RESEARCH ARTICLE

Combined Application of Gadoxetic Acid Disodium-Enhanced Magnetic Resonance Imaging (MRI) and Diffusion-Weighted Imaging (DWI) in the Diagnosis of Chronic Liver Disease-Induced Hepatocellular Carcinoma: A Meta-Analysis

Xiang Li¹, Chenxia Li¹, Rong Wang¹, Juan Ren², Jian Yang¹*, Yuelang Zhang¹*

¹ Department of Diagnostic Radiology, The First Affiliated Hospital of Xi’an Jiaotong University, Xi’an, Shaanxi Province, China, ² Department of Radiotherapy, The First Affiliated Hospital of Xi’an Jiaotong University, Xi’an, Shaanxi, China

These authors contributed equally to this work.

* cjr.yangjian@vip.163.com (JY); zhyl_003@163.com (YZ)

Abstract

Objective

Gadoxetic acid disodium (Gd-EOB-DTPA) is a magnetic resonance imaging (MRI) contrast agent to target the liver cells with normal function. In clinical practice, the Gd-EOB-DTPA produces high quality hepatocyte specific image 20 minutes after intravenous injection, so DWI sequence is often performed after the conventional dynamic scanning. However, there are still some disputes about whether DWI sequence will provide more effective diagnostic information in clinical practice. This study aimed to explore the diagnostic value of combining Gd-EOB-DTPA-enhanced MRI and DWI in the detection of hepatocellular carcinoma (HCC) in patients with chronic liver disease.

Methods

A systematic literature search was performed in the PubMed and Cochrane library database up to March 2015. The quality assessment of diagnostic accuracy studies (QUADAS) was used to evaluate the quality of studies. Heterogeneous test on the included literature was performed by using the software Review Manager 5.3. The MetaDiSc 1.4 software was used to calculate the pooled sensitivity, specificity, positive likelihood ratio and negative likelihood ratio; meanwhile the summary receiver operating characteristics (SROC) curve was drawn to compare the diagnostic performance.

Results

A total of 13 literatures were included in this study. In 8 literatures regarding HCC diagnosis based on Gd-EOB-DTPA-enhanced MRI, the pooled sensitivity: 0.90 (95% confidence
interval (CI): 0.88–0.93); specificity: 0.89 (95% CI: 0.85–0.92); positive likelihood ratio: 8.60 (95% CI: 6.20–11.92); negative likelihood ratio: 0.10 (95% CI: 0.08–0.14) were obtained. The area under curve (AUC) and Q values were 0.96 and 0.90, respectively. In 5 literatures relating to HCC diagnosis by combination of Gd-EOB-DTPA-enhanced MRI and DWI sequence, the pooled sensitivity: 0.88 (95% CI: 0.85–0.91), specificity: 0.96 (0.94–0.97), positive likelihood ratio: 19.63 (12.77–30.16), negative likelihood ratio: 0.10 (0.07–0.14) were obtained. The AUC value was 0.9833 and Q value was 0.9436. The AUC value of comprehensive evaluation method was significantly higher than that of Gd-EOB-DTPA-enhanced MRI alone (P<0.05).

**Conclusion**

Combination of Gd-EOB-DTPA-enhanced MRI and DWI sequence significantly improves in both the diagnostic accuracy and specificity of chronic liver disease-associated HCC.

**Introduction**

As a most common malignant tumors, hepatocellular carcinoma (HCC)’s mortality ranks third in all death of malignant tumors in developing countries [1]. Chronic liver disease including cirrhosis, is one of the most important factors contributing to the multistep progression of hepatocarcinogenesis, from benign regenerative nodules to early HCC, and finally to overt HCC [2].

Currently the diagnosis of hepatocellular carcinoma (HCC) is primarily based on imaging. Gadoxetic acid disodium (Gd-EOB-DTPA) is a liver specific contrast agent with unique EOB group, which can be uptake specifically by normal hepatocyte (about 50% uptake rate), thereby producing enhancement effect in liver cells 20 min after Gd-EOB-DTPA administration [3]. Therefore, it could provide useful information to distinguish abnormal hepatocytes (including HCC) from normal ones [4]. Golffieri. R. et al had shown that EOB-MRI has the capability of identifying the HCC precursors and portraying their biological behaviors, thus rapidly becoming a key imaging tool for the diagnosis of HCC and its precursors [5]. Furthermore, one study demonstrated that magnetic resonance imaging (MRI) using gadoxetic acid provided more accurate diagnosis in discriminating focal nodular hyperplasia (FNH) from hepatic adenoma (HA), identification of early HCC and pre-operative assessment of metastasis in liver parenchyma [6]. Diffusion-weighted imaging (DWI) can provide cellular information of HCC and also has been widely applied in lesion detection, lesion characterization, and assessment of treatment response to chemotherapeutic agents. Some researchers had revealed that diffusion-weighted MRI can provide additional information to differentiate HCC from DN or other pseudotumoral lesions [7,8]. Actually, diffusion-weighted MRI does provide enhanced diagnostic value in the detection and characterization of focal liver lesions [9,10]. Recently, Chen. J. et al had demonstrated that DWI had excellent and moderately high diagnostic accuracy for the detection of well-differentiated HCC and poorly-differentiated HCC, respectively [11].

In clinical practice, the Gd-EOB-DTPA produces high quality hepatocyte specific image 20 minutes after intravenous injection, so DWI sequence is often performed after the conventional dynamic scanning for both shorten the duration of the examination as a whole and provide target cellular and architectural changes through the differences in tissue diffusivity. Saito K. et al research had shown that the injection of Gd-EOB-DTPA followed by scan of DWI...
sequence did not affect the enhanced HCC diagnosis by Gd-EOB-DTPA [12]. There are still some disputes about whether DWI sequence will provide more effective diagnostic information in clinical practice. Some studies have shown that combined DWI sequences and hepatocyte specific contrast agent is conducive to differentiation of benign and malignant hepatic lesions [13–15]. However, some recent reports suggested that the added DWI sequence cannot significantly improve detection efficiency of malignant liver disease [16–18]. In this study, we performed meta-analysis in view of evidence based medicine, to make a comprehensive, objective and accurate evaluation on the HCC detection efficiency by combined application of Gd-EOB-DTPA-enhanced MRI and DWI sequences.

