve was 0.96 (95% CI 0.94–0.98). Heterogeneity was found to originate potentially from the type of benign lesion. A subgroup analysis showed that differentiating between hemangiomas, cysts, and malignant liver lesions produced a significantly higher diagnostic accuracy than that of solid liver lesions.

Conclusion: Our meta-analysis indicated that ADC could be promising for characterizing liver lesions among Asians, indicating that the ADC value is a promising diagnostic criterion candidate. Meanwhile, the use of dual *b* values could be sufficient for liver lesion characterization. However, large-scale, high-quality trials should be conducted to identify specific standards, including cut-off values for further development of diffusion-weighted imaging as a routine clinical application among Asian populations.

Abbreviations: ADC = apparent diffusion coefficient, AFB1= aflatoxin B1, CI = confidence interval, CT = computed tomography, DOR = diagnostic odds ratio, DWI = diffusion-weighted imaging, FLLs = focal liver lesions, HBV= hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, IARC = International Cancer Research Center, IVIM = intravoxel incoherent motion imaging, LR = likelihood ratio, MRI = magnetic resonance imaging, QUADAS = Quality Assessment of Diagnostic Studies, Sen = sensitivity, Spe = specificity, SROC = summary receiver-operating characteristic, WHO = World Health Organization.

Keywords: apparent diffusion coefficients, diagnostic accuracy, liver cancer, meta-analysis

1. Introduction

Globally, the prevalence of liver cancer in the general population has been increasing dramatically. Because of its late diagnosis and poor prognosis, liver cancer has become the second leading cause of cancer-related mortality worldwide.[1] A large amount of data show that the incidence of liver cancer varies significantly worldwide. According to the latest research by the International Cancer Research Center (IARC), liver cancer occurs more often in Eastern countries, and Asian males are the most vulnerable population.[1,2] In contrast to other malignancies, the prevalence and biology of liver cancer display large differences between Asian and Western countries; these differences indicate the potential existence of geographic and ethnic differences.[3]

Approximately 748,300 new cases are diagnosed with liver cancer in 2008, whereas over 80% of them live in developing countries.[1] The highest rate of yearly diagnosis is reported to appear in Asian-Pacific regions, the medium in black, and the lowest in the white and American Indian/Alaska natives.[1,4,5] Particularly, China alone is host to nearly half of the world's total new cases.[6] The geographic and ethnic variability in the prevalence and diagnosis rates is largely explained by different risk factors of liver cancer. The hepatitis B virus (HBV) or

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hepatitis C virus (HCV) infection, which accounts for the overwhelming majority of all the liver cancer cases, is more prevalent in the Asian-Pacific nations.[5,7–9] Meanwhile, aflatoxin is an important risk factor for the development of liver cancer in parts of Africa and Asia. For example, aflatoxin exposure lead to 27% to 60% of primary liver cancer in Sudan.[10] However, the majority of liver cancer in the United States and several other low-risk Western countries are thought to result from alcohol-related cirrhosis and nonalcoholic fatty liver disease, associated with metabolic syndrome.[11–13] Furthermore, the differences of liver cancer between Western and Asian countries produce significant impacts on making treatment choices and evaluating prognosis. In Asia, the proportion of patients presenting with resectable hepatocellular carcinoma (HCC) is as low as 10% to 15%, which is half that of lower incidence regions, such as the United States and Europe.[14] When advanced HCCs were treated with sorafenib, which was the only approved systemic therapy, the median overall survival was 10.7 months in Western patients and 6.5 months in Asian patients.[15,16]

The above-mentioned evidences demonstrate the remarkable difference in the diagnostic rates, susceptibility, etiology, treatment, and prognosis of liver cancer between Western and Asian nations. Therefore, it is impractical to develop universal guidelines for all patients with liver cancer. Since an early and accurate diagnosis is important for determining the appropriate treatment modality and improving the prognosis of liver cancer,[17–19] it is very essential to provide a novel, unique, and powerful diagnostic method to distinguish malignant liver lesions from benign ones, especially for Asians who are at high risk for liver cancer from both the geographic and ethnic perspectives. Currently, early diagnosis mainly depends on medical imaging. However, the differential diagnosis between malignant tumors (eg, HCC and metastases) and benign liver lesions (cysts, hemangiomas, and focal nodular hyperplasia) remains a formidable challenge for radiologists. To accurately diagnose liver lesions, a large array of imaging modalities, such as liver ultrasound, spiral computed tomography (CT), and magnetic resonance imaging (MRI), have been widely used in clinical practice.

