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HEPATOBILIARY-PANCREAS

The diagnostic value of Gd-EOB-DTPA-MRI for the diagnosis of focal nodular hyperplasia: a systematic review and meta-analysis

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Abstract
Objective We aimed to systematically review the gadoxetic acid-enhanced magnetic resonance imaging (Gd-EOB-DTPA-MRI) findings of focal nodular hyperplasia (FNH) and its diagnostic value.
Methods A thorough literature search was conducted in Ovid-MEDLINE and EMBASE databases to identify studies evaluating Gd-EOB-DTPA-MRI findings of FNH. To evaluate the frequency of characteristic imaging findings on Gd-EOB-DTPA-MRI, pooled proportions of high/iso signal intensity (SI) on the hepatobiliary phase (HBP), arterial enhancement, high/iso SI on the portal-venous phase (PVP) or equilibrium phase (EP), and the central scar were calculated. Meta-analysis was performed to evaluate the diagnostic accuracy of high/iso SI on HBP for distinguishing FNH from hepatocellular adenoma.
Results A review of 96 articles identified ten eligible articles with 304 patients with FNHs for meta-analysis. Pooled proportion of the Gd-EOB-DTPA-MRI findings showed that high/iso SI on the HBP, arterial enhancement, and high/iso SI on the PVP/EP were observed in 93% (95% CI, 90–97%), 99% (95% CI, 97–100%), and 97% (95% CI, 95–99%) of FNHs, respectively, while a central scar was observed in 61% of FNHs (95% CI, 47–74%). High/iso SI on the HBP was highly accurate for distinguishing FNH from hepatocellular adenoma, with a summary sensitivity of 93.9% (95% CI, 89.1–97.1%) and a specificity of 95.3% (95% CI, 88.4–98.7%).
Conclusions High/iso SI on the HBP of Gd-EOB-DTPA-MRI is characteristic and a prevalent finding of FNHs and can be helpful in the management of patients with FNH.
Key Points
- *The vast majority (94–97 %) of FNHs show high/iso SI on HBP.*
- *High/iso SI on HBP was accurate for distinguishing FNH from hepatocellular adenoma.*
- *HBP of Gd-EOB-DTPA-MRI can reduce unnecessary biopsies for the diagnosis of FNHs.*

Keywords Focal nodular hyperplasia · Gadoxetic acid · Gd-EOB-DTPA · Magnetic resonance imaging · Hepatocellular adenoma

Introduction

In general, a ″leave me alone″ lesion is a benign lesion that is so radiologically characteristic that additional tests, such as a biopsy or surgery, are unnecessary. One of the essential goals of diagnostic liver imaging is to distinguish ″leave me alone″ lesions from a list of differential diagnoses in order to prevent wasting of medical resources. For example, focal nodular hyperplasia (FNH) is a benign lesion that does not require any specific treatment. FNH can be a ″leave me alone″ lesion if an imaging test confirms the diagnosis of FNH without a list of differential possibilities [1, 2]. If the imaging results are inconclusive or lack diagnostic confidence, a liver biopsy should be performed [3]. Therefore, a confident and correct imaging diagnosis of FNHs is important in order to avoid unnecessary biopsy and surgery. However, it is still difficult to make a confident diagnosis of FNHs based on routine

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dynamic computed tomography (CT) or magnetic resonance imaging (MRI) using a conventional extracellular contrast agent.

Since the approval of gadoxetic acid (Gd-EOB-DTPA, Eovist® in the USA; Primovist® outside the USA; Bayer Schering, Berlin, Germany) by the U.S. Food and Drug Administration in 2008, the use of gadoxetic acid has been rapidly increasing worldwide. Gadoxetic acid is a dual-function contrast agent that combines the properties of an extracellular contrast agent for dynamic imaging and a hepatocellular-specific agent. Approximately 50 % of the injected dose is taken up by functioning hepatocytes and excreted in bile, thus enabling tumour characterization according to the presence or absence of functioning hepatocytes [4–7].

To date, several reports have shown that the hepatobiliary phase (HBP) of gadoxetic acid-enhanced MRI (Gd-EOB-DTPA-MRI) is particularly helpful for the diagnosis of FNHs, as most FNHs show high or iso signal intensity (SI) relative to the liver parenchyma on the HBP, unlike most other solid tumours in the liver [8–17]. FNH is a non-neoplastic condition formed by mono-acinar nodules composed of normal-functioning hepatocytes and abnormal bile ducts that do not communicate with the surrounding biliary system. These characteristics account for the typical, persistent contrast uptake of gadoxetic acid in functioning hepatocytes within the FNH and for the high/iso SI seen on the HBP [15].

Currently, at least in our institution, when routine dynamic CT or MRI is inconclusive for the diagnosis of FNH, Gd-EOB-DTPA-MRI replaces the liver biopsy as the next diagnostic step. However, some physicians are not convinced regarding the value of gadoxetic acid-MRI for the diagnosis of FNH, due to a lack of sufficient evidence.

Several individual studies have been performed to evaluate the diagnostic value of Gd-EOB-DTPA-MRI for the diagnosis of FNH; however, the majority of these studies have been retrospective, descriptive studies with low-level evidence [8–17]. To our knowledge, there has been no attempt to generate a systematic summary regarding the imaging findings and diagnostic value of Gd-EOB-DTPA-MRI that would have a great impact on more evidence-based management of patients with FNHs. To this end, we performed this systematic review and meta-analysis to evaluate the frequency of the characteristic findings of FNH on Gd-EOB-DTPA-MRI, as well as the value of these characteristic findings for the diagnosis of FNH.