**Materials and Methods**

**Literature Search**

Literatures were searched from PubMed, Cochrane library database and reference as the main source of data, using terms combining any two keywords from (“diffusion-weighted magnetic resonance imaging” or “DWMRI” or “DWI”), (“Gadoxetic-acid-enhanced MRI” or “Gd-EOB-DTPA enhanced MRI”) and (“hepatocellular carcinoma” or “liver neoplasms”). Last search update to March 15, 2015. Literatures were screened from the title, abstract, intensive reading full-text, and reviews, comments, letters, animal models and case reports were excluded.

**Inclusion and Exclusion Criteria**

Inclusion criteria: (1) English literature; (2) subjects were patients with chronic liver disease with more than 30 cases; (3) the objective of research was to evaluate HCC diagnostic efficiency in hepatocyte specific phase or combined application of hepatocyte specific phase and DWI; (4) gold standard for HCC diagnosis was pathological examination or imaging follow-up; (5) data analysis was based on the number of lesions, the original data can be directly or indirectly provided, and indicators for HCC diagnosis can be calculated, including the true positive (TP) value, false positive (FP) value, false negative (FN) value, true negative (TN) value; (6) the quality of literature was evaluated using the quality assessment of diagnostic accuracy studies (QUADAS), and when there were more than 9 “Yes” from a total of 14 questions, the literature can be incorporated into the study, when there were more than 4 “No” or “Unclear”, the literature will be excluded [19,20]. Exclusion criteria: (1) review literature, system evaluation, letters, comments or animal models; (2) in addition to HCC, the study object was also suffering from other malignant lesions; (3) the research subject was less than 30 cases.

**Data Extraction and Quality Evaluation**

Data extraction was performed by three investigators independently who also performed the database searches, and any lack of clarity or disagreement was resolved through discussion. The investigators abstracted data from each study to obtain information on author, publication year, sample size, number of lesions, characteristics of the study population (age, gender), the size of the hepatocellular carcinoma, gold standard selection, types of liver disease and study design type (prospective, retrospective), diagnostic method, equipment and directly or indirectly obtained indicators really positive (TP) value, false positive (FP) value, false negative (FN) value, true negative (TN) value, sensitivity (Se) and specificity (Sp). The quality of relevant studies were further evaluated using the quality assessment of diagnostic accuracy studies (QUADAS) tool. It includes 14 items to assess risk of bias, source of variation and reporting quality. The answer to each item was “yes,” “no,” or “unclear.”
Statistical Analysis

Review Manager 5.3 software was used to analyze the heterogeneity of the research, and the Q test was applied to calculate the inconsistency index $I^2$ value. Due to the low sensitivity of Cochrane Q test, the significance level $\alpha = 0.1$ was adopted for conservation [21,22], and $P > 0.1$ indicates there is no statistical heterogeneity between studies, $P < 0.1$ indicates there is heterogeneity. $I^2$ was used to quantitatively evaluate heterogeneity, and when $I^2 < 25\%$, fixed effect model was used for meta-analysis; when $25\% < I^2 < 50\%$, random effect model was used; when $I^2 > 50\%$, the sources of heterogeneity was analyzed firstly, if there was no obvious clinical heterogeneity and the sources of heterogeneity cannot be found, the random effect model was used. The MetaDiSc 1.4 software was used to perform meta-analysis based on various indicators, including sensitivity (Se), specificity (Sp), positive likelihood ratio (+LR), negative likelihood ratio (−LR). All indicators were represented as pooled results and the 95% confidence interval (CI). In addition, the summary receiver operating characteristics (SROC) curve was constructed to make comprehensive evaluation on the diagnostic tests. Z tests was performed to determine the difference in AUC between the two diagnostic methods, with $P < 0.05$ regarded as statistically significant. In this paper, funnel plot was drawn to judge whether there is a publication bias. If there is no bias, the graph is symmetric funnel shape. On the contrary, any deviations in the graph prove the existence of publication bias. However, there is no need for publication bias test for the diagnostic method from less literature.

Results

Literature Selection

Database was searched using keywords and the search scope was expanded by reference literature, and a total of 848 articles were obtained. Firstly, through extensive reading the title and abstract, a total of 769 literatures were excluded, including reviews, comments, letters and animal models. After careful reading abstract, 45 articles were excluded. Then after intensive reading the full-text, other 21 articles were excluded. Finally this study included 13 articles, including 8 articles regarding HCC diagnosis based on Gd-EOB-DTPA-enhanced MRI [23–30], and 5 articles relating to HCC diagnosis by combination of Gd-EOB-DTPA-enhanced MRI and DWI sequence [31–35]. The flow chart of the literature selection is shown in Fig 1.

Data Extraction and Quality Assessment

This study included 13 literatures, with the case number of 945 (485 cases of evaluation on Gd-EOB-DTPA-enhanced MRI, 460 cases of evaluation on combined application of Gd-EOB-DTPA-enhanced MRI and DWI), and total lesion number of 1385 (720 lesions of evaluation on Gd-EOB-DTPA-enhanced MRI, 665 lesions of evaluation on combined application of Gd-EOB-DTPA-enhanced MRI and DWI). Detailed information of the included literature is shown in Table 1. In addition, the various indicators obtained directly or indirectly from each study were shown in Table 2, including true positive (TP) value, false positive (FP) value, false negative (FN) value, true negative (TN) value, sensitivity (Se) and specificity (Sp). Among 8 literatures of evaluation on Gd-EOB-DTPA-enhanced MRI, there are 2 literatures with lesion size $\leq 3.0$ cm [27,29], 2 literatures used pathological diagnosis as the only gold standard [28,29], and 2 literatures were prospective study [26,28]. Among 5 literatures of evaluation on combined application of Gd-EOB-DTPA-enhanced MRI and DWI, there was 1 literature with lesion size $\leq 3.0$ cm [34], and all 5 literatures used pathological diagnosis as the only gold standard. In literature of Lee MH et al [32], only part of the patients underwent DWI, and detail characteristics (age, gender) and lesion size had not been record. Additionally, of the 5
Literatures identified through database searching (n=848)