With recent progresses in imaging techniques, MRI has developed into a valuable tool for the noninvasive diagnosis and characterization of liver lesions. Diffusion-weighted imaging (DWI), as a new parametric MRI approach, has gained significant attention in oncologic imaging, because it allows not only a morphological evaluation but also functional and pathological evaluations of various diseases.[20–23] DWI is a noninvasive MRI method based on the information of water proton mobility, which is well-known as Brownian motion. Brownian motion has primarily been applied in brain imaging, mainly for the evaluation of ischemic stroke, intracranial tumors, and demyelinating diseases.[24–26] With the current development of the advanced respiratory gating technique and sensitivity encoding, abdominal DW-MRI has been increasingly used in diseases of the liver, the imaging of which was formerly restricted by respiratory movement. DWI has been used to assess the degree of hepatic fibrosis,[27–30] detect hepatic lesions,[31–34] and differentiate malignant from benign lesions[32,35–41] independently from T1 and T2 relaxation times and without the need for contrast agent administration.

The apparent diffusion coefficient (ADC), as a quantitative parameter of DWI, can reflect tissue diffusibility by mono-exponential fitting of DWI data obtained through different field gradients (b values). Due to microstructural tissue changes, malignant tumors generally restrict water diffusion, whereas benign lesions do not. Benign lesions have significantly higher ADC values than malignant lesions. Therefore, the ADC was thought to have the potential to differentiate benign from malignant hepatic lesions. Several studies[32,35–41] have indicated that the reported ADC values of benign and malignant hepatic lesions ranged from 1.55 to 7.58 and 0.68 to 3.15 ($\times 10^{-3}$ mm^2/s), respectively, resulting in several recommended ADC cut-off values, but there were also variable degrees of overlap between these values. In these studies, different DWI sequence parameters, such as the set of b values or the use of the parallel imaging technique, may lead to different ADC values for liver lesions, consequently resulting in various cut-off values for differentiating malignant and benign lesions, and overlapping ADC values for malignant and benign lesions.

A previous meta-analysis of 6 studies was performed to evaluate the diagnostic value of quantitative diffusion-weighted MRI for differentiating between malignant and benign focal liver lesions (FLLs).[42] However, one-third of the selected studies were from HBV-endemic Asian populations, whereas the remaining studies were from Western countries. As mentioned above, the neglect of the regional differences in liver cancer may produce a certain deviation in the pooled results. In a meta-analysis of diseases with obvious regional differences, the previous results may cover up the notable heterogeneity between the studies. Therefore, a study that limited the research subjects to Asian individuals would be more likely to reveal the accuracy of the ADC in the quantitative diagnosis of liver cancer in endemic areas, which is more valuable for diagnostic purposes in practice. In our meta-analysis, the related articles were updated, and the overall accuracy of the ADC for the differential diagnosis between benign and malignant liver lesions was assessed only in Asian patients.

2. Methods

2.1. Search strategy

A literature search of PubMed, Ovid, and Embase/Medline was performed using the following keywords and MeSH terms: ["Diffusion Magnetic Resonance Imaging," "Diffusion weighted images," "apparent diffusion coefficient," "DWI," "ADC"] and ["cancer," "neoplasm" and "liver," "Hepatocellular Carcinoma"] without language restrictions. The last search was updated on May 27, 2014. We also performed a manual search of the reference lists of the included studies and review articles to identify additional eligible studies. Since a meta-analysis is a systematic summary and statistical analysis of the results of published studies, ethical approval was not necessary for this study.

2.2. Study selection

Two reviewers independently reviewed all the studies that met the following inclusion criteria: the patients of the included studies were Asian; the ADC values for the differential diagnosis between benign and malignant liver lesions were calculated and were not combined with other MR series; the reference standards included a histopathological analysis (performed at surgery and biopsy) or follow-up; and the published data must be sufficient to form 2×2 tables. Studies that did not meet all the inclusion criteria were excluded. Animal studies, reviews, and letters were also excluded. The most recent publication or publication with the largest

sample size was included when the authors published several studies using the same subjects.

2.3. Data extraction

The full manuscripts of the included articles were independently reviewed by 2 reviewers. We extracted the following data: author, country of origin, publication year, number of patients, patient enrollment, study design, ADC values of malignant and benign lesions, "gold standard," and *b* values. The numbers of true-positive, false-positive, true-negative, and false-negative data were collected to construct a 2×2 table. Any disagreements were resolved by consensus.

2.4. Quality assessment

Two observers independently assessed the methodological quality of the included studies using the Quality Assessment of Diagnostic Studies (QUADAS) instrument.[43] Each item was scored as "yes" (1), "no" (−1), or "unclear" (0). The disagreements were resolved by consensus discussion. QUADAS scores range from 0 to 14, and a score ≥10 indicates a high-quality study.

