BMJ Open

Detection of hepatocellular carcinoma in a population at risk: iodine-enhanced multidetector CT and/or gadoxetic acid-enhanced 3.0 T MRI

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To cite: Qiong L, Jie Z, Zhong Z, *et al*. Detection of hepatocellular carcinoma in a population at risk: iodine-enhanced multidetector CT and/or gadoxetic acid-enhanced 3.0 T MRI. *BMJ Open* 2022;**12**:e058461. doi:10.1136/bmjopen-2021-058461

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-058461).

Received 17 October 2021
Accepted 24 January 2022

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ABSTRACT

Objective To evaluate the diagnostic performance of iodine-enhanced multidetector CT and gadoxetic acid-enhanced 3.0 Tesla (T) MRI for detection of hepatocellular carcinoma of patients.

Design Retrospective, multicentre cohort study.

Setting The Gong'an County People's Hospital, Gong'an County, China and the First People's Hospital of Jingzhou City, China.

Participants Reports of CT, MRI and liver biopsies/histopathology data of a total of 815 patients who at risk were reviewed.

Primary and secondary outcome measures The lesions that possessed detection in the plain scan phase, enhanced arterial phase and/or enhanced portal phase of CT images and the lesions that possessed enhancements in the plain scan phase, enhanced arterial phase, enhanced portal phase and/or hepatobiliary phases of MRI were considered hepatocellular carcinoma. The decision of hepatocellular carcinoma was made based on the current Liver Imaging and Data Reporting System for diagnosing hepatocellular carcinoma.

Results True positive hepatocellular carcinoma (563 vs 521, p=0.0314), true negative hepatocellular carcinoma (122 vs 91, p=0.0275), false positive hepatocellular carcinoma (88 vs 123, p=0.0121), false negative hepatocellular carcinoma (42 vs 80, p=0.0005), specificity (58.10 vs 42.52, p=0.0478) and negative clinical utility (0.1 vs 0.073, p=0.0386) were superior for gadoxetic acid-enhanced 3.0 T MRI than those of iodine-enhanced multidetector CT. Sensitivity and accuracy for gadoxetic acid-enhanced 3.0 T MRI were 93.06% and 77.40 %, respectively, and those for iodine-enhanced multidetector CT were 86.69% and 75.09 %, respectively. Likelihood to detect hepatocellular carcinoma for gadoxetic acid-enhanced 3.0 T MRI was 0–0.894 diagnostic confidence/lesion, and that for iodine-enhanced multidetector CT was 0–0.887 diagnostic confidence/lesion.

Conclusion Gadoxetic acid-enhanced 3.0 T MRI facilitates the confidence of initiation of treatment of hepatocellular carcinoma.

Level of evidence III.

Technical efficacy stage 4.

Strengths and limitations of this study

- A retrospective study investigated the confidence of initiation of treatment of hepatocellular carcinoma through gadoxetic acid-enhanced 3.0 T MRI and iodine-enhanced multidetector CT among 815 patients at the risk.
- The major finding is that the single imaging modality for the detection of hepatocellular carcinoma is always incomplete.
- The study did not take account experiences of observers.
- The study did not discuss intraobserver agreements.
- A retrospective analysis and lack of prospective dynamic study.

INTRODUCTION

In China, hepatocellular carcinoma is the second largest cause of cancer-related death.[1] Screening by imaging modalities in people at increased risk of hepatocellular carcinoma is decreased mortality.[2] MRI facilitates the decision of treatment in hepatocellular carcinoma.[3] The current guidelines are recommending contrast-enhanced CT and/or contrast-enhanced MRI for the detection of hepatocellular carcinoma.[4–10] These guidelines are also recommending fetoprotein measurements and ultrasound diagnosis every 6 months in high-risk patients.[11] However, diagnosis of hepatocellular carcinoma according to these guidelines may possess false-negative and false-positive results,[12] which are overcome by alternative imaging methods using contrast agents[13] and/or biopsies.[4 5 9] CT and MRI methods of diagnosis of hepatocellular carcinoma are costly.[12] In contrast, contrast-enhanced ultrasound is cost-effective.[14] However, small hepatocellular carcinoma has difficulties in detecting using CT, MRI or ultrasound method(s).[15] CT and MRI are required waiting time and which is