- Literatures were deleted through extensive reading the title and referring to the inclusion and exclusion criteria (n=769)

- Literatures excluded after careful reading abstract (n=45)
  - 7 Subjects were less than 30 cases
  - 11 Evaluation on HCC diagnosis was used DWI alone
  - 13 Subjects also had other malignant lesions other than HCC
  - 9 The study purpose was to explore the image characteristics or diagnosis criteria
  - 2 Data has been updated
  - 2 Data analysis was based on the patients’ characteristics
  - 1 Chinese literatures

- Literatures excluded after careful reading full-text (n=21)
  - 9 Subjects had diseases other than chronic liver disease or disease of unknown etiology
  - 1 Male patients alone
  - 3 Complete data can not be obtained
  - 5 Non case-control study
  - 3 “unclear” or > 4 “no” in QUADAS

This study included 13 literatures
- 8 literatures evaluating Gd-EOB-DTPA-enhanced MRI in HCC diagnosis
- 5 literatures evaluating Gd-EOB-DTPA-enhanced MRI and DWI sequence in HCC diagnosis

Fig 1. Flow diagram of study selection.
doi:10.1371/journal.pone.0144247.g001

literatures, 2 literatures [32,35] with b values of 0 and 800 sec/mm², 2 literatures [31,34] with 0, 100 and 800 sec/mm², and 1 literature [33] with 1000 sec/mm². Hyperintense on DWI was considered as primary assessment criteria in sensitivity and specificity analysis for hepatocellular carcinoma, although apparent diffusion coefficient which is used to other analysis was calculated in one literature [35]. One study [8] found DWI with b value of 1000 sec/mm² has a sensitivity of 79.0% according to the difference of signal intensity between liver lesions and adjacent hepatic parenchyma. Another research [34] demonstrated on b = 800 sec/mm² images the sensitivity performed by different observers is 79.9%, 77.7% and 78.8% respectively, which is similar to b = 1000 sec/mm² images. So, various b values have a little influence on the result of this research. The evaluations on the design characteristics based on the QUADAS tool are shown in Table 3.

Heterogeneity Test and Publication Bias

Fig 2A shows heterogeneity test results from included literatures regarding HCC diagnosis based on Gd-EOB-DTPA-enhanced MRI. Clearly, there is no statistical heterogeneity between different studies (P = 0.34), and the fixed effect model can be used for meta-analysis (I² = 11%). The summary diagnostic OR was 1.17 (95% CI: 0.73–1.89); Fig 2B displays heterogeneity test results from included literatures relating to HCC diagnosis by combination of Gd-EOB-DTPA-enhanced MRI and DWI sequence. There is no statistical heterogeneity between different studies (P = 0.33), and fixed effect model can be still used for meta-analysis (I² = 14%). The summary diagnostic OR was 0.72 (95% CI: 0.43–1.19). Funnel plot (Fig 3) shows
concentrated distribution of each point with symmetrical funnel shape, which indicates that there is no publication bias (P = 0.305, Egger's test).

Meta-Analysis

In 8 literatures regarding HCC diagnosis based on Gd-EOB-DTPA-enhanced MRI, the pooled sensitivity: 0.90 (95% confidence interval (CI): 0.88–0.93); specificity: 0.89 (95% CI: 0.85–0.92); positive likelihood ratio: 8.60 (95% CI: 6.20–11.92); negative likelihood ratio: 0.10 (95% CI: 0.08–0.14) were obtained (Fig 4). In 5 literatures relating to HCC diagnosis by combination of Gd-EOB-DTPA-enhanced MRI and DWI sequence, the pooled sensitivity: 0.88 (95% CI: 0.85–0.91), specificity: 0.96 (0.94–0.97), positive likelihood ratio: 19.63 (12.77–30.16), negative likelihood ratio: 0.10 (0.07–0.14) were obtained (Fig 5). As shown in Fig 6, in Gd-EOB-DTPA-enhanced MRI group and combined Gd-EOB-DTPA-enhanced MRI and DWI group, the area under the curve (AUC) of SROC were 0.9595 and 0.9833; Q/C3 values were 0.9037 and 0.9436, respectively. The above data demonstrated that combined Gd-EOB-DTPA-enhanced MRI and DWI group had higher specificity, with no overlapping 95% confidence intervals, the positive likelihood ratio reached 19.63 with practical significance, and AUC value, the comprehensive evaluation index of diagnosis test, was higher than Gd-EOB-DTPA-enhanced MRI group (P = 0.019). The negative likelihood ratio and sensitivity were similar between two groups.

Table 1. Basic characteristics of included literatures.

| Author       | Year | Cases | Lesion | M/F | Age(Scope) | Size(Scope) | Gold standard | Study design | Basic disease | Diagnosis | Equipment  |
|--------------|------|-------|--------|-----|-------------|-------------|---------------|--------------|---------------|-----------|------------|
| Ahn SS[23]   | 2010 | 59    | 113    | 50/9| 57 (29–75)  | 2.8 (0.4–11) | P*/R²         | R            | C*           | 1         | 1.5T+3.0T  |
| Baek CK[24]  | 2012 | 51    | 73     | 43/8| ND² (32–80) | 2.98(0.2–10) | P/I           | R            | C/H²         | 1         | 3.0T       |
| Bashir MR[25]| 2013 | 100   | 125    | 57/43| 57.9(29–91) | ND           | P/I           | R            | C            | 1         | 1.5T+3.0T  |
| Di Martino M[26]| 2010 | 58 | 109    | 39/19| 63(35–84)   | 1.8(0.3–7.0) | P/I           | P            | C            | 1         | 1.5T       |
| Haradome H[27]| 2011 | 52   | 60     | 60/15| 54.7(42–67) | 1.74(0.5–2.8) | P/I           | R            | C            | 1         | 1.5T       |
| Kim SH[28]   | 2009 | 62    | 83     | 54/8| 55(31–76)   | 2.9 (0.5–10.5)| P             | P            | C/H         | 1         | 3.0T       |
| Rhee H[29]   | 2012 | 34    | 60     | 30/4| 57(30–66)   | 1.44 (0.4–3.0) | P/I           | R            | C/H         | 1         | 3.0T       |
| Sun HY[30]   | 2010 | 69    | 97     | 56/13| ND          | 1.37 ± 0.41  | P/I           | R            | C            | 1         | 3.0T       |
| Hwang J[31]  | 2014 | 63    | 160    | 54/9| 52(33–68)   | 2(0.5–7.8)   | P             | R            | C/H²        | 2         | 3.0T       |
| Lee MH[32]   | 2011 | 40    | 42     | UN  | UN³        | UN           | P             | R            | C            | 2         | 3.0T       |
| Ooka Y[33]   | 2013 | 54    | 87     | 40/14| 68±10.5    | 1.84(0.3–6.5) | P             | R            | C            | 2         | 1.5T       |
| Park MJ[34]  | 2012 | 260   | 323    | 185/75| 55.1±7.9   | * ≤ 2.0      | P             | R            | L¹          | 2         | 3.0T       |
| Inchingolo R[35]| 2015 | 43  | 53     | 34/9| 66(46–82)  | 2.17(1–4)    | P             | R            | C            | 2         | 1.5T       |