2.5. Statistical analysis

STATA version 12.0 and Meta-Disc version 1.4 (Universidad Completeness, Madrid, Spain) software were used for the meta-analysis. For each study, the sensitivity (Sen), specificity (Spe), positive likelihood ratio (LR+), negative likelihood ratio, and diagnostic odds ratio (DOR), along with their 95% confidence intervals (CIs), were graphically displayed using forest plots. We constructed summary receiver-operating characteristic (SROC) curves on a per-study basis to show the summary trade-off between sensitivity and specificity. The threshold effect was assessed by Spearman rank correlation test and the shape of the SROC curve. If the threshold effect was thought to be absent, a bivariate model was used. Cochran *Q* test was used to assess the presence of statistical heterogeneity, and the I^2 test was used to estimate the magnitude of heterogeneity. If the *Q* test showed a *P* value <0.05 or the I^2 test revealed a heterogeneity $>50\%$, a random-effects model was constructed. Then, we performed subgroup and meta-regression analyses based on patient enrollment, sample size, number of *b* factors, quality score, and type of benign lesions to investigate potential sources of heterogeneity. If the heterogeneity analysis could not identify the data sources, a descriptive analysis was then performed among the groups or a sensitivity analysis was conducted to verify the stability of the results. Publication bias was examined visually by inspecting the funnel plots.

3. Results

3.1. Characteristics of the included studies

Figure 1 outlines the selection process. Initially, the searched keywords identified 405 articles after removing duplications. We reviewed the titles and abstracts of all the articles and excluded

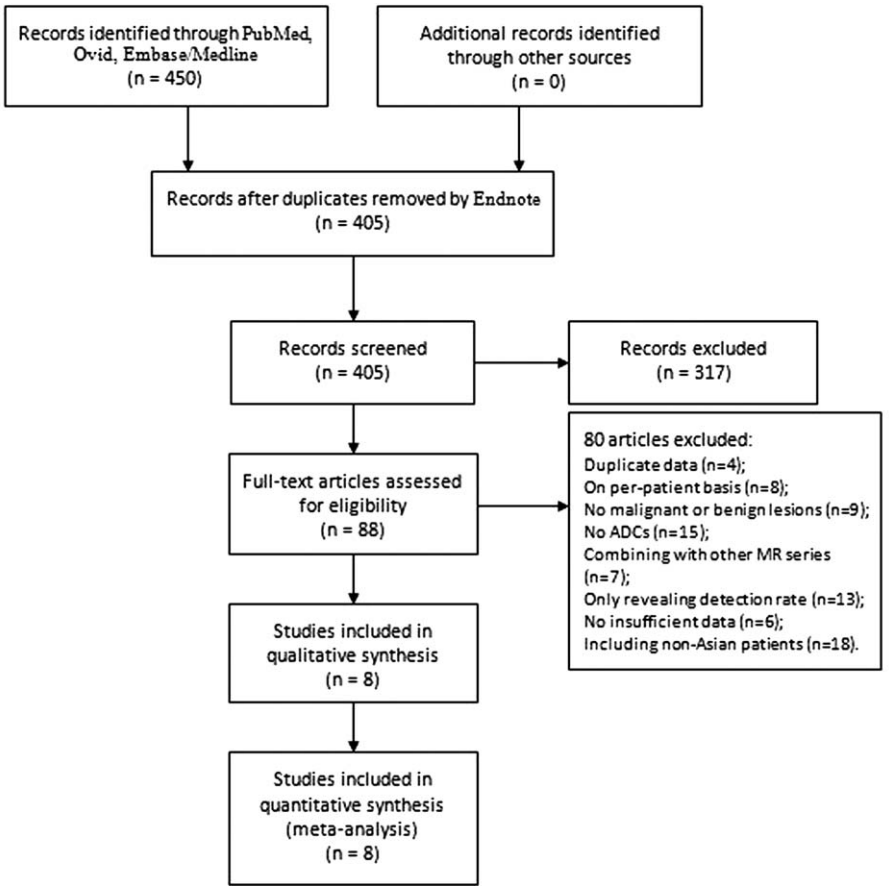

Figure 1. Flow chart of the articles identified and included in this meta-analysis.

Table 1

Baseline characteristics and methodological quality of all the included studies.

Author	Nation (region)	Year	Patients, no.	Lesions, no.	Malignant, no.	Benign, no.	*b*, s/mm^2	Patient enrollment	Sensitivity,,%	Specificity, %	Quality score
Ichikawa et al., 1998	Japan	1998	46	74	HCC (48), metastasis (15)	Hemangioma (11)	1.6 and 55	ND	91	100	5
Kim et al., 1999	Japan	1999	70	92	HCC (35), metastasis (18), CCC (1)	Hemangioma (16), cyst (21) Angiomyolipoma (1)	3, 57, 192, 408, 517, 705, and 846	Conse	98	80	5
Muhi et al., 2009	Japan	2009	73	98	HCC (86)	DNs (12)	500 and 1000	Conse	52	100	13
Motosugi et al., 2010	Japan	2010	80	155	Hypervascular HCC	Nodular pseudolesion	500 and 1000	ND	67	100	8
Watanabe et al., 2014	Japan	2013	74	120	Metastasis (34), HCC (32)	Hemangioma (33), cysts (21)	0, 10, 20, 30, 50, 80, 100, 200, 400, and 800	Conse	89	98	7
Xu et al., 2010	China	2010	54	59	HCC (40)	DNs (19)	0 and 500	ND	58	79	10
Yang et al., 2011	Korea	2011	45	97	HCC (12), metastasis (26), CCC (13)	Hemangioma (19), cysts (27)	0, 50, and 800	ND	96	88.9	10
									98	86.7	
Yoon et al., 2014	Korea	2014	142	157	HCC (81), CCC (3), metastasis (35)	Hemangioma (23), FNH (8), cysts (27), adenoma (5), cyst (12)	0, 25, 50, 75, 100, 200, 500, and 800	ND	88	89.2	9