Methods

Literature search strategy

A computerized search of the MEDLINE and EMBASE databases was performed to find relevant original literature regarding the imaging findings and diagnostic accuracy of Gd-EOB-DTPA-MRI in patients with FNH. The following search terms were used: (focal nodular hyperplasia OR FNH) AND (magnetic resonance imaging OR MRI) AND (eovist OR gadoxetic OR primovist OR Gd-EOB-DTPA). The start date was not set. Our search was limited to human subjects and English-language studies. We continued updating the literature search until 1 January 2014. To expand the search, we screened the bibliographies of articles for other suitable articles. Endnote version X7 (Thomson Reuters, New York, NY, USA) was used for the management of the literature.

Inclusion criteria

Studies or subsets of studies investigating the imaging findings and diagnostic accuracy of Gd-EOB-DTPA-MRI in patients with FNH were eligible for inclusion. Studies or subsets of studies satisfying all of the following criteria were included: (a) population: patients who were evaluated for FNH using Gd-EOB-DTPA-MRI imaging, and studies that contained data for at least ten consecutive patients; (b) reference standard: studies with FNH confirmed by pathological diagnosis as well as by radiological diagnosis were comprehensively included to reflect the ″real world″ clinical situation, in which patients with inconclusive imaging tend to undergo biopsy, whereas patients with typical imaging findings tend to be managed conservatively. Inclusion of only pathologically proven FNHs would result in a selection bias, excluding patients with FNH who received their diagnosis based on typical imaging findings without biopsy; (c) study design: all observational studies (retrospective or prospective); and (d) outcomes: results that were reported in sufficient detail to evaluate the frequency of characteristic findings of Gd-EOB-DTPA-MRI and/or those with a diagnostic value for differentiating FNHs from other types of tumours.

Exclusion criteria

The exclusion criteria were as follows: (a) case reports and case series with sample sizes smaller than ten patients, or studies with a potential selection bias, i.e., a non-consecutive series of patients; (b) review articles, editorials, letters, comments, and conference proceedings; (c) studies whose topics were other than the imaging findings or the diagnostic accuracy of Gd-EOB-DTPA-MRI for FNH; (d) studies with insufficient data for meta-analysis of the imaging findings and its diagnostic accuracy; or (e) studies with overlapping patients and data. Two reviewers (C.H.S. and K.W.K.) selected literature reports independently using a standardized form. Disagreements were very minor and were resolved by consensus.

Data extraction

From the selected studies, we extracted the following data from each source onto standardized data forms: (a) study characteristics: authors, year of publication, hospital or medical school, years of patient recruitment, sample size, and study design; (b) demographic and clinical characteristics of patients: mean age, reference standards, and types of tumours other than FNH for comparison, if included in the study; (c) imaging characteristics: we extracted criteria of the positive imaging findings for binary assessment, i.e., high/iso SI of tumours on the HBP, the presence of a central scar, arterial enhancement, and high/iso SI on the portal venous phase [PVP] or equilibrium phase [EP] (i.e., lack of delayed washout); and (d) outcome: we filled out the binary assessment data form of imaging findings of FNH and/or the other tumour for comparison according to the criteria described above. One reviewer (C.H.S.) extracted data from the studies, and the second reviewer (K.W.K.) double-checked the accuracy of the extracted data.

Quality assessment

The methodological quality of the included studies was assessed independently by two reviewers (C.H.S. and K.W.K.), using tailored questionnaires from the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) criteria [18]. Disagreements were very minor and were resolved by consensus.

Data synthesis and statistical analysis

The pooled proportions of the positive imaging findings, i.e., cases with FNH showing positive imaging findings / total cases with FNH, were adopted as the main indices for this meta-analysis, in order to evaluate the frequency of these imaging findings in the patients with FNHs. The positive imaging findings were high/iso SI of tumours on the HBP of Gd-EOB-DTPA-MRI, the presence of a central scar, arterial enhancement, and high/iso SI on the PVP or EP (i.e., lack of delayed washout).

The diagnostic accuracy of high/iso SI on the HBP for distinguishing FNH from hepatocellular adenoma was assessed using a bivariate random-effects approach [23]. We constructed a two-by-two table with true positive (FNH with high/iso SI), false negative (FNH with low SI), false positive (hepatocellular adenoma with high/iso SI), and true negative (hepatocellular adenoma with low SI). When zero counts occurred in any of the cells in the two-by-two table, 0.5 was added to all the cell values for a continuity correction. We then calculated the summary sensitivity, specificity, positive likelihood ratio (LR) and negative LR using the two-by-two table. The summary receiver operating characteristic (sROC) curve was calculated by Moses and Littenberg′s approach. We also calculated another global measure of test efficacy, Q*, which is the intersection of the estimated sROC curve with the line where specificity equals sensitivity [19].

The meta-analytic pooling was based on the inverse variance method for calculating weights; and the pooled proportion and its 95 % confidence interval (CI) were obtained using the DerSimonian-Liard random effects model. Heterogeneity of the pooled data was assessed using the Cochran Q method and quantified with I^2 statistics [20]. An I^2 value greater than 50 % was considered to indicate substantial heterogeneity. In pooling the proportion of imaging findings of FNHs, a publication/reporting bias was visually assessed using the funnel plot, and the statistical significance was tested using the Egger′s test [21]. Publication bias-adjusted pooled estimates, i.e., adjusted pooled proportions, were also obtained using the trim-and-fill method [22]. If the original unadjusted pooled proportion and the trim-and-fill adjusted pooled proportion agreed, the results were regarded to be robust for publication bias.