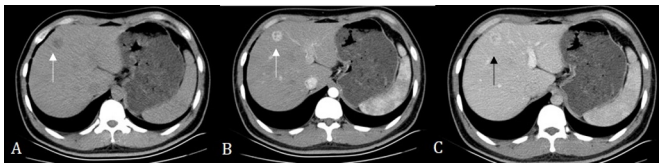

Figure 1 Criteria for hepatocellular carcinoma during multiphase CT. (A) Plain scan phase. (B) Enhanced arterial phase. (C) Enhanced portal phase. An arrow indicates enhancing nodule (hepatocellular carcinoma).

sometimes contradicted for treatment(s). In such conditions, contrast-enhanced ultrasound is the method used for the diagnosis of hepatocellular carcinoma[14] but all imaging modalities have not satisfactory performances. The poor diagnostic performances of the imaging modalities are due to overlapping imaging features especially for small hepatocellular carcinoma.[16] Therefore, the ideal single imaging index test is necessary, which is controversial for the diagnosis of hepatocellular carcinoma.

The objectives of the retrospective analysis of cross-sectional study were to compare the diagnostic performance on diagnosing hepatocellular carcinoma between iodine-enhanced multidetector CT and gadoxetic acid-enhanced 3.0 Tesla (T) MRI of patients who at risk using liver biopsy and pathology as the reference standard.

MATERIALS AND METHODS

Inclusion criteria

Patients who had alcoholism with liver disease, liver cirrhosis, hepatitis B or C virus infection and/or fatty liver and underwent CT, MRI and pathology for detection of hepatocellular carcinoma were included in the study.

Exclusion criteria

Patients whose complete data were not available at the institutes were excluded from analyses. Indeterminate biopsies were not used in the analysis.

Multidetector CT scan

A 64-sliced multidetector CT scanner (SOMATOM Sensation 64; Siemens Healthineers, Forchheim, Germany) was used for CT examinations. The examinations parameters were 2–5 mm a reconstruction thickness, 120–130 kV, and 360–365 mA. Plain scan phase (25–40 s), enhanced arterial phase (70–95 s) and enhanced portal phase (175–185 s) phases were evaluated. A total of 1.75 mL/kg (not more than 150 mL) containing 300 mg/mL concentrated iodine (Daiichi Pharmaceutical, Tokyo, Japan) was injected at a 3.5–4 mL/s rate using a power injector (OptiVantage; Guerbet, Villepinte, France) for contrast-enhanced images.[12] The multidetector CT images have performed by radiologists who had at least 7 years of experience in hepatic imaging.

Image analysis of multiphase CT

The lesions that possessed enhancements in the plain scan phase (figure 1A), enhanced arterial phase (figure 1B) and/or enhanced portal phase (figure 1C) were considered as hepatocellular carcinoma. Indicative but non-conclusive parameters, for example, the fibrous capsule was included. Other than these parameters were considered benign lesions.[16] Image analyses have been performed by radiologists who had at least 7 years of experience in hepatic imaging.

MRI scans

3.0 T MRI scanner (Skyra; Siemens Healthineers, Forchheim, Germany) was used for MRI scans. A total of 0.1 mL/kg gadoxetic acid (Eovist or Primovist; Bayer HealthCare, Berlin, Germany) was injected using a power injector. Hepatocellular phase images were evaluated after 20 min of injection. T1-weighted imaging, T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI), out-of-phase imaging and hepatobiliary phase imaging were derived. MRI scans have been performed by radiologists who had at least 7 years of experience in hepatic imaging.

Image analysis of MRI

The lesions that possessed enhancements in the plain scan phase (figure 2A), contrast enhancements in the enhanced arterial phase (figure 2B), the enhanced portal phase (figure 2C) and/or hepatobiliary phases (figure 2D) were considered as hepatocellular carcinoma. Indicative but non-conclusive parameters, for example, mild hyperintensity on T2WI and nodular early enhancement were included. Other than these parameters were considered benign lesions.[16] Image analyses have been performed by radiologists who had at least 7 years of experience in hepatic imaging.