CCC = cholangiocellular carcinoma, Conse = consecutive, DN = dysplastic nodule, FNH = focal nodular hyperplasia, HCC = hepatocellular carcinoma, ND = not documented, No. = number.

317 articles. After reading the full texts of the remaining articles, 8 studies, including a total of 661 benign lesions and 598 malignant lesions that met all the inclusion criteria, were included, and a 2×2 contingency table was completed. Five, 1, and 2 studies were conducted in Japan, China, and Korea, respectively. The extracted useable data and the study characteristics of each article are summarized in Table 1. In the study by Yang et al,[32] an analysis of DWI images was performed independently by 2 observers; thus, 2 subsets of data from the study were included. Therefore, we extracted 9 subsets of data from all 8 studies.

3.2. Assessment of study quality

The quality of the included studies affects the quality and reliability of a meta-analysis. Using the QUADAS tool, we scored every item of the included papers, and the results are shown in Table 1. Most of the included studies in this meta-analysis lacked consensus regarding a gold standard and used a "histopathology analysis and/or intraoperative sonography and/or careful surgical inspection and palpation of the liver and/or cross-sectional image follow-up (at least 6 months)." The absence of a time interval between the histopathological confirmation and the index tests in most studies was another major problem. The interval time information is crucial because the disease can progress fast. Furthermore, in test accuracy studies, the interpretation of the results of the index test may be influenced by knowledge of the results of the reference standard, and vice versa. This is known as review bias and may exaggerate the diagnostic accuracy. As the index test, DWI was always performed first, and the interpretation of the DWI results was usually conducted without knowledge of the results of the reference standard. However, only a few articles provided detailed information on whether the individuals interpreting the pathology were blinded from the DWI results. Additionally, descriptions of the selection criteria, available clinical data, and uninterpretable results were often not reported.

3.3. Threshold effect analysis and publication bias

The threshold effect analysis was assessed using Spearman rank correlation test and the shape of the SROC curve. Spearman correlation coefficient ($r = 0.367$, $P = 0.332$) and the lack of a "shoulder-arm" shape in the SROC curve indicated the absence of a threshold effect that could cause variations in accuracy estimates among the individual studies. Deek funnel plot was assessed and revealed no presence of publication bias ($P = 0.167$).

3.4. Quantitative data synthesis

Figures 2–6 show the forest plots of the Sen, Spe, DOR, LR+, and LR− for the differential diagnosis between benign and malignant liver lesions in 9 subsets of data from all 8 studies. We plotted the fitted SROC curve (Fig. 7); overall, the AUC was 0.96 (95% CI 0.94–0.98). The SROC curve suggested that the ADC was a very good tool for differentiating malignant from benign liver lesions. Based on a P value <0.05 and I^2 $>50\%$ of the pooled DOR, notable heterogeneities were likely to exist.

3.5. Subgroup and meta-regression analyses

The results of the subgroup analysis are presented in Table 2. The patients' enrollment (consecutive vs nonconsecutive or unclear), sample size, number of *b* factors, and quality scores did not significantly influence the sensitivity of the diagnostic accuracy of the test. The subgroup and meta-regression analyses confirmed

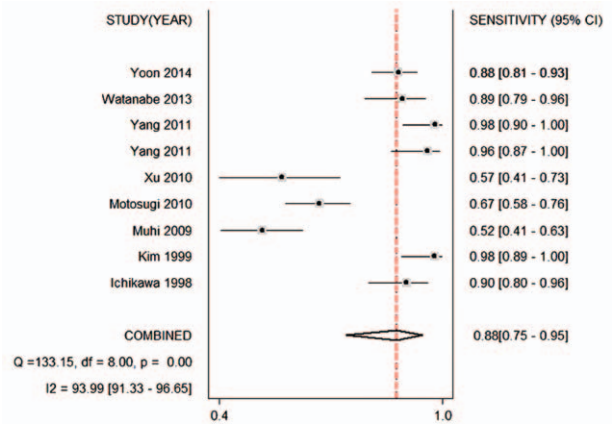

Figure 2. Forest plot of the pooled sensitivity of the ADC for the differential diagnosis of benign and malignant lesions in Asian populations. The summary sensitivity was 0.88 (95% CI 0.75–0.95). ADC = apparent diffusion coefficient, CI = confidence interval.