For the statistical analysis, Meta-Disc version 1.4 (Meta-Disc, Unit of Clinical Biostatistics team of the Romany Cajal Hospital, Madrid, Spain) and R version 3.0.2 (The R Foundation for Statistical Computing) were used.

Results

Literature search

Our study selection process is described in Fig. 1. The literature search in Ovid-MEDLINE and EMBASE databases generated 96 initial article candidates, and 78 articles were screened for eligibility after removing the duplicates. Of those articles, 61 were excluded after review of the titles and abstracts, consisting of 31 review articles; 14 case reports or series containing less than ten relevant patients; seven letters, editorials or conference abstracts; and nine articles that were not in the field of interest of this study. The full texts of the remaining 17 articles were retrieved. A search of the bibliographies of these articles resulted in no additional eligible studies. Of the 17 articles, seven articles were further excluded after reviewing the full text, i.e., these seven studies were not in the field of interest [7, 23–28]. Finally, ten eligible studies with a total sample size of 304 patients with 381 cases of FNHs were included in this meta-analysis [8–17].

Characteristics of the included studies

The detailed characteristics of the ten included studies are summarized in Table 1. Eight were retrospective studies [8, 10–16, 28], whereas two used prospective registries [9, 17]. In

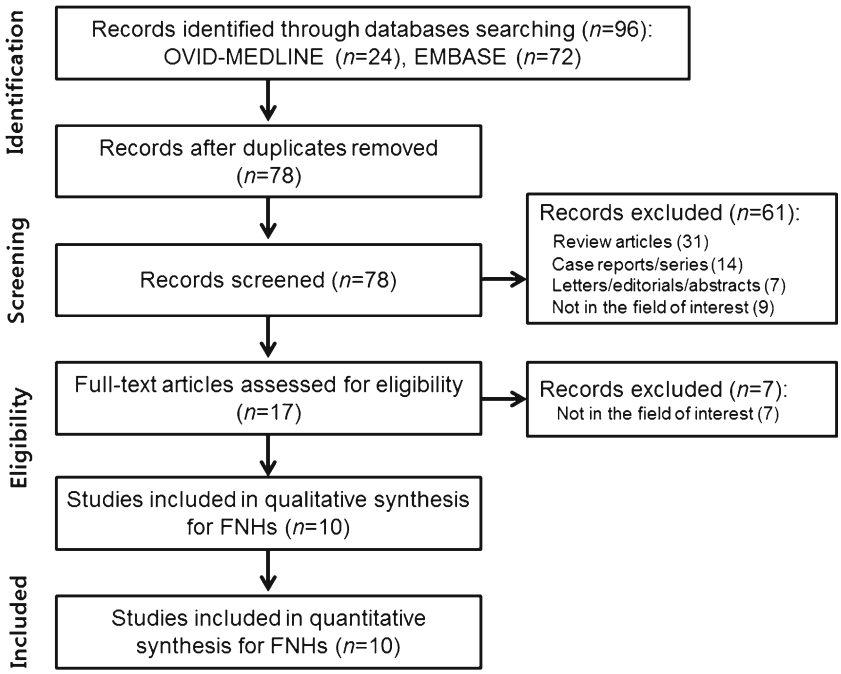

Fig. 1 Flow diagram of the study selection process

terms of the demographic characteristics of the included studies, the mean patient age ranged from 33.8 to 46.1 years (median 39 years). The quality of the included studies, as assessed by the QUADAS-2 tool, was moderate overall, with all of the studies satisfying four or more of the seven total items [18]. Blinding of the imaging analysis to the reference standards (QUADAS-2 Domain 3) was not clearly stated in many studies, likely due to the retrospective nature of the studies. Diagnostic confirmation of an FNH was made by means of pathological diagnosis (n=143) or radiological diagnosis (n=228). Pathological diagnosis was based on histological examination of a surgically resected specimen or a biopsy specimen. Radiological diagnosis was based on typical imaging features and follow-up on dynamic CT or MR, mainly related to the homogeneous and intense enhancement in the arterial phase and iso-attenuation seen on unenhanced, PVP, and EP images.

For evaluation of the SI of liver lesions on Gd-EOB-DTPA-MRI, slightly different definitions of lesion SI have been used across studies, although these criteria were basically identical in terms of the relative lesion SI compared with the surrounding liver parenchyma. Specifically, four studies [9–11, 17] used a subjective visual score comparing a lesion and the surrounding liver parenchyma, i.e., high SI, iso SI, and low SI. Two studies [8, 14] used the lesion SI compared with that of the surrounding liver parenchyma, i.e., high, >1.05; iso, 0.95–1.05; and low, <0.95. Three studies [12, 15, 16] used a four-point to six-point scale to describe the lesion SI compared to the surrounding liver parenchyma.

Regarding the papers that evaluate diagnostic accuracy of Gd-EOB-DTPA-MRI on differentiating FNHs from other types of liver masses, there were four studies differentiating FNHs from hepatocellular adenoma only [10, 14, 15, 23], which allowed us to calculate the pooled sensitivity and specificity of the HBP. In these four studies, a total of 165 cases of FNHs and 87 cases of hepatocellular adenomas were included.