*ND, not documented.
*UN, unclear.
*P, Pathological follow up.
*²I, Imaging follow up.
*³R, Retrospective study.
*⁴P, Prospective study.
*⁵C, Cirrhosis.
*⁶H, Hepatitis.
*⁷L, Chronic liver disease.
*¹, Gd-EOB-DTPA-enhanced MRI
*², Gd-EOB-DTPA-enhanced MRI and DWI
doi:10.1371/journal.pone.0144247.t001
Discussion

To the best of our knowledge, this is the first meta-analysis on the diagnostic performance of HCC using MR imaging with Gd-EOB-DTPA and DWI sequence. After systematic review and evaluation, this study included 13 literatures, among which 8 is to evaluate Gd-EOB-DTPA-enhance MRI, and 5 is to comprehensively evaluate Gd-EOB-DTPA-enhance MRI and DWI sequence in diagnosis of chronic liver disease associated HCC. In diagnostic method of combined evaluation, the pooled specificity was significantly higher than that in Gd-EOB-DTPA-enhance MRI, suggesting that the diagnostic methods greatly reduce misdiagnosis rate. In addition, the pooled positive likelihood ratio reaches 19.63, which indicates that the possibility of HCC is very high, if the diagnosis of the suspected cases is positive. However, one single index cannot reflect the whole test reaction, with only reference value. SROC curves, which are used to make a full and accurate evaluation on the diagnostic tests, are drawn according to the ratio of various studies. The results show that combined evaluation of Gd-EOB-DTPA-enhance MRI and DWI has higher AUC value than Gd-EOB-DTPA-enhance MRI alone (P < 0.05). This indicates the combined diagnostic method can acquire more diagnostic information and make more accurate evaluation of HCC in chronic liver disease.

To investigate heterogeneity is the key to understand the possible factors affecting the estimation accuracy, and whether it is appropriate to evaluate combination of different studies. Threshold effect is one of the important causes for the heterogeneity of the diagnostic tests [39]. Threshold analysis was performed in studies on HCC diagnostic evaluation by combined diagnostic method and Gd-EOB-DTPA-enhance MRI alone, and the Spearman rank correlation coefficient were -0.429 (P = 0.289) and -0.700 (P = 0.188), respectively. This result indicates that the heterogeneity among sensitivity, specificity, positive likelihood ratio and negative likelihood ratio was not caused by the threshold effect. Subsequently, meta regression analysis was performed on literatures evaluating diagnostic value by Gd-EOB-DTPA-enhance MRI, to

Table 2. Various indicators of included literatures.

| Author       | Year | TP  | FP  | FN  | TN  | Se  | Sp  |
|--------------|------|-----|-----|-----|-----|-----|-----|
| Ahn SS[23]   | 2010 | 77  | 2   | 7   | 27  | 91.7| 93.1|
| Baek CK[24]  | 2012 | 67  | 4   | 6   | 33  | 91.8| 89.2|
| Bashir MR[25]| 2013 | 63  | 14  | 7   | 42  | 90.9| 74.2|
| Di Martino M[26]| 2010 | 74  | 2   | 13  | 20  | 85  | 91  |
| Haradome H[27]| 2011 | 52  | 4   | 8   | 35  | 86.7| 89.7|
| Kim SH[28]   | 2009 | 78  | 1   | 5   | 48  | 94  | 97.96|
| Rhe H[29]    | 2012 | 27  | 5   | 2   | 26  | 93.1| 83.9|
| Sun HY[30]   | 2010 | 41  | 2   | 3   | 51  | 96.2| 93.2|
| Hwang J[31]  | 2014 | 89  | 3   | 24  | 44  | 78.8| 91.5|
| Kim BH[32]   | 2011 | 21  | 2   | 10  | 8   | 68  | 73  |
| Ooka Y[33]   | 2013 | 83  | 15  | 4   | 339 | 95.4| 95.7|
| Park MJ[34]  | 2012 | 165 | 4   | 14  | 140 | 92.4| 97.5|
| Inchingolo R[35]| 2015 | 41  | 0   | 1   | 11  | 97.6| 100 |

aTP, true positive value.
bFP, false positive value.
cFN, false negative value.
dTN, true negative value.
eSe, sensitivity.
fSp, specificity.

doi:10.1371/journal.pone.0144247.t002
### Table 3. Evaluation on included and excluded literatures.  