Previously examined interpretation reports of all imaging cases were reviewed retrospectively. The lesions considered as hepatocellular carcinoma as long as any of imaging feature was present. The decision of hepatocellular carcinoma was made based on the current Liver

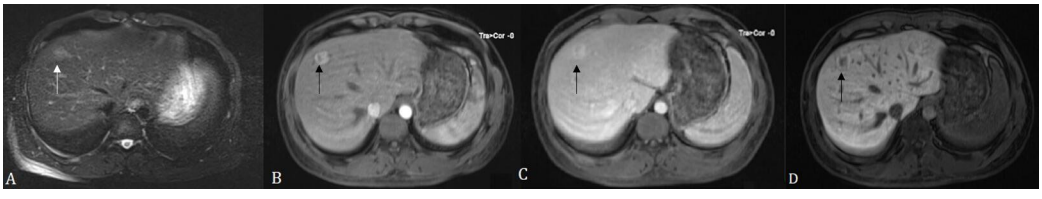

Figure 2 Criteria for hepatocellular carcinoma during MRI scans. (A) Plain scan phase. (B) Enhanced arterial phase. (C) Enhanced portal phase. (D) Enhanced hepatobiliary-specific phase. An arrow indicates enhancing nodule (hepatocellular carcinoma).

Imaging and Data Reporting System for diagnosing hepatocellular carcinoma.[17]

Liver biopsy and histopathology

The results of imaging modalities were confirmed by ultrasound guided fine needle liver biopsy followed by histopathology. Histopathological review was done by single pathologist.

Diagnostic performance

Sensitivity, specificity,[18] accuracy,[19] positive clinical utility and negative clinical utility for index tests were calculated according to equations 1–5 as follows:

$$\text{Sensitivity} = \frac{\text{True positive hepatocellular carcinoma detected by index test}}{\text{True positive hepatocellular carcinoma detected by index test} + \text{False negative hepatocellular carcinoma detected by index test}} \quad (1)$$

$$\text{Specificity} = \frac{\text{True negative hepatocellular carcinoma detected by index test}}{\text{True negative hepatocellular carcinoma detected by index test} + \text{False positive hepatocellular carcinoma detected by index test}} \quad (2)$$

$$\text{Accuracy} = \frac{\text{True positive hepatocellular carcinoma detected by index test} + \text{True negative hepatocellular carcinoma detected by index test}}{\text{Total numbers of lesions evaluated}} \quad (3)$$

$$\text{Positive clinical utility} = \text{Sensitivity} \times \text{Positive predictive value} \quad (4)$$

$$\text{Negative clinical utility} = \text{Specificity} \times \text{Negative predictive value} \quad (5)$$

Clinical significance

The clinical significance was evaluated as a function of beneficial score analyses. The beneficial score was evaluated as per equation 6[3]:

$$\text{Beneficial score} = \frac{\text{True positive hepatocellular carcinoma detected by index test}}{\text{Total numbers of lesions evaluated}} - \left(\frac{\text{False-positive hepatocellular carcinoma detected by index test}}{\text{Total numbers of lesions evaluated}} \times \frac{\text{The level of diagnostic confidence above which treatment was initiated}}{1 - \text{The level of diagnostic confidence above which treatment was initiated}} \right) \quad (6)$$

True positive hepatocellular carcinoma

Hepatocellular carcinoma was detected by index test and by liver biopsy/histopathology.

True negative hepatocellular carcinoma

Hepatocellular carcinoma was not detected by index test and by liver biopsy/histopathology.

False-positive hepatocellular carcinoma

Hepatocellular carcinoma was detected by index test but not detected by liver biopsy/histopathology.

False-negative hepatocellular carcinoma

Hepatocellular carcinoma was not detected by index test but detected by liver biopsy/histopathology.

Statistical analysis

InStat V.3.01, GraphPad Software, San Diego, California, USA was used for statistical analyses purposes. The χ^2 test was performed for statistical analyses purposes. All results were considered significant if $p<0.05$.

Patient and public involvement

This was a retrospective; multicentre cohort study and no patients were involved in the study design or in setting the research questions or the outcome measures directly. No patients were asked for advice on interpretation or writing of the results.

RESULTS

Study population

From 15 January 2017 to 1 May 2021, a total of 839 patients were screened for hepatocellular carcinoma by multiphase CT and 3.0 T MRI at the Gong'an County People's Hospital, Gong'an County, Hubei, China and the First People's Hospital of Jingzhou City, Hubei, China. Among them, complete data of 24 patients were not available in the hospital records. Therefore, excluded from the analysis. CT, MRI and liver biopsies/histopathology data of a total of 815 patients who had alcoholism, liver cirrhosis, hepatitis B or C virus infection and/or fatty liver were reviewed retrospectively.