Frequency of Gd-EOB-DTPA-MRI findings

The pooled proportions of various imaging findings for the diagnosis of FNH are summarized in Table 2, and the corresponding forest plots are shown in Fig. 2. The high/iso SI seen on the HBP showed a pooled proportion of 93 % (95 % CI, 90–97 %). With regard to the other imaging findings, the pooled proportion was the highest for the arterial enhancement (99 %; 95 % CI, 97–100 %), followed by high/iso SI on the PVP or EP (97 %; 95 % CI, 95–99 %) and the presence of a central scar (61 %; 95 % CI, 47–74 %). These results imply that most FNHs show persistent enhancement from the arterial phase through the PVP and EP without delayed washout, while a central scar is present in only 61 % of FNHs.

Borderline heterogeneity was found in the pooled proportion of high/iso SI on the HBP (I^2=58.7 %), probably due to the difference in the evaluation of SI of the liver lesions. Compared to other studies with a proportion greater than 90 %, the studies of An et al. [8] and Van Kessel et al.[16] showed proportions of high/iso SI on the HBP that were 77 % and 73 %, respectively. Indeed, these two studies divided the imaging findings of FNH on the HBP into seven and six patterns, respectively, while other studies adopted a simpler grading system.

Table 1 Characteristics of the included studies

First author (year of publication)	Affiliation (study period)	Mean age	Comparison Group	No. Total FNH patients	No. Total FNH	No. Pathologically proven FNH	No. Radiologically or Clinically proven FNH	Lesion Evaluation
An HS et al. (2013)	Konkuk University School of Medicine, Korea (2009–2012)	33.8	FNH only	30	30	26	4	Lesion signal intensity compared with surrounding liver parenchyma: high, >1.05; iso, 0.95–1.05; low, <0.95
Bieze M et al. (2012)	Academic Medical Center, Netherlands (2008–2010)	39.0	FNH vs. Hepatocellular adenoma	28	28	28	0	Subjective visual score comparing lesion and surrounding liver parenchyma: high; iso; low
Grazioli L et al. (2012)	University of Brescia, Itlay (2007–2011)	41.7	FNH vs. Hepatocellular adenoma	58	68	24 (patients)	34 (patients)	Subjective visual score comparing lesion and surrounding liver parenchyma: high; iso; low
Grieser C et al. (2013)	Charite-Universitatsmedizin Berlin, Germany (2005–2012)	39.0	FNH only	27	36	36	0	Subjective visual score comparing lesion and surrounding liver parenchyma: high; iso; low
Gupta RT et al. (2012)	Duke University Medical Center, Mount Sinai School of Medicine, Wake Forest University School of Medicine (2007–2011)	37.1	FNH only	30	51	0	51	Lesion signal intensity compared with surrounding liver parenchyma: 0, hyperintense; 1, isointense; 2, mildy hyperintense; 3, strongly hypreintense
Haimerl M et al. (2013)	University Medical Center Regensburg, Germany (2009–2010)	NA	FNH only	14	14	0	14	NA
Mohajer K et al. (2012)	University of Wisconsin (2008–2010)	34.5	FNH vs. Hepatocellular adenoma	34	34	2	32	Lesion signal intensity compared with surrounding liver parenchyma: high, >1.05; iso, 0.95–1.05; low, <0.95
Purysko AS et al. (2012)	The Cleveland Clinic Foundation (2008–2010)	45.0	FNH vs. Hepatocellular adenoma	35	35	8	27	Lesion signal intensity compared with surrounding liver parenchyma (1 through 5): 1, hypointense; 5, hyperintense
Van Kessel CS et al. (2013)	University Medical Center, Utrecht (2007–2011)	46.0	FNH only	26	26	6	20	Lesion signal intensity compared with surrounding liver parenchyma: 1, markedly hypointense; 2, moderately hypointense; 3, isointense but visible due to mass effect; 4, moderately hyperintense; 5, markedly hyperintense; 6, not visible
Zech CJ et al. (2008)	European EOB Study Group (15 European centres in eight different countries)	NA	FNH only	59	59	13	46	Subjective visual score comparing lesion and surrounding liver parenchyma: high; iso; low

FNH indicates focal nodular hyperplasia; NA, not available

Table 2 Summary of the meta-analytic pooled proportions for the imaging findings

Imaging Findings	No. of Studies	No. of Cases	Summary Estimate			p value† for Reporting Bias	Trim-and-Fill Estimate	
			Pooled Proportion (95 % CI)	P value for Heterogeneity*	I^2 %§		No. of Missing Studies	Adjusted Pooled Proportion (95 % CI)
High/iso SI on the HBP	10	381	93 % (90–97 %)	< 0.01	58.7	< 0.01	5	97 % (92-102 %)
Presence of central scar	7	287	61 % (47–74 %)	< 0.01	85.9	0.79		
Arterial enhancement	6	210	99 % (97–100 %)	0.69	0.0	0.13		
High/iso SI on the PVP or EP	6	210	97 % (95–99 %)	0.83	0.0	0.22		

*p value by Cochran-Q method to test the heterogeneity of the pooled data. Values <0.10 indicate substantial heterogeneity

§ I^2 is the Higgin′s index for heterogeneity and values greater than 50 % indicate substantial heterogeneity

† p values are to test publication/reporting bias using the Egger′s test. p values less than 0.1 indicate significant bias

Abbreviations: SI = signal intensity; HBP = hepatobiliary phase; PVP = portal-venous phase; EP = equilibrium phase

No substantial heterogeneity was found in the pooled proportion of arterial enhancement and high/iso SI on the PVP or EP, while heterogeneity was present in pooling proportion of the presence of a central scar (I^2=85.9 %). This apparent heterogeneity could be attributed to the subjective nature of the findings of a central scar, which may lead to inter-observer variability.