| Author       | Case representation | Clear inclusion criteria | Gold standard reliability | Time between gold standard and test | Sample accepts criteria | Same gold standard | Gold standard independence | Clear test description | Blinded test | Blinded gold standard | Obtained same clinical data | Difficult interpretation of results | Exit explanation |
|--------------|---------------------|--------------------------|---------------------------|-----------------------------------|-------------------------|-------------------|--------------------------|------------------------|--------------|----------------------|-----------------------------|-----------------------------------|------------------|
| Included literature |
| Ahn SS       | Y                   | Y                        | Y                          | Un                                | Y                      | Y                 | Y                        | Y                      | Un          | Y                    | Y                          | Y                                 | Y                |
| Baek CK      | Y                   | Y                        | Y                          | Un                                | Y                      | Y                 | Y                        | Y                      | Un          | Y                    | Y                          | Y                                 | Y                |
| Bashir MR    | Y                   | Y                        | Y                          | Y                                 | N                      | Y                 | Y                        | Y                      | Un          | Y                    | Y                          | Y                                 | Y                |
| Di MartiN M  | Y                   | Y                        | Y                          | Y                                 | N                      | Y                 | Y                        | Y                      | Y           | Y                    | Y                          | Y                                 | Y                |
| Haradome H   | Y                   | Y                        | Y                          | Un                                | Y                      | Y                 | Y                        | Y                      | Y           | Y                    | Y                          | Y                                 | Y                |
| Kim SH       | Y                   | Y                        | Y                          | Y                                 | Y                      | Y                 | Y                        | Y                      | Y           | Y                    | Y                          | Y                                 | Y                |
| Rhee H       | Y                   | Y                        | Y                          | Un                                | Y                      | Y                 | Y                        | Y                      | Y           | Y                    | Y                          | Y                                 | Y                |
| Sun HY       | Y                   | Y                        | Y                          | Y                                 | Y                      | Y                 | Y                        | Y                      | Y           | Y                    | Y                          | Y                                 | Y                |
| Inchingolo R | Y                   | Y                        | Y                          | Y                                 | Y                      | Y                 | Y                        | Y                      | Y           | Y                    | Y                          | Y                                 | Y                |
| Hwang J      | Y                   | Y                        | Y                          | Un                                | Y                      | Y                 | Y                        | Y                      | Y           | Y                    | Y                          | Y                                 | Y                |
| Lee MH       | Y                   | Y                        | Y                          | Y                                 | Y                      | Y                 | Y                        | Y                      | Y           | Y                    | Y                          | Y                                 | Y                |
| Ooka Y       | Y                   | Y                        | Y                          | Un                                | Y                      | Y                 | Y                        | Y                      | Y           | Y                    | Y                          | Y                                 | Y                |
| Park MJ      | Y                   | Y                        | Y                          | Y                                 | Y                      | Y                 | Y                        | Y                      | Y           | Y                    | Y                          | Y                                 | Y                |
| Excluded literature |
| Baird AJ     | Y                   | Un                       | Y                          | Y                                 | Y                      | Y                 | Y                        | Y                      | Y           | Y                    | Y                          | Y                                 | N                |
| Granito A    | Y                   | Y                        | Y                          | Un                                | Y                      | N                 | Y                        | Un                     | Y           | Y                    | Y                          | Y                                 | Y                |
| Takahashi M  | N                   | Y                        | Y                          | Y                                 | Y                      | Y                 | Y                        | Y                      | Un          | Un                   | N                          | Y                                 | Y                |

*aThe quality of literature was evaluated using the quality assessment of diagnostic accuracy studies (QUADAS) [20]

*b literature excluded by more than 4 in “no” or “Unclear” answer in QUADAS

Y, Yes; Un, Unclear; N, No.

doi:10.1371/journal.pone.0144247.t003
**Fig 2. Heterogeneity test results.** (A) the estimates for Gd-EOB-DTPA-enhanced MRI in HCC diagnosis. (B) the estimates for combination of Gd-EOB-DTPA-enhanced MRI and DWI sequence in HCC diagnosis.

doi:10.1371/journal.pone.0144247.g002

**Fig 3. Funnel plot of the estimates for Gd-EOB-DTPA-enhanced MRI in HCC diagnosis.** (A) sensitivity analysis. (B) specificity analysis. (C) positive likelihood ratio analysis. (D) negative likelihood ratio analysis.

doi:10.1371/journal.pone.0144247.g003
Fig 4. Forest plots of the estimates for Gd-EOB-DTPA-enhanced MRI in HCC diagnosis. (A) sensitivity analysis. (B) specificity analysis. (C) positive likelihood ratio analysis. (D) negative likelihood ratio analysis.

doi:10.1371/journal.pone.0144247.g004

Fig 5. Forest plots of the estimates for combination of Gd-EOB-DTPA-enhanced MRI and DWI sequence in HCC diagnosis.

doi:10.1371/journal.pone.0144247.g005
explore the sources of heterogeneity [39,40]. Evaluation covariates included case number, lesion number, lesion size, average age, the experiment design type and the equipment. The results showed that the above covariates were not sources of heterogeneity ($P > 0.05$) (Table 4), which might be caused by limited number of the included literatures. Due to small number of included literatures in the comprehensive evaluation method, it is not suitable for meta regression analysis. Although the source of heterogeneity is not found, the combined statistics obtained from this study still have some reference value. On evaluation HCC diagnosis by Gd-EOB-DTPA-enhance MRI, the pooled sensitivity and specificity of our study are similar to those of Wu LM [41], with more precise 95% confidence interval. In the specificity analysis of

![Fig 6. Summary receiver operating characteristic curves (SROC).](image)

(A) SROC curve for Gd-EOB-DTPA-enhanced MRI in HCC diagnosis. (B) SROC curve for combination of Gd-EOB-DTPA-enhanced MRI and DWI sequence in HCC diagnosis.

doi:10.1371/journal.pone.0144247.g006

### Table 4. Meta regression analysis.

| Variable            | Coefficient | Standard error | $P$ value | RDOR [95%CI]    |
|---------------------|-------------|----------------|-----------|-----------------|
| Cte.                | 32.418      | 14.3682        | 0.2656    | —               |
| Mean age $^a$       | -0.495      | 0.2772         | 0.3252    | 0.61 (0.02;20.65) |
| Patient             | -0.049      | 0.0358         | 0.4009    | 0.95 (0.60;1.50)  |
| Lession             | 0.041       | 0.0505         | 0.5692    | 1.04 (0.55;1.98)  |
| Study design        | 1.436       | 1.2792         | 0.4633    | 4.20 (0.00;48126481.50) |
| Diameter $^b$       | -0.742      | 1.2436         | 0.6575    | 0.48 (0.00;3470717.50) |
| Equipment           | -2.000      | 0.8555         | 0.8535    | 0.82 (0.00;43030.13) |

$^a$Baek CK [24] The average age was not recorded, and was replaced by the mean of the age range.