Demographical and clinical conditions

Data of a total of 562 (69 %) male and 253 (31 %) female were reviewed retrospectively. The demographical and clinical conditions of patients before index tests are reported in online supplemental table 1.

Diagnostic performance

Iodine-enhanced multidetector CT has reported enhancements in the plain scan phase in 75 (9 %) lesions, enhancements of contrast in enhanced arterial phase in 281 (35 %) lesions, enhancements of contrast in enhanced portal phase in 288 (35 %) lesions and no characteristics in 171 (21 %) lesions. However, gadoxetic acid-enhanced 3.0 T MRI has reported enhancements in the plain scan phase in 79 (10 %) lesions, enhancements of contrast in enhanced arterial phase in 271 (33 %) lesions, enhancements of contrast in enhanced portal phase in 239 (30 %) lesions, enhancements of contrast in enhanced hepatobiliary phases in 60 (7 %) lesions and no characteristics in 166 (20 %) lesions. Liver biopsies and histopathology results reported 639 (78 %) hepatocellular carcinoma and 176 (22 %) benign nodules. The flow diagram of multiphase CT, 3.0 T MRI and liver biopsies/histopathology data which were reviewed retrospectively is presented in figure 3.

Diagnostic parameters of gadoxetic acid-enhanced 3.0 T MRI were inferior to those of liver biopsy and histopathology results ($p<0.05$ for all). True positive hepatocellular carcinoma, true negative hepatocellular carcinoma, false positive hepatocellular carcinoma, and false negative hepatocellular carcinoma were superior for gadoxetic acid-enhanced 3.0 T MRI than those of iodine-enhanced multidetector CT ($p<0.05$ for all). Sensitivity, specificity, accuracy, positive clinical utility and negative clinical utility of gadoxetic acid-enhanced 3.0 T MRI were better to those of iodine-enhanced multidetector CT (but not statistically significant, $p>0.0500$ for all, χ^2 test). However, diagnostic parameters of gadoxetic acid-enhanced 3.0 T MRI plus iodine-enhanced multidetector CT were