In the Funnel′s plots and Egger′s test, a significant publication bias was noted only for the pooled proportion of the high/iso SI on the HBP (Fig. 3). After adjusting for publication bias using the trim-and-fill approach, the adjusted pooled proportion for the high/iso SI on the HBP was 97 % (95 % CI, 92–102 %), which was still similar to the unadjusted values, and as expected, the adjusted pooled proportion retained statistical significance, thus indicating that the results were robust to bias (Table 2).

Diagnostic accuracy of the HBP

In the four studies that analysed the diagnostic accuracy of high/iso SI on the HBP for distinguishing FNH from hepatocellular adenoma, the bivariate random-effect meta-analysis showed a very high summary sensitivity of 93.9 % (95 % CI, 89.1–97.1 %) and a specificity of 95.3 % (95 % CI, 88.4–98.7 %) (Table 3). It also showed a positive summary LR (15.6; 95 % CI 6.6-36.4) and a low negative LR (0.083; 95 % CI, 0.047-0.146), both of which indicate the very high discriminatory powers of positive and negative test results, respectively. In general, a positive LR greater than ten and a negative LR less than 0.1 provide convincing diagnostic evidence [29]. The summary ROC curve is illustrated in Fig. 4. The Q* of sROC curve is 0.94. The closer Q* is to 1, the closer the test is to perfect accuracy, thus suggesting that HBP is an excellent diagnostic tool to distinguish FNH from hepatocellular adenoma.

Discussion

There is currently growing evidence that Gd-EOB-DTPA-MRI can distinguish FNH from other solid hypervascular liver tumours with high diagnostic confidence [8–17]. That is mainly because the vast majority of FNHs show high/iso SI on the HBP, while other solid liver tumours rarely show high/iso SI on the HBP [13]. Indeed, the pre-existing literature included in our meta-analysis consistently present high/iso SI on the HBP as a highly characteristic imaging finding of FNHs on Gd-EOB-DTPA-MRI, as evidenced by the unadjusted and the publication bias-adjusted pooled proportions of 93 % (95 % CI, 90–97 %) and 97 % (95 % CI, 92–102 %), respectively.

On dynamic CT/MRI with conventional extracellular contrast agent, the key imaging findings to diagnose FNHs are a central scar and arterial enhancement without delayed washout [30]. However, these typical findings are not always present on dynamic CT/MRI. According to previous literature reports, a macroscopic central scar occurs in approximately 50 % of FNHs and is often absent in FNHs that are less than 3 cm [30, 31]. Indeed, in our meta-analysis, FNHs showed arterial enhancement in 99 % (95 % CI, 97–100 %) and a lack of delayed washout (i.e., high/iso SI on PVP or EP) in 97 % (95 % CI, 95-99 %), whereas a central scar was present in only 61 % (95 % CI 47–74 %) of FNHs. Therefore, on dynamic CT/MRI, a confident diagnosis of FNH may be difficult in cases without a central scar, which is part of the typical appearance of FNHs, and such cases thus warrant liver biopsy or surgical resection.

The finding of high/iso SI on the HBP of Gd-EOB-DTPA-MRI of focal liver mass allows radiologists to greatly reduce the differential diagnosis possibilities and to confidently diagnose FNH while considering all of the other imaging findings, such as arterial enhancement, lack of delayed washout, and a central scar. In this regard, Gd-EOB-DTPA-MRI can