$^b$Two categorical variable analysis was performed according to the diameter of liver cell carcinoma $>$3cm or $\leq$3cm.

RDOR, relative diagnostic odds ratios.

doi:10.1371/journal.pone.0144247.t004
the combined evaluation method, P value was 0.23 and I² value was 28.6%, which indicates the results was homogeneous and have reference value.

Combination of Gd-EOB-DTPA-enhanced MRI and DWI sequence has considerable significance in the diagnosis of HCC. Several studies reported that most HCCs with various degree of differentiation demonstrate hypointensity on gadoxetic-acidenhanced HBP images, which was due to the change in expression of OATP1B3, a liver-specific human drug transporter [3,42]. However, early-enhancing non-tumorous (EN) hepatic lesions may occasionally present with hypointensity during the hepatocyte phase, thus causing a diagnostic dilemma [43]. In addition, in clinical practice, HCCs frequently demonstrate atypical and inconclusive enhancement patterns different from the characteristic enhancement pattern of typical HCCs, and this may cause a delay in diagnosis [44]. Recently the Japan Society of Gastroenterology and Hepatology has proposed clinical practice guidelines and suggested that a nodular lesion showing an atypical imaging pattern on dynamic CT should be further examined by gadoxetic acid-enhanced MR imaging or contrast-enhanced ultra-sonography [45]. Inchingolo R et al. reported that suspicion should be raised for HCC, or at least high-grade dysplastic nodules (HGDN), when existing hyperintensity on DWI, especially in association with hypointensity on hepatobiliary phase, and low lesion-to-liver ratios, thus helping the characterization of atypically enhancing lesions [35]. Also, one study demonstrated that hyper-intensity on both T2WI and DW imaging are conducive to the diagnosis of hypervascular HCCs smaller than 1 cm [46]. Therefore, the addition of DW imaging to gadoxetic acid-enhanced MR imaging could be a promising strategy for both detection and characterization of HCC. Additionally, the authors of one recent research [33] suggest that a comprehensive evaluation using gadoxetic acid-enhanced MRI including a gradient dual-echo sequence and DWI is superior to CTAP/CTHA for the pre-therapeutic detection of HCC, regardless of nodule size.

Compared with other meta-analysis of diagnostic tests, this study has the following advantages: (1) In comprehensive evaluation on HCC diagnosis by Gd-EOB-DTPA-enhance MRI and DWI, all the gold standard was pathological examination; (2) All included literatures are acquired after detailed and clear literature screening process, and all cases had a history of chronic liver disease; (3) Before meta-analysis, heterogeneity analysis was performed using Review Manager 5.3 software, and to ensure homogeneity between various included studies; (4) More detailed data extraction was performed in all literatures for in-depth analysis and research.

The limitations of this study are as follows: firstly, the number of included literatures is limited; especially there are only 5 literatures on comprehensive consideration method. Though the included literature was small, the total number of subjects was up to 945 cases, including 460 cases with comprehensive consideration method. Of the total 1385 lesions, 665 lesions were diagnosed by comprehensive consideration method. All literatures were screened by QUADAS tools, with high quality and representative for each study. Secondly, most included literatures were retrospective studies, with only 2 prospective studies. However, the final diagnosis was not known for all researchers in the process of imaging diagnosis. In addition, the gold standard used was pathological examination or imaging follow-up, which was in accordance with the clinical diagnostic criteria, and can make accurate judgments of HCC.

**Conclusion**

Compared with Gd-EOB-DTPA-enhance MRI, combined evaluation method increases diagnosis accuracy and specificity of HCC in chronic liver disease. Further studies with larger sample remain to be needed to investigate diagnostic value in HCC by combined application of Gd-EOB-DTPA-enhance MRI and DWI.
Supporting Information

S1 Fig. PRISMA 2009 Flow Diagram.
(DOC)

S1 Table. PRISMA 2009 Checklist.
(DOC)

Acknowledgments

This work was supported technically by the Clinical Research Center, the First Affiliated Hospital, Xi’an Jiaotong University, China.

Author Contributions

Conceived and designed the experiments: YZ JY. Performed the experiments: CL RW JR. Analyzed the data: XL. Contributed reagents/materials/analysis tools: XL CL RW JR. Wrote the paper: XL. Revised the manuscript: JY YZ.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010 Dec 15; 127(12):2893–917. doi:10.1002/ijc.25516 PMID: 21351269.

2. Choi BI, Takayasu K, Han MC. Small hepatocellular carcinomas and associated nodular lesions of the liver: pathology, pathogenesis, and imaging findings. AJR Am J Roentgenol 1993 Jun; 160(6):1177–87. PMID: 8386818.

3. Kudo M Will Gd-EOB. MRI change the diagnostic algorithm in hepatocellular carcinoma? Oncology 2010 Jul; 78 Suppl 1:87–93. doi:10.1159/000315235 PMID: 20616589.

4. Lee JM, Yoon JH, Kim KW. Diagnosis of hepatocellular carcinoma: newer radiological tools. Semin Oncol 2012 Aug; 39(4):399–409. doi:10.1053/j PMID: 22846858.

5. Golffieri R, Garzillo G, Ascanio S, Renzulli M. Focal lesions in the cirrhotic liver: their pivotal role in gadoxetic acid-enhanced MRI and recognition by the Western guidelines. Dig Dis 2014; 32(6):696–704. doi:10.1159/000368002 PMID: 25376286.

6. Palmucci S. Focal liver lesions detection and characterization: The advantages of gadoxic acid-enhanced liver MRI. World J Hepatol 2014 Jul 27; 6(7):477–85. doi:10.4254/wjh.v6.i7.477 PMID: 25067999.

7. Xu PJ, Yan FH, Wang JH, Shan Y, Ji Y, Chen CZ. Contribution of diffusion-weighted magnetic resonance imaging in the characterization of hepatocellular carcinomas and dysplastic nodules in cirrhotic liver. J Comput Assist Tomogr 2010 Jul; 34: 506–512. doi: 10.1097/RCT.0b013e3181da3671 PMID: 20657216.