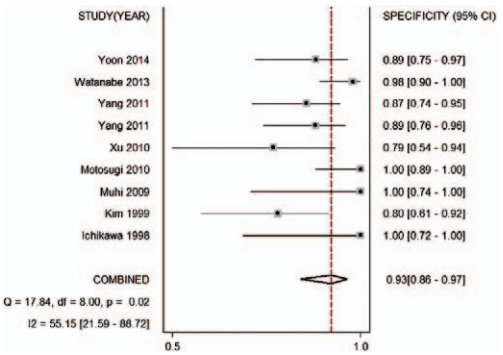

Figure 3. Forest plot of the pooled specificity of the ADC for differential diagnosis of benign and malignant lesions in Asian populations. The summary specificity was 0.93 (95% CI 0.86–0.97). ADC = apparent diffusion coefficient, CI = confidence interval.

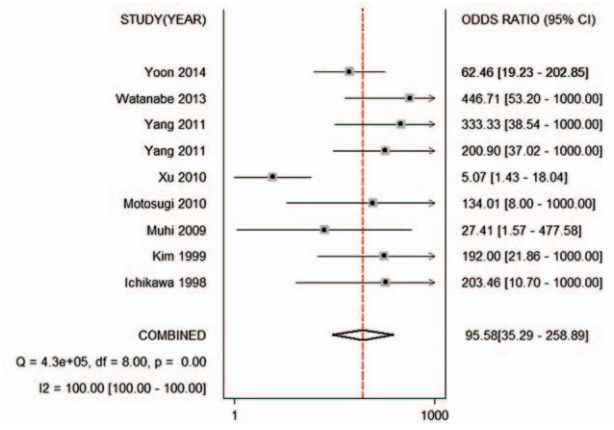

Figure 4. Forest plot of the pooled odds ratio of the ADC for differential diagnosis of benign and malignant lesions in Asian populations. The summary odds ratio was 95.58 (95% CI 35.29–258.89). ADC = apparent diffusion coefficient, CI = confidence interval.

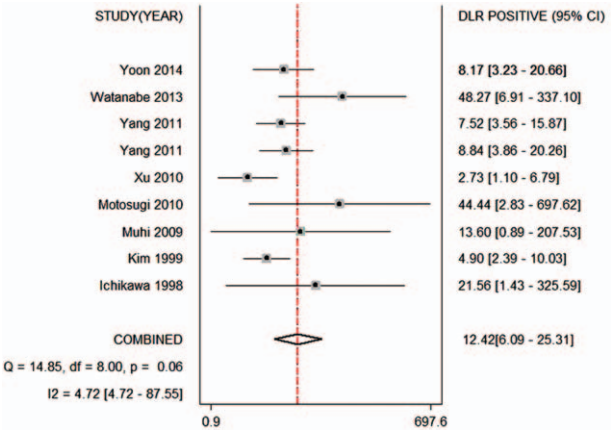

Figure 5. Forest plot of the positive likelihood ratio of the ADC for the differential diagnosis of benign and malignant lesions in Asian populations. The summary positive likelihood ratio was 12.42 (95% CI 6.09–25.31). ADC = apparent diffusion coefficient, CI = confidence interval.

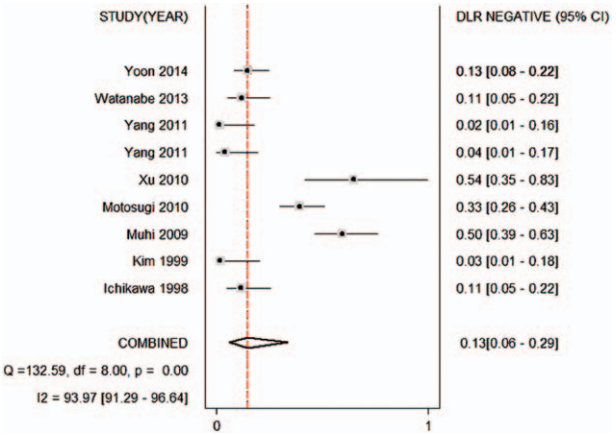

Figure 6. Forest plot of the negative likelihood ratio of the ADC for the differential diagnosis of benign and malignant lesions in Asian populations. The summary negative likelihood ratio was 0.13 (95% CI 0.06–0.29). ADC = apparent diffusion coefficient, CI = confidence interval.

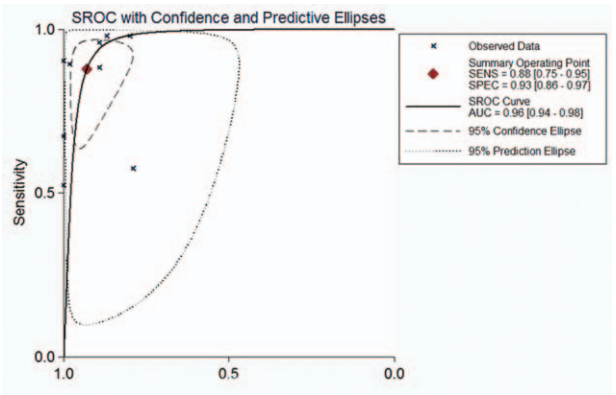

Figure 7. Summary receiver operating characteristic (SROC) curves of the ADC for the differential diagnosis of benign and malignant lesions in Asian populations. ADC = apparent diffusion coefficient.