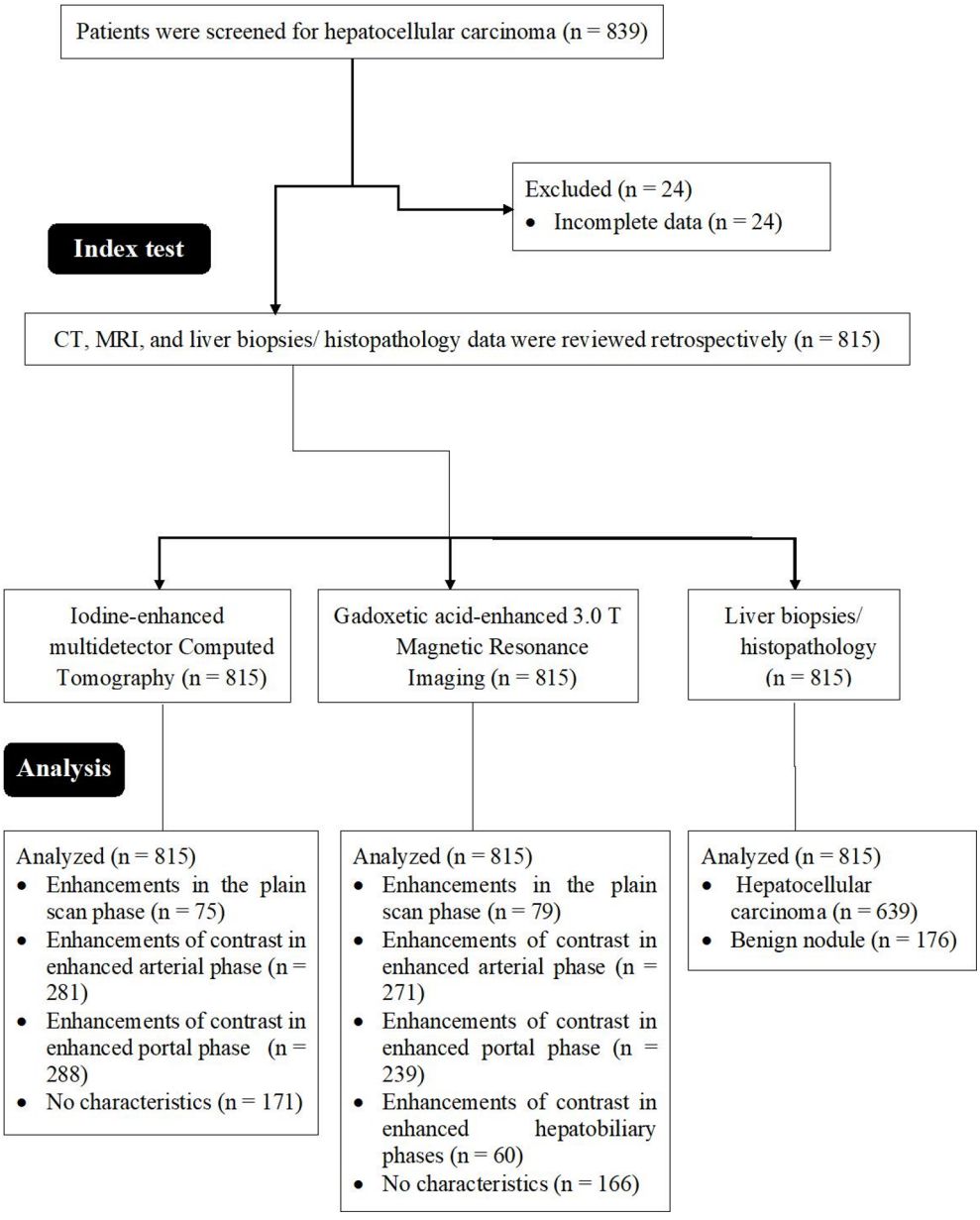

Figure 3 The flow diagram of CT, MRI and liver biopsies, and histopathology data were reviewed retrospectively.

identical with those of liver biopsy and histopathology results (p>0.05 for all, χ^2 test). The details of the diagnostic performance of index tests are reported in table 1.

Clinical significance

Likelihood to detect hepatocellular carcinoma for liver biopsies/histopathology was 0–1 diagnostic confidence/lesion, that for gadoxetic acid-enhanced 3.0 T MRI plus iodine-enhanced multidetector CT was 0–1 diagnostic confidence/lesion, that for gadoxetic acid-enhanced 3.0 T MRI was 0–0.894 diagnostic confidence/lesion, and that for iodine-enhanced multidetector CT was 0–0.887 diagnostic confidence/lesion. Above 0.894 diagnostic confidence/lesion gadoxetic acid-enhanced 3.0 T MRI had the risk of overdiagnosis and above 0.887 diagnostic confidence/lesion, iodine-enhanced multidetector CT had the risk of overdiagnosis. The details of the clinical significance of the index tests are reported in figure 4.

DISCUSSION

The study found that iodine-enhanced multidetector CT had fewer values for sensitivity, specificity and accuracy than those of gadoxetic acid-enhanced 3.0 T MRI. The results of diagnostic parameters of the current study were consistent with those of a retrospective study of imaging evaluation of hepatocellular carcinoma on patients with have suspected liver cancer considering the Asia-pacific clinical practice guidelines as reference standard,[3] a prospective study of four different image datasets on in cirrhotic patients considering the pathological findings as reference standard,[16] a comparative study of CT and

Table 1 Diagnostic performance of index tests

Parameters	Liver biopsies and histopathology	Gadoxetic acid-enhanced 3.0 T MRI			Iodine-enhanced multidetector CT					Iodine enhanced multidetector CT plus gadoxetic acid-enhanced 3.0 T MRI		
Total numbers of lesions evaluated	**815**	**815**	**P value***	**df**	**815**	**P value***	**df**	**P value†**	**df**	**815**	**P value***	**df**
True positive hepatocellular carcinoma	639 (78)	563 (69)	<0.0001	1	521 (64)	<0.0001	1	0.0314	1	635 (78)	0.8573	1
True negative hepatocellular carcinoma	176 (22)	122 (15)	0.0007	1	91 (11)	<0.0001	1	0.0275	1	171 (21)	0.8088	1
False positive hepatocellular carcinoma	0 (0)	88 (11)	<0.0001	1	123 (15)	<0.0001	1	0.0121	1	5 (0.5)	0.0732	1
False negative hepatocellular carcinoma	0 (0)	42 (5)	<0.0001	1	80 (10)	<0.0001	1	0.0005	1	4 (0.5)	0.1331	1
Sensitivity (%)	100	93.06	0.0209	1	86.69	0.0006	1	0.2386	1	99.37	0.3161	1
Specificity (%)	100	58.10	<0.0001	1	42.52	<0.0001	1	0.0478	1	97.16	0.2446	1
Accuracy (%)	100	77.40	<0.0001	1	75.09	<0.0001	1	0.8685	1	98.90	0.1331	1
Positive clinical utility	0.639	0.606	<0.0001	1	0.558	<0.0001	1	0.5659	1	0.636	0.9761	1
Negative clinical utility	0.176	0.100	<0.0001	1	0.073	<0.0001	1	0.0386	1	0.17	0.8111	1