8. Vandecaveye V, De Keyzer F, Verslype C, Op de Beeck K, Komuta M, Topal B, et al. Diffusion-weighted MRI provides additional value to conventional dynamic contrast-enhanced MRI for detection of hepatocellular carcinoma. Eur Radiol 2009 Oct; 19(10):2456–66. doi: 10.1007/s00330-009-1431-5 PMID: 19440718.

9. Parikh T, Drew SJ, Lee VS, Wong S, Hecht EM, Babb JS, et al. Focal liver lesion detection and characterization with diffusion-weighted MR imaging: comparison with standard breath-hold T2-weighted imaging. Radiology 2009 Mar; 246(3):812–22. doi: 10.1148/radiol.2463070432 PMID: 18223123.

10. Chen ML, Zhang XY, Qi LP, Shi QL, Chen B, Sun YS. Diffusion-weighted images (DWI) without ADC values in assessment of small focal nodules in cirrhotic liver. Chin J Cancer Res 2014 Feb; 26(1):38–47. doi: 10.3978/j.issn.1000-9604.2014.01.07 PMID: 24653625.

11. Chen J, Wu M, Liu R, Li S, Gao R, Song B. Preoperative evaluation of the histological grade of hepatocellular carcinoma with diffusion-weighted imaging: a meta-analysis. PLoS One 2015 Feb 6; 10(2):e0117661. doi: 10.1371/journal.pone.0117661 PMID: 25658359.

12. Saito K, Araki Y, Park J, Metoki R, Katsuyama H, Nishio R, et al. Effect of Gd-EOB-DTPA on T2-weighted and diffusion-weighted images for the diagnosis of hepatocellular carcinoma. J Magn Reson Imaging 2010 Jul; 32(1):229–34. doi: 10.1002/jmri.22219 PMID: 20578029.
13. Kim HS, Kim SH, Kang TW, Song KD, Choi D, Park CK. Value of gadoxetic acid-enhanced and diffusion-weighted MR imaging in evaluation of hepatocellular carcinomas with atypical enhancement pattern on contrast-enhanced multiphasic MDCT in patients with chronic liver disease. Eur J Radiol 2015 Apr; 84(4):555–62. doi: 10.1016/j.ejrad.2014.12.023 PMID: 25617950.

14. Holzapfel K, Eiber MJ, Fingerle AA, Bruegel M, Rummery EJ, Gaa J. Detection, classification, and characterization of focal liver lesions: Value of diffusion-weighted MR imaging, gadoxetic acid-enhanced MR imaging and the combination of both methods. Abdom Imaging 2012 Feb; 37(1):74–82. doi: 10.1007/s00261-011-9758-1 PMID: 21597893.

15. Kim MY, Kim YK, Park HJ, Park MJ, Lee WJ, Choi D. Diagnosis of focal liver lesions with gadoxetic acid-DTPA-enhanced MR imaging and 64-section multidetector CT in the Detection of hepatocellular carcinoma in cirrhotic patients. Radiology 2010 Sep; 256(3):806–18. doi: 10.1148/radiol.2563091574 PMID: 19977608.

16. Di Martino M, Di Miscio R, De Filippis G, Lombardo CV, Saba L, Geiger D, et al. Detection of small (< 2 cm) HCC in cirrhotic patients: added value of diffusion MR-imaging. Abdom Imaging 2013 Dec; 38(6):1254–62. doi: 10.1007/s00261-013-0009-5 PMID: 23857505.

17. Zhao XT, Li WX, Chai WM, Chen KM. Detection of small hepatocellular carcinoma using gadoxetic acid-enhanced MRI: Is the addition of diffusion-weighted MRI at 3.0T beneficial? J Dig Dis 2014 Mar; 15(3):137–45. doi: 10.1111/1751-2980.12119 PMID: 24354621.

18. Marks RM, Ryan A, Heba ER, Tang A, Wolfson TJ, Gamst AC, et al. Diagnostic per-patient accuracy of an abbreviated hepatobiliary phase gadoxetic acid-enhanced MRI for hepatocellular carcinoma surveillance. AJR Am J Roentgenol 2015 Mar; 204(3):527–35. doi: 10.2214/AJR.14.12986 PMID: 25714281.

19. Wu LM, Xu JR, Hua J, Chen J, Hu J. A pooled analysis of diffusion-weighted imaging in the diagnosis of hepatocellular carcinoma in chronic liver diseases. J Gastroenterol Hepatol 2013 Feb; 28(2):227–34. doi: 10.1111/jgh.12054 PMID: 23190006.

20. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol 2003 Nov 10; 3:25. PMID: 14606960.

21. Mocellin S, Lens MB, Pasquali S, Pilati P, Chiarion Sileni V. Interferon alpha for the adjuvant treatment of cutaneous melanoma. Cochrane Database Syst Rev 2013 Jun 18; 6:CD008955. doi: 10.1002/14651858.CD008955.pub2 PMID: 23775773.

22. Touma Z, Farra C, Hamdan A, Shamseddine W, Uthman I, Hourani H, et al. TNF polymorphisms in patients with Behcet disease: a meta-analysis. Arch Med Res 2010 Feb; 41(2):142–6. doi: 10.1016/j.arcmed.2010.02.002 PMID: 20470944.

23. Ahn SS, Kim MJ, Lim JS, Hong HS, Chung YE, Choi JY. Added value of gadoxetic acid-enhanced hepatobiliary phase MR imaging in the diagnosis of hepatocellular carcinoma. Radiology 2010 May; 255(2):459–66. doi: 10.1148/radiol.10091388 PMID: 20413759.

24. Baek CK, Choi JY, Kim KA, Park MS, Lim JS, Chung YE, et al. Hepatocellular carcinoma in patients with chronic liver disease: a comparison of gadoxetic acid-enhanced MRI and multiphasic MDCT. Clin Radiol 2012 Feb; 67(2):148–56. doi: 10.1016/j.crad.2011.08.011 PMID: 21920517.

25. Bashir MR, Gupta RT, Davenport MS, Allen BC, Jaffe TA, Ho LM, et al. Hepatocellular carcinoma in a North American population: does hepatobiliary MR imaging with Gd-EOB-DTPA improve sensitivity and confidence for diagnosis? J Magn Reson Imaging 2013 Feb; 37(2):398–406. doi: 10.1002/jmri.23818 PMID: 23011874.