Table 2

Subgroup analysis.

Study characteristics	Summary sensitivity, % [95% CI]	*P*	Summary specificity, % [95% CI]	*P*
Patient enrollment		0.98		0.55
Conse	0.756 [0.691, 0.814]		0.927 [0.856, 0.970]	
ND	0.879 [0.726, 0.952]		0.904 [0.849, 0.940]	
Total number of samples		0.59		0.07
>100	0.803 [0.754, 0.845]		0.959 [0.908, 0.987]	
<100	0.903 [0.703, 0.974]		0.878 [0.809, 0.924]	
Quality score		0.36		0.39
<10	0.896 [0.852, 0.928]		0.957 [0.835, 0.990]	
≥10	0.861 [0.516, 0.973]		0.878 [0.796, 0.930]	
b Values		0.35		0.73
Dual *b* value	0.865 [0.690, 0.957]		0.935 [0.829, 0.934]	
Multi *b* value	0.906 [0.862, 0.940]		0.909 [0.843, 0.954]	
Etiology		0.87		0.19
HBV-epidemic	0.886 [0.730, 0.957]		0.965 [0.823, 0.994]	
HCV-epidemic	0.907 [0.707, 0.975]		0.867 [0.793, 0.917]	
Type of benign lesions		0		0.59
Cystic liver nodules	0.939 [0.905, 0.964]		0.904 [0.852, 0.942]	
Solid liver nodules	0.606 [0.543, 0.668]		0.937 [0.845, 0.982]	
Field strength				
1.5T	0.880 [0.687, 0.961]		0.914 [0.816, 0.962]	

CI = confidence interval, Conse = consecutive, HBV = hepatitis B virus, HCV = hepatitis C virus, ND = not documented, T = Tesla.

that the ADC for the differential diagnosis between hemangiomas, cysts, and malignant liver lesions yielded a significantly higher sensitivity than that of solid lesions. We included articles performed with 3.0-T and 1.5-T device. We attempted to reveal whether magnetic field strength influenced the pooled accuracy, but failed due to the relatively small number of included studies (2 reports) utilizing 3.0-T devices. Then we excluded these 2 reports and calculated an overall sensitivity of 0.880 (95% CI 0.687, 0.961) and specificity of 0.914 (95% CI 0.816, 0.962).

4. Discussion

The ADC value, which is a quantitative parameter of DWI technology, is extremely sensitive to the pathological changes associated with liver cancer. Low ADC values were found in malignant tumors as a result of high cellularity, increased nuclear/cytoplasmic ratios, and massive macromolecular proteins, which restricted the diffusion of water molecules in the intracellular space.[44,45] In addition, DWI can suppress the signals of other structures, such as vascular structures and bile ducts.[46] Therefore, DWI is thought to be a new and excellent MRI approach that can provide information on oncological, morphological, and pathological changes.

The incidence of liver cancer varies widely worldwide, with high rates in sub-Saharan Africa and eastern and south-eastern Asia, and a low incidence in Europe and the Americas.[1,47] Liver cancer in adults occurs primarily as 3 histological types: HCC, cholangiocarcinoma, and metastasis. According to data from the World Health Organization (WHO), the most common form of liver cancer is HCC, which accounts for 70% to 85% of the total primary liver cancer burden worldwide.[48] The pathology of this type of liver cancer exhibits some ethnic and regional differences between Asian and Western countries. According to Song et al's[49] comparative study using the paraffin sections of resected HCC specimens from American and Korean patients, tumor size was significantly larger in the American group (mean 10.96 ± 5.37 cm) compared with the Asian group (mean 5.60 ± 4.11 cm). Regarding tumor pathology, tumors in Asians were more often poorly differentiated and accompanied by invasions of adjacent organs and blood vessels. The data showed that pathological differences in liver cancer were indeed present between regions.