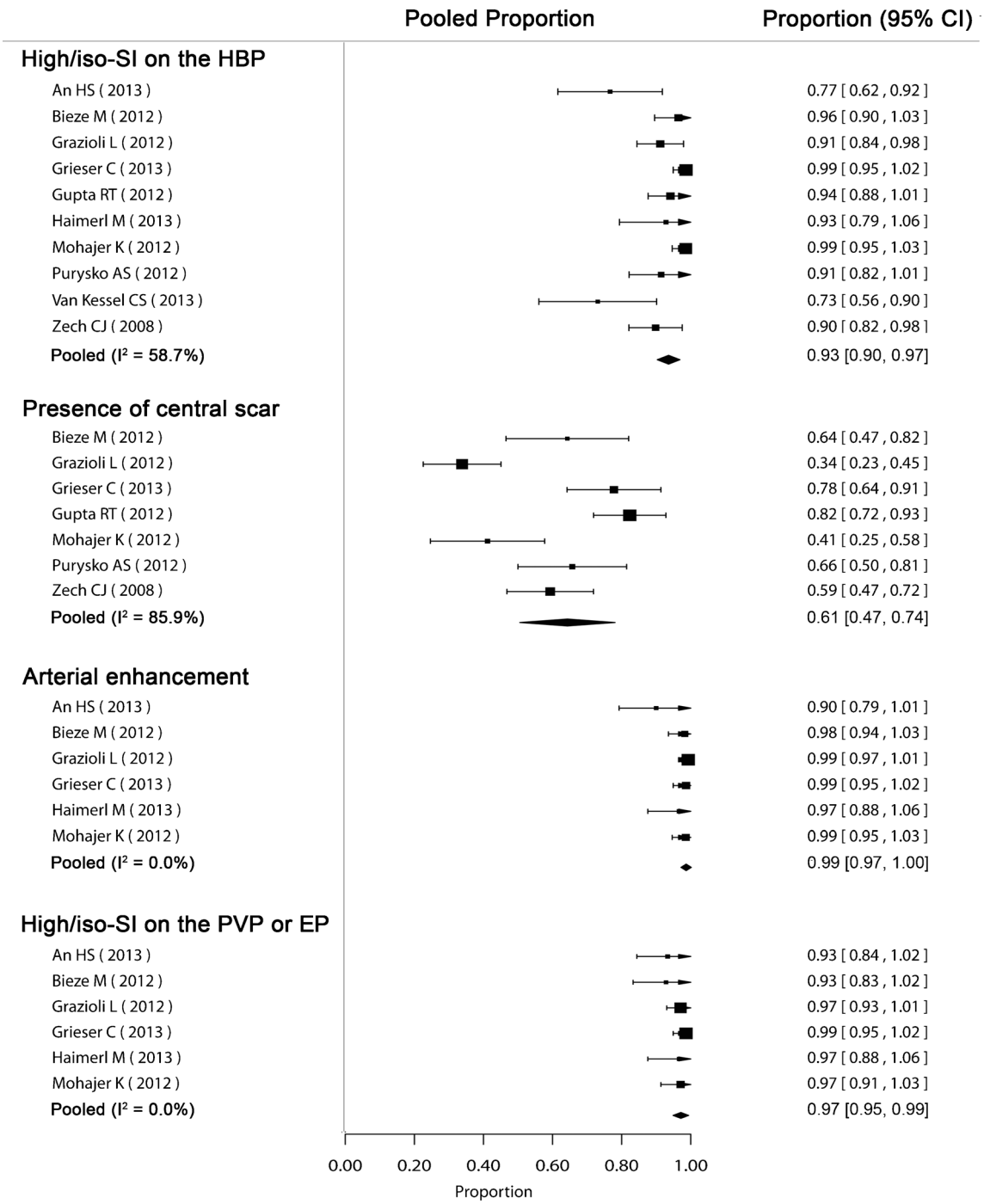

Fig. 2 Forest plots to show the pooled proportions of high/iso signal intensity of FNHs on the hepatobiliary phase, the presence of a central scar, arterial enhancement, and high/iso signal intensity on the portal-venous phase or the equilibrium phase

contribute to reducing the number of indeterminate or inconclusive cases that require invasive biopsy or surgery.

The differential diagnosis of incidental hypervascular liver masses includes hemangioma, FNH, hepatocellular adenoma, hypervascular metastasis, and primary liver cancer. According to the American College of Radiology (ACR) Appropriateness Criteria for initial characterization of liver lesions, we classified them into typical benign (i.e., leave-me-alone lesion); typical malignant, usually warranting histological confirmation; and indeterminate masses requiring further imaging evaluation or biopsy [32]. On dynamic CT/MRI with extracellular contrast agent, hemangioma is generally easily identified as a typical benign mass due to its characteristic enhancement pattern. The majority of hypervascular metastases and primary liver cancers can be identified as typical malignancies. However, differentiating FNH from