26. Di Martino M, Marin D, Guerini A, Baski M, Galati F, Rossi M, et al. Intraindividual comparison of gadoxetic acid disodium-enhanced MR imaging and 64-section multidetector CT in the Detection of hepatocellular carcinoma in patients with cirrhosis. Radiology 2010 Sep; 256(3):806–16. doi: 10.1148/radiol.10091334 PMID: 20720069.

27. Haradome H, Graziolli L, Tinti R, Morone M, Motosugi U, Sano K, et al. Additional value of gadoxetic acid-DTPA-enhanced hepatobiliary phase MR imaging in the diagnosis of early-stage hepatocellular carcinoma: comparison with dynamic triple-phase multidetector CT imaging. J Magn Reson Imaging 2011 Jul; 34(1):69–78. doi: 10.1002/jmri.22588 PMID: 21598343.

28. Kim SH, Kim SH, Lee J, Kim MJ, Jeon YH, Park Y, et al. Gadoxetic acid-enhanced MRI versus triple-phase MDCT for the preoperative detection of hepatocellular carcinoma. AJR Am J Roentgenol 2009 Jun; 192(6):1675–81. doi: 10.2214/AJR.08.1262 PMID: 19457834.

29. Rhee H, Kim MJ, Park MS, Kim KA. Differentiation of early hepatocellular carcinoma from benign hepatocellular nodules on gadoxetic acid-enhanced MRI. Br J Radiol 2012 Oct; 85(1018):e387–44. doi: 10.1259/bjr/13212920 PMID: 22553295.

30. Sun HY, Lee JM, Shin CI, Lee DH, Moon SK, Kim KW, et al. Gadoxetic acid-enhanced magnetic resonance imaging for differentiating small hepatocellular carcinomas (< = 2 cm in diameter) from arterial enhancing pseudolesions: special emphasis on hepatobiliary phase imaging. Invest Radiol 2010 Feb; 45(2):96–103. doi: 10.1097/RLI.0b013e3181c5f0a7 PMID: 20057319.
31. Hwang J, Kim YK, Kim JM, Lee WJ, Choi D, Hong SS. Pretransplant diagnosis of hepatocellular carcinoma by gadoxetic acid-enhanced and diffusion-weighted magnetic resonance imaging. Liver Transpl 2014 Dec; 20(12):1436–46. doi: 10.1002/lt.23974 PMID: 25103727.

32. Lee MH, Kim SH, Park MJ, Park CK, Rhim H. Gadoxetic acid-enhanced hepatobiliary phase MRI and high-b-value diffusion-weighted imaging to distinguish well-differentiated hepatocellular carcinomas from benign nodules in patients with chronic liver disease. AJR Am J Roentgenol 2014 Dec; 20(12):1436–46.

33. Ooka Y, Kanai F, Okabe S, Ueda T, Shimofusa R, Ogasawara S, et al. Gadoxetic acid-enhanced MRI compared with CT during angiography in the diagnosis of hepatocellular carcinoma. Magn Reson Imaging 2013 Jun; 31(5):748–54. doi: 10.1016/j.mri.2012.10.028 PMID: 23218794.

34. Park MJ, Kim YK, Lee MW, Lee WJ, Kim YS, Kim SH, et al. Small hepatocellular carcinomas: improved sensitivity by combining gadoxetic acid-enhanced and diffusion-weighted MR imaging patterns. Radiology 2012 Sep; 264(3):761–70. doi: 10.1148/radiol.12112517 PMID: 22843769.

35. Inchingolo R, De Gaetano AM, Curione D, Ciresa M, Miele L, Pompili M, et al. Role of diffusion-weighted imaging, apparent diffusion coefficient and correlation with hepatobiliary phase findings in the differentiation of hepatocellular carcinoma from dysplastic nodules in cirrhotic liver. Eur Radiol 2015 Apr; 25(4):1087–96. doi: 10.1007/s00330-014-3500-7 PMID: 23199022.

36. Takahashi M, Shimada T, Kamezaki H, Sekimoto T, Kanai F, et al. Characterization of hepatic lesions (≤30 mm) with liver-specific contrast agents: a comparison between ultrasound and magnetic resonance imaging. Eur J Radiol 2013 Jan; 82(1):75–84. doi: 10.1016/j.ejrad.2012.05.035 PMID: 23116806.

37. Van Beers BE, Pastor CM, Hussain HK. Primovist, Eovist: what to expect? J Hepatol 2012 Aug; 57(2):421–9. doi: 10.1016/j.jhep.2012.01.031 PMID: 22504332.

42. Goshima S, Kanematsu M, Watanabe H, Kondo H, Mizuno N, Kawada H, et al. Gadoxetate disodium-enhanced MR imaging: differentiation between early-enhancing non-tumorous lesions and hypervascular hepatocellular carcinomas. Eur J Radiol 2011 Aug; 79(2):e108–12. doi: 10.1016/j.ejrad.2011.04.041 PMID: 21592707.

43. Yoon SH, Lee JM, So YH, Hong SH, Kim SJ, Han JK, et al. Multiphasic MDCT enhancement pattern of hepatocellular carcinoma smaller than 3 cm in diameter: tumor size and cellular differentiation. AJR Am J Roentgenol 2009 Dec; 193(6):W482–9. doi: 10.2214/AJR.08.1818 PMID: 19933622.

44. Kudo M, Izumi N, Kokudo N, Matsui O, Sakamoto M, Nakashima O, et al. Manage-ment of hepatocellular carcinoma in Japan: Consensus-Based Clinical Practice Guidelines proposed by the Japan Society of Hepatology (JSH) 2010 updated version. Dig Dis 2011; 29(3):339–64. doi: 10.1159/000327577 PMID: 21829027.

45. Kim JE, Kim SH, Lee SJ, Rhim H. Hypervascular hepatocellular carcinoma 1 cm or smaller in patients with chronic liver disease: characterization with gadoxetic acid-enhanced MRI that includes diffusion-weighted imaging. AJR Am J Roentgenol 2011 Jun; 196(6):W758–65. doi: 10.2214/AJR.10.4394 PMID: 21606265.