This phenomenon subsequently results in subtle differences in diagnostic criteria and clinical management. Currently, ultrasound has been commonly used for the early detection of HCC in clinical practice. Patients with an increased risk of developing HCC from the United States are recommended to undergo screening with ultrasound and serum AFP measurements every 6 to 12 months, whereas the Asian Oncology Summit suggested that these screening tests should be conducted every 3 to 6 months,[3,14,50] which implies that regional diversities may be a factor influencing the diagnostic performance of various diagnostic methods. Similar to ultrasound, ethnic and regional differences should also be considered as important influential factors in other types of radiology studies. In this study, DWI was chosen as the diagnostic method for malignant neoplasms in the liver. For further study, we extracted the ADC values of primary liver lesions derived from both European and Asian patients. The relevant data are summarized in Table 3. In Asia, the ranges of the mean ADC values of HCC, hepatic metastasis, and hemangiomas were approximately 0.68 to 3.15, 1.06 to 2.55, and 2.00 to 7.58 ($\times 10^{-3}$ mm^2/s), respectively,[35–39,41] whereas the corresponding ADC values for European patients were 0.94 to 1.19, 0.87 to 1.16, and 1.55 to 1.89 ($\times 10^{-3}$ mm^2/s), respectively.[51–55] The ADC ranges for each lesion in Asia vary greatly from those in Europe, which supports our viewpoint that geographic heterogeneity cannot be ignored when estimating the diagnostic accuracy of ADC values in liver diseases.

For the above reasons, we attempted to analysis the diagnosis performance of ADC for both Asian and Western countries, but failed. The probable reason was that the population of Western countries is quite transient and has complicated composition, and the articles included for Western countries did not provide definite information of clinical value of ADC for different races and ethnicities. On the contrary, Asian population is relatively simple, and the majority of the Asians belong to yellow race.

Table 3

The ADC values ($\times 10^{-3}$mm^2/s) of the main types of FLLs and the cut-off values ($\times 10^{-3}$mm^2/s) for differentiating between malignant and benign FLLs in both Asian and European studies.

	Author	HCC	Metastases	Cyst	Hemangiomas	Cut-off
Asia	Yoon et al., 2014	ND	ND	2.786 ± 0.27	ND	1.4
	Watanabe et al., 2014	1.10 ± 0.26	1.06 ± 0.39	2.83 ± 0.29	2.00 ± 0.45	1.4
	Motosugi et al., 2010	ND	ND	ND	ND	0.84
	Muhi et al., 2009	0.68–0.91	ND	ND	ND	0.81
	Kim et al., 1999	0.97 ± 0.31	1.06 ± 0.50	2.91 ± 1.51	2.04 ± 1.01	1.6
	Ichikawa et al., 1998	3.15 ± 1.80	2.55 ± 1.65	ND	7.58 ± 1.88	NO
Europe	Girometti et al., 2013	1.19 ± 0.38	0.87 ± 0.25	ND	ND	1.5
	Onur et al., 2012	ND	ND	ND	ND	1.23–1.99
	Cieszanowski et al., 2012	0.94 (0.876–1.0)	1.05 (0.934–1.169)	2.45 (1.282–2.621)	1.55 (1.465–1.641)	1.25
	Filipe et al., 2013	1.18 ± 0.17	1.16 ± 0.25	2.77 ± 0.58	1.89 ± 0.33	1.5
	Soyer et al., 2011	ND	ND	ND	1.77 ± 0.29	1.4–1.5

ADC = apparent diffusion coefficient, FLL = focal liver lesion, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, ND = not documented.

Therefore, in this meta-analysis, we only focused on studies performed in Asia and identified 8 independent studies in the literature. Finally, a total of 661 benign liver lesions and 598 malignant liver lesions were included. Based on systematic calculations of the relevant data, the overall Sen, Spe, and DOR of the ADC were 0.88 (95% CI 0.75–0.95), 0.93 (95% CI 0.86–0.97), and 95.58 (95% CI 35.29–258.89), respectively. Overall, the area under the SROC curve was 0.96 (95% CI 0.94–0.98). These results indicate that the ADC value is a good tool for differentiating between benign lesions and malignant tumors in Asian patients. Regardless of geographic differences, a previous meta-analysis of 6 diagnostic studies revealed pooled Sen and Spe values of 0.86 (95% CI 0.83–0.90) and 0.84 (95% CI 0.78–0.88), respectively.[42] Compared with previous data, the relatively better results revealed by our analysis suggested that the ADC value may be more applicable for discriminating malignant from benign liver lesions in Asian populations.

However, there was notable heterogeneity in the Sen and DOR values in the studies analyzed. Therefore, an exploration of the source of heterogeneity to determine the potential impact factors rather than the computation of a single summary measure was an important goal of our meta-analysis.[56] First, the influences of the threshold effect and publication bias on the heterogeneity of the systematic reviews were assessed, but no evidence of influence was found. Second, meta-regressions were performed, which demonstrated that none of the study designs, sample sizes, or quality scores directly influenced the calculation of the ADC value for differentiation between malignant and benign hepatic lesions. Furthermore, HBV infection was the most common cause of liver cancer among Asians, except in Japan, where HCV positivity was detected in 80% of patients (1–3).[57–59] The regression analysis showed no significant differences between HBV-endemic (Korea and China) and HCV-endemic countries (Japan), indicating that etiology was not sufficient to influence the diagnostic accuracy of the ADC in Asians. DW-MRI examinations performed with a 3.0-T device seemed to result in nudging sensitivity and sensitivity upward. After we excluded 2 articles that utilized DW-MRI examinations with a 3.0-T device, the pooled Sen of 0.880 (95% CI 0.687, 0.961) and Spe of 0.914 (95% CI 0.816, 0.962) showed little difference from the primary results. These results revealed that there are other factors causing variations in accuracy estimates across individual studies.