Categoric data are presented as frequency (percentage) and continuous data are presented as mean±SD.
The χ^2 test for independence was performed for statistical analysis.
A $p<0.05$ was considered significant.
*Concerning liver biopsies and histopathology.
†Comparisons between Iodine enhanced multidetector CT and Gadoxetic acid-enhanced 3.0 T MRI.
CT, multiphase computed tomography; MRI, 3.0 T magnetic resonance imaging.

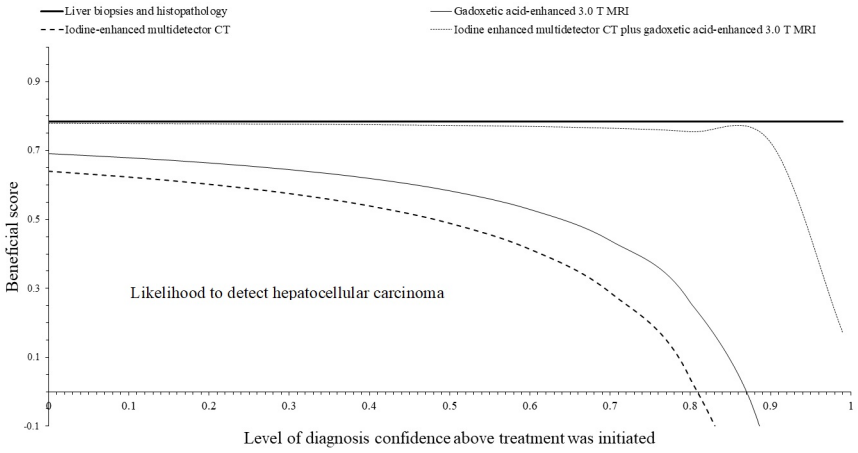

Figure 4 Clinical significances of the index tests.

MRI with on chronic liver diseases patients considering the biopsy data as reference standard.[20] Iodine-enhanced multidetector CT has a lack of ability for differentiation of dysplastic nodules from small hepatocellular carcinoma.[16] Gadoxetic acid enhances the sensitivity of MRI.[21 22] Combining hepatobiliary-phase hypointensity of gadoxetic acid-enhanced 3.0 T MRI and hyperintensity on DWI allows diagnosis of hepatocellular carcinoma.[23] Gadoxetic acid-enhanced 3.0 T MRI can better diagnose hepatocellular carcinoma than iodine-enhanced multidetector CT.

Likelihood to detect hepatocellular carcinoma for liver biopsies/histopathology and that for gadoxetic acid-enhanced 3.0 T MRI plus iodine-enhanced multidetector CT was the same. Combined gadoxetic acid-enhanced 3.0 T MRI and iodine-enhanced multidetector CT had almost the same diagnostic parameters as those of liver biopsies/histopathology to detect hepatocellular carcinoma. The results of the combined index tests of the current study were consistent with those of a retrospective study,[3] a prospective study of three different image datasets on population of cirrhotic patients considering a composite algorithm as reference standard,[24] and observation study on CT and MRI.[25] However, integrated interpretation across imaging modalities is not allowed by the current Liver Imaging and Data Reporting System,[17] the European Association for the Study of the Liver and he American Association for the Study of Liver Diseases recommendations.[24] Therefore, the combination of gadoxetic acid-enhanced 3.0 T MRI and iodine-enhanced multidetector CT is not valid.