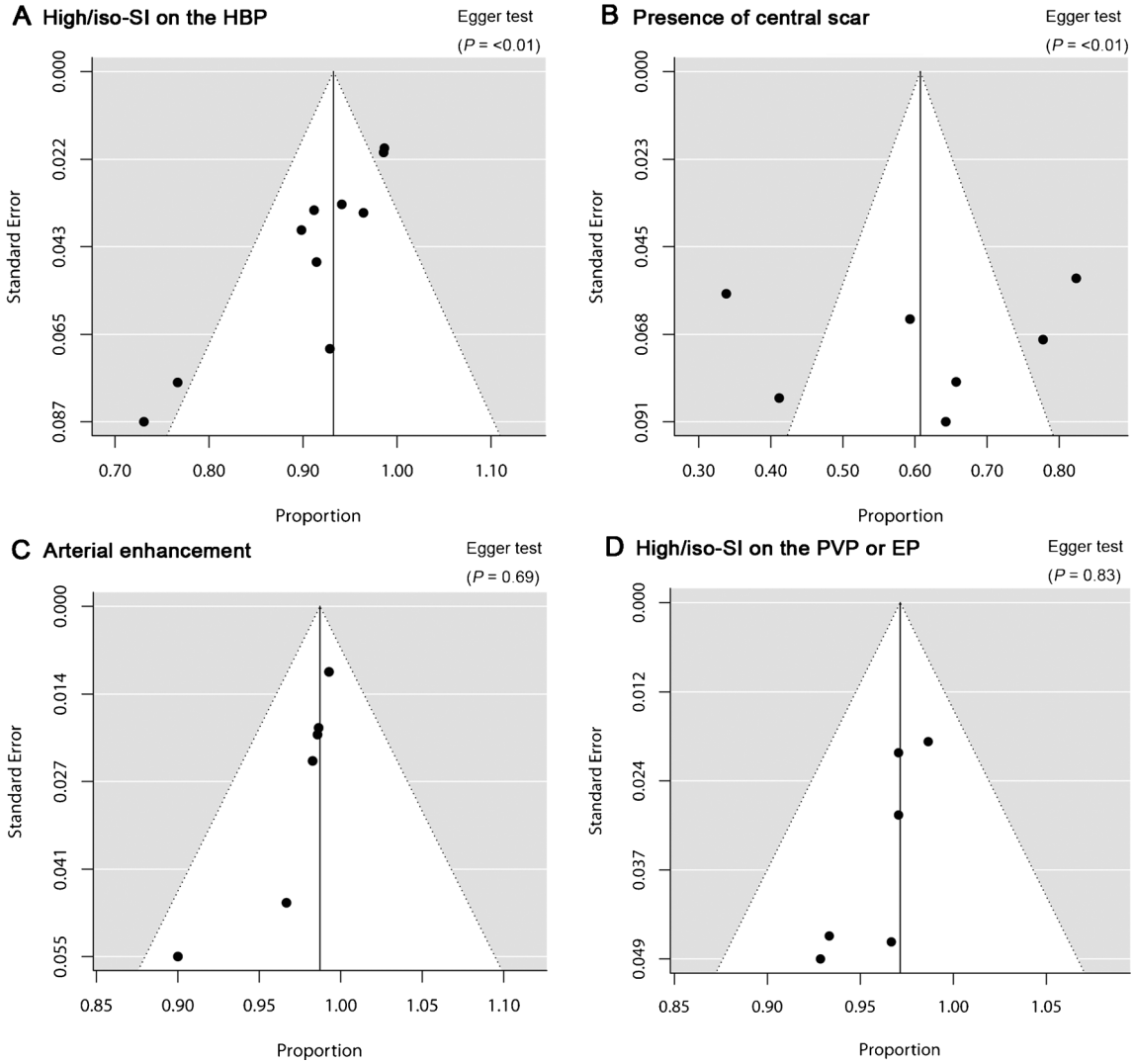

Fig. 3 Funnel plots for the visual assessment of publication bias

hepatocellular adenoma often leads to diagnostic difficulty, and thus the lesion is classified as an indeterminate mass. Distinction of FNH from hepatocellular adenoma is clinically important because each is managed differently. FNH does not

Table 3 Summary of the bivariate indices of diagnostic accuracy of high/iso SI on the HBP

Study	*N*	True Positive	True Negative	False Positive	False Negative	Sensitivity	Specificity	Positive LR	Negative LR
Bieze M (2012)	52	27	23	1	1	96.4 %	95.8 %	23.1	0.04
Grazioli L (2012)	111	62	40	3	6	91.2 %	93.0 %	13.1	0.10
Mohajer K (2012)	40	34	6	0	0	100.0 %	100.0 %	13.8	0.02
Purysko AS (2012)	47	32	12	0	3	91.4 %	100.0 %	23.5	0.10
Summary indices (95 % CI)	250					93.9 % (89.1–97.1 %)	95.3 % (88.4–98.7 %)	15.6 (6.7–36.4 %)	0.08 (0.05–0.15 %)
P value for Heterogeneity*						0.124	0.535	0.948	0.473
I^2 %§						47.9 %	0.0 %	0.0 %	0.0 %

*p value using the Cochran-Q method to test the heterogeneity of the pooled data. Values <0.10 indicate substantial heterogeneity

§ I^2 is the Higgin′s index for heterogeneity and values greater than 50 % indicate substantial heterogeneity

Abbreviations: SI = signal intensity; HBP = hepatobiliary phase

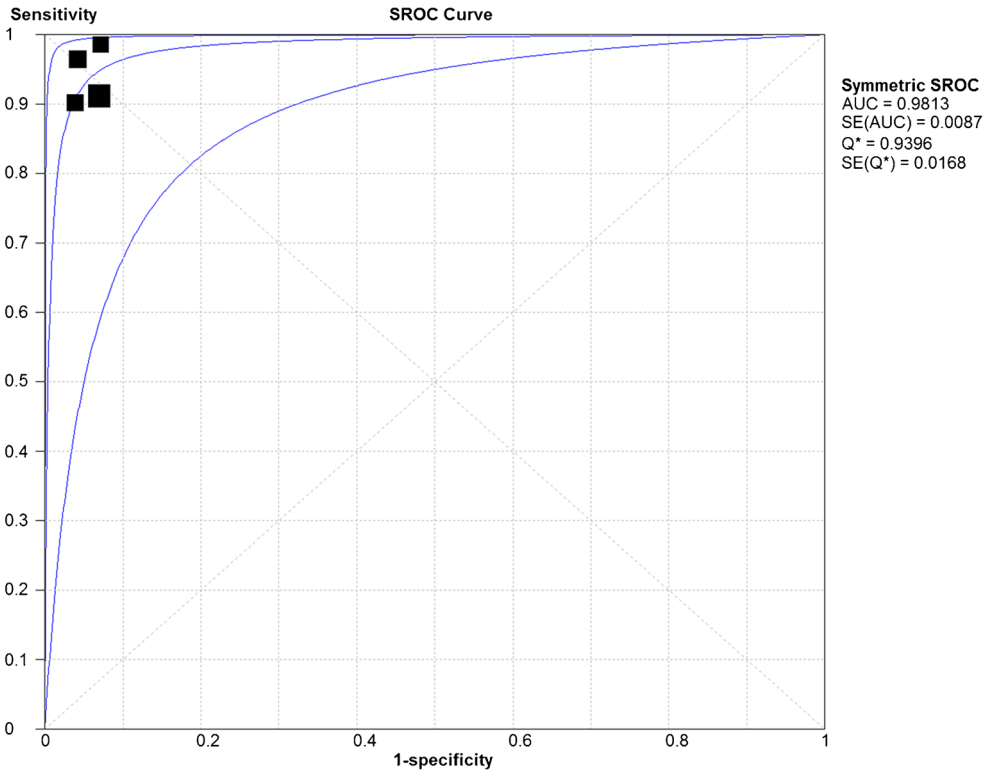

Fig. 4 The summary ROC curve of Gd-EOB-DTPA-MRI to differentiate FNH from hepatocellular adenoma