The type of benign lesion can directly affect the diagnostic accuracy of ADC values. "Benign" lesions in 4 papers included predominantly cysts and hemangiomas and very few focal nodular hyperplasias (FNHs) or adenomas. In the other 3 articles, benign lesions consisted of only solid liver nodules (focal nodular hyperplasia or adenoma). As revealed previously, the ADC values of cysts and hemangiomas were significantly higher due to their higher fluid content, resulting in more freedom of water molecules. In contrast, malignant lesions showed the lowest ADC values, likely because of their increased cellular density and the resultant restricted diffusion of water molecules.[60,61] Therefore, ADC values were extremely reliable for distinguishing cysts and hemangiomas from malignant lesions, which were mainly solid lesions. However, ADC values were not effective in distinguishing between benign and malignant solid lesions. Considerable overlap of solid benign lesions and solid malignant lesions was observed. This resemblance was likely attributable to a similar restriction of water motion and a hypercellular nature. This overlap of solid benign lesions and malignant lesions limited the value of DWI in differentiating solid liver masses. The above results showed that ADC values were more helpful in differentiating malignant lesions from cysts and hemangiomas. Given that ADC values exhibited an excellent diagnostic performance for cystic lesions of the liver, we suggest that an analysis of ADC values should be routinely applied when it is difficult to make a definite diagnosis for complicated hepatic cystic lesions.

Diffusion gradient factor *b* (number, range, first *b* value, maximum *b* value) was 1 of the most important parameters affecting the results of the ADC calculation. To date, there has been a lack of consensus regarding optimal *b* values for diagnosing liver diseases. The various *b* values in the included studies made the ranges and thresholds of the ADC values difficult to interpret; therefore, we explored whether *b* values were the source of heterogeneity. Six sets of data distinguished malignancies from benign liver lesions with a dual *b* value, whereas the other sets used multi *b* values. In some studies,[62] ADC values resulting from at least 3 *b* values were associated with optimal imaging. Woo et al[63] reported that 8 *b* values would be better than 3 or 4 *b* values and that intravoxel incoherent motion imaging-derived parameters would provide more accurate and comprehensive information. However, Taouli et al[64] found equivalent results for the characterization of focal hepatic lesions by using dual *b* values and 4 *b* values. Similar to Taouli et al, our results revealed that the number of *b* values used for the ADC calculation was not sufficient to cause significant heterogeneity. No statistically significant difference was found between the diagnostic accuracy of dual *b* values and multi *b* values. Because multi *b* values cannot provide extra information,

but instead require long measurement times,[65] we suggest that the use of dual *b* values is sufficient for the characterization of FLLs.

In our study, we performed thorough literature searches and careful data extraction to assess the diagnostic accuracy of the ADC among Asian patients. The results based on a meta-analysis showed that the ADC values had excellent performance in assessing the malignancy of FLLs. Therefore, we reviewed all the relevant articles and extracted the ADC values of the main types of liver lesions to attempt to identify relative standardized criteria. Unfortunately, the heterogeneities of the data were too significant to achieve unified data with high clinical significance in Asia. For example, the maximum cut-off values (1.6×10^{-3} mm^2/s) were almost double the minimum values (0.81×10^{-3} mm^2/s), which confused doctors regarding their clinical application. This notable difference may be attributed to the different tumor sizes, pathological types, and range of *b* values described in various studies. Although existing data made it impossible to provide definite cut-off values, the results showed that ADC values play an excellent role in the differential diagnosis of hepatic lesions. Thus, ADC values are anticipated to be a promising diagnostic criterion for distinguishing malignant and benign FLLs, and should be routinely used in clinical practice. Similar meta-analyses are required to investigate the best cut-off values that are applicable for Asian patients when more relevant studies have been published.

5. Conclusions

In conclusion, ADC values showed a high diagnostic performance in distinguishing malignant from benign liver lesions. Ethnic and regional differences do exist in the clinical management of liver cancer, and ADC values may be particularly applicable for the Asian population. ADC values showed a better diagnostic performance for cystic lesions than solid lesions, and could be used as a promising method for definitively diagnosing hepatic cystic lesions. Meanwhile, dual *b* values could be sufficient for the characterization of FLLs, whereas multi *b* values may be unnecessary. Because it is a high-risk area for liver cancer, Asia urgently requires an accurate, efficient, and early diagnostic method to improve prognosis and reduce cancer-related mortality. Therefore, as a promising candidate, ADC data-sharing between different Asian countries and large-sample, multicenter clinical trials are required to establish specific standards for DWI analysis protocols and cut-off values for diagnosis.

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