Gadoxetic acid-enhanced 3.0 T MRI and iodine-enhanced multidetector CT both reported false-positive and false-negative hepatocellular carcinoma. The hepatic arterioportal shunt can show arterial phase hyperenhancement without washout and/or focal hyperintensity on T2WI of the liver.[3] Blood flow distribution, liver cirrhosis and hepatic parenchymal distortion can show enhancements of benign liver nodules.[26] The hepatocellular carcinoma was not detected because the imaging method detected intermediate nodules instead of hepatocellular carcinoma.[12] Also, small hepatocellular carcinomas do not show enhancement after washout.[24] The results of false predictive values of the current study were consistent with those of a retrospective study.[3] The single imaging modality for the detection of hepatocellular carcinoma is always incomplete.

The likelihood to detect hepatocellular carcinoma for gadoxetic acid-enhanced 3.0 T MRI was higher than that of iodine-enhanced multidetector CT. The results of the likelihood to detect hepatocellular carcinoma of the current study were consistent with those of a retrospective study.[3] Gadoxetic acid-enhanced 3.0 T MRI facilitates the confidence of initiation of treatment of hepatocellular carcinoma in the patients at the risk.

Sensitivity, accuracy and positive clinical utility among the diagnostic parameters were superior for gadoxetic acid-enhanced 3.0 T MRI than those of iodine-enhanced multidetector CT but there were no significant differences between them. Detection of hepatocellular carcinoma by imaging modalities was depended on multiple factors, for example, the scanning parameters, scanning sequence, contrast agents (gadoxetic acid or iodine), type of lesion (eg, nonsuspicious benign lesions) and lesion sizes.[27] A further study is required to evaluate imaging modalities considering such factors.

The study makes valid observations and the results could be useful to readers in selecting appropriate procedures in screening patients with hepatocellular carcinoma. However, there are several limitations of the study, for example, retrospective analysis and lack of prospective dynamic study. Although gadoxetic acid-enhanced 1.5 T MRI is cost-effective than that of 3.0 T MRI,[28] the study did not use 1.5 T gadoxetic acid-enhanced MRI. The possible justification for the same is that gadoxetic acid-enhanced 3.0 T MRI has better detection and quality images for smaller lesions.[29] The sampling errors of liver biopsies following histopathology[24] were not taken into account. Fine-needle aspiration cytopathology has severe limitations in low grade/early hepatocellular carcinoma. The experiences of readers have effects over the results of gadoxetic acid-enhanced 3.0 T MRI[30] but the study did

not take account experiences of observers and did not discuss intraobserver agreements.

CONCLUSIONS

The study investigates the detection of hepatocellular carcinoma with help of dynamic contrast in the CT and MRI. Gadoxetic acid-enhanced 3.0 T MRI can better diagnose hepatocellular carcinoma than iodine-enhanced multidetector CT. Although the likelihoods to detect hepatocellular carcinoma for liver biopsies/histopathology and that for gadoxetic acid-enhanced 3.0 T MRI plus iodine-enhanced multidetector CT are the same, the combination of gadoxetic acid-enhanced 3.0 T MRI and iodine-enhanced multidetector CT is not valid. Gadoxetic acid-enhanced 3.0 T MRI facilitates the confidence of initiation of treatment of hepatocellular carcinoma in the patients at the risk.

Acknowledgements The authors are thankful for the radiological and non-radiological staff of the Gong'an County People's Hospital, Gong'an County, Hubei, China and the First People's Hospital of Jingzhou City, Hubei, China.

Contributors All authors have read and approved the manuscript for publication. LQ was project administrator, contributed to supervision, resources, methodology and the literature review of the study. ZJi contributed to conceptualisation, resources, methodology, validation and the literature review of the study. ZZ contributed to the investigation, methodology, resources, the literature review and the software of the study. SW contributed to data curation, formal analyses, resources, the literature review and the methodology of the study. ZJu contributed to software, methodology, data curation, visualisation and the literature review of the study. LL contributed to formal analyses, the literature review, methodology, resources and software of the study. CJ contributed to the literature review, methodology and resources of the study, draft, and edited the manuscript for intellectual content. All authors agreed to be accountable for all aspects of work ensuring integrity and accuracy. CJ is responsible for the overall content as the guarantor. The guarantor accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval The designed protocol (FPHJ1524 dated 9 May 2021) was approved by the First People's Hospital of Jingzhou City review board and the Chinese society of clinical oncology. The study reporting adheres to the law of China and the V2008 Declarations of Helsinki. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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