require any further diagnostic workup or specific treatment. Hepatocellular adenoma requires histological confirmation, and surgical resection is often indicated for high-risk tumours, such as those with haemorrhage or malignant transformation [33–35].

In four studies that evaluated the diagnostic accuracy of the HBP of Gd-EOB-DTPA-MRI for distinguishing FNH from hepatocellular adenoma, Gd-EOB-DTPA-MRI was highly accurate in that the pooled sensitivity and specificity were 93.9 % and 95.3 %, respectively. That is mainly because FNH shows high/iso SI in comparison to the adjacent liver parenchyma, while hepatocellular adenoma is generally hypointense in HBP.

Differentiating FNH from other hypervascular liver masses sometimes leads to diagnostic problems. So far, there is little evidence that directly evaluates the diagnostic accuracy of Gd-EOB-DTPA-MRI on distinguishing FNH from other hypervascular liver masses. Instead, there is consistent evidence that Gd-EOB-DTPA-MRI is superior to dynamic CT/MRI with an extracellular contrast agent, particularly for the detection and characterization of liver metastases and hepatocellular carcinomas [13, 24]. In order to adopt Gd-EOB-DTPA-MRI as the next standard diagnostic step for the evaluation of hypervascular liver masses when dynamic CT/MRI is inconclusive, further evidence is warranted to determine its diagnostic accuracy for differentiating FNH (i.e., leave-me-alone lesions) from other malignant hypervascular liver masses and hepatocellular adenomas.

Before Gd-EOB-DTPA became commercially available in 2008, gadobenate dimeglumine (Gd-BOPTA, Multihance®, Bracco Diagnostics) was the most commonly used hepatocellular-specific MRI contrast agent. Both contrast agents have dual functions, combining properties of extracellular agents for dynamic imaging and hepatocellular-specific agents for HBP imaging. The HBP imaging of Gd-BOPTA-enhanced MRI is also very excellent for benign lesion identification among hypervascular liver lesions, having shown a sensitivity, specificity, and diagnostic accuracy, as well as a positive predictive value and a negative predictive value when evaluating 910 hypervascular lesions in 550 patients [36]. According to a recent study that directly compared the diagnostic performance of two contrast agents on the same patients, when focusing on the diagnosis of FNH, Gd-BOPTA is superior to Gd-EOB-DTPA due to significantly higher lesion contrast ratios in the arterial and late venous phases [12]. Indeed, the arterial enhancement of vessels and lesions in Gd-EOB-DTPA-enhanced MRI is lower than that in Gd-BOPTA-enhanced MRI [37]. However, Gd-EOB-DTPA has HBP occurring faster than it does in Gd-BOPTA (10–30 minutes versus 60–120 minutes after injection of contrast agents), making Gd-EOB-DTPA more convenient to use [12]. In this regard, the use of Gd-EOB-DTPA has increased rapidly since its approval, despite the drawback of its weak arterial enhancement.

The strengths of our study include the use of validated systematic review methods and the reporting of study results

according to standard reporting guidelines [Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)] [38]. In addition, robust statistical procedures were used to estimate the presence of any reporting bias, and we then used the trim-and-fill method to adjust the bias.

Our study has several limitations. First, unlike the usual meta-analysis of diagnostic studies, we intended to obtain a meta-analytic summary regarding the proportion of individual imaging findings of FNH. We believe that this information is relevant to and directly helpful for making an image-guided management decision for FNHs. Second, the usual outcome of diagnostic accuracy, e.g., sensitivity and specificity, was obtained in the meta-analysis, which includes only FNHs and hepatocellular adenomas and does not represent actual daily clinical practice where FNHs should be differentiated from various hepatic lesions. Third, pathologically proven FNHs as well as radiologically diagnosed FNHs were included in some studies in our meta-analysis so as to comprehensively include all studies evaluating the imaging findings of FNH. This may result in an incorporation bias and may overestimate the diagnostic accuracy of the index test. However, excluding patients′ radiologically diagnosed FNHs may result in serious selection bias (i.e., verification bias), because many patients receive their diagnosis based on typical imaging findings in daily practice. Finally, we excluded grey literature such as letters, conference abstracts, or unpublished data, which may raise issue of publication bias. However, it was very difficult to extract accurate data for meta-analysis.

In conclusion, the current evidence in the literature consistently shows that the HBP of Gd-EOB-DTPA-MRI noninvasively depicts the morphologic and functional characteristics of FNHs and aids in differentiating FNHs from hepatocellular adenomas. Although the evidence of diagnostic accuracy of Gd-EOB-DTPA-MRI for the differential diagnosis of hypervascular liver masses has not been sufficient, the consistent evidence favouring Gd-EOB-DTPA-MRI for the confident diagnosis of FNH should be considered in the management of patients with suspected FNH on dynamic CT/MRI.

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