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META-ANALYSIS

Value of intravoxel incoherent motion in detecting and staging liver fibrosis: A meta-analysis

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Abstract

BACKGROUND

Liver fibrosis (LF) is a common pathological feature of all chronic liver diseases. With the accumulation of extracellular matrix in the fibrotic liver, true molecular water diffusion and perfusion-related diffusion are restricted. Intravoxel incoherent motion (IVIM) can capture the information on tissue diffusivity and microcapillary perfusion separately and reflect the fibrotic severity with diffusion coefficients.

AIM

To investigate the diagnostic performance of IVIM in detecting and staging LF with histology as a reference standard.

METHODS

A comprehensive literature search was conducted to identify studies on the diagnostic accuracy of IVIM for assessment of histologically proven LF. The stages of LF were classified as F0 (no fibrosis), F1 (portal fibrosis without septa), F2 (periportal fibrosis with few septa), F3 (septal fibrosis), and F4 (cirrhosis) according to histopathological findings. Data were extracted to calculate the pooled sensitivity, specificity, positive and negative likelihood ratios, and diagnostic odds ratio, as well as the area under the summary receiver operating characteristic curve (AUC) in each group.

RESULTS

A total of 12 studies with 923 subjects were included in this meta-analysis with 5 studies (n = 465) for LF ≥ F1, 9 studies (n = 757) for LF ≥ F2, 4 studies (n = 413) for LF ≥ F3, and 6 studies (n = 562) for LF = F4. The pooled sensitivity and specificity were estimated to be 0.78 (95% confidence interval: 0.73-0.82) and 0.81 (0.74-0.86) for LF ≥ F1 detection with IVIM; 0.82 (0.79-0.86) and 0.80 (0.75-0.84) for staging F2 fibrosis; 0.85 (0.79-0.90) and 0.83 (0.77-0.87) for staging F3 fibrosis, and 0.90 (0.84-0.94) and 0.75 (0.70-0.79) for detecting F4 cirrhosis, respectively. The AUCs for LF

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≥ F1, F2, F3, F4 detection were 0.862 (0.811-0.914), 0.883 (0.856-0.909), 0.886 (0.865-0.907), and 0.899 (0.866-0.932), respectively. Moderate to substantial heterogeneity was observed with inconsistency index (I^2) ranging from 0% to 77.9%. No publication bias was detected.

CONCLUSION
IVIM is a noninvasive tool with good diagnostic performance in detecting and staging LF. Optimized and standardized IVIM protocols are needed to further improve its diagnostic accuracy in clinical practice.

Key words: Liver fibrosis; Liver cirrhosis; Intravoxel incoherent motion; Diffusion weight imaging; Diffusion magnetic resonance imaging; Meta-analysis

Core tip: Intravoxel incoherent motion (IVIM) can separately evaluate the change of true molecular diffusion and perfusion-related diffusion caused by liver fibrosis (LF). This is the first meta-analysis to investigate the performance of IVIM for LF detection and staging with comprehensive diagnostic estimates. The results showed that IVIM is a valuable tool in noninvasively detecting and staging LF. However, field strength, the number and distribution of b-values, as well as the triggering methods affect the diagnostic accuracy. There is still a need to establish an optimized and standardized IVIM protocol for LF diagnosis in clinical practice.

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INTRODUCTION

Liver fibrosis (LF) is characterized by the excessive accumulation of extracellular matrix (primarily collagen type I)[1]. It is a common pathological feature of chronic liver disease caused by various etiologies, which may progress to hepatic dysfunction, portal hypertension, and even hepatocellular carcinoma, resulting in increased morbidity and mortality[2]. Early or intermediate LF is considered to be reversible with timely medical intervention and anti-fibrotic treatments[3]. Hence, early detection and accurate staging of LF is of great clinical significance in making appropriate therapeutic decisions and evaluating patient prognosis.

Liver biopsy is the current reference standard in detecting and staging LF. According to histologic scoring systems, the spectrum of fibrosis severity can be divided into several stages, for example, semi-quantitatively scoring as F0 (no fibrosis), F1 (portal fibrosis without septa), F2 (periportal fibrosis with few septa), F3 (septal fibrosis) and F4 (cirrhosis) in the METAVIR system[4]. However, liver biopsy is invasive, observer-dependent, and prone to sampling variability[5], all which hampers its widespread use in clinical practice; thus, a noninvasive method to quantify LF is urgently needed. Recently, magnetic resonance imaging (MRI) techniques have been increasingly applied to LF detection and staging and could possibly be a noninvasive alternative to liver biopsy[6].

Diffusion-weighted imaging (DWI) can capture the information of Brownian motion (random motion of water molecules) and quantitatively reflect the degrees of extracellular matrix accumulation *via* apparent diffusion coefficient (ADC), which has been previously reported as a good diagnostic tool in LF[7-9]. However, the diffusion process would be mimicked and confounded by the blood flow in capillaries (perfusion process), thereby affecting diffusion MRI measurements[10]. Intravoxel incoherent motion (IVIM), a bi-exponential model based on DWI, allows for the separate evaluation of true molecular diffusion and perfusion-related diffusion, which is more informative than DWI[10,11]. Although several recent studies focused on the diagnostic performances of IVIM in LF staging, there were discrepancies in the reported results among studies[12-15]. In 2016, Zhang *et al*[16] conducted a meta-analysis

on this topic; however, due to the limited number of included studies, they only performed pooled weighted mean difference to compare the difference of IVIM parameters among LF stages, and failed to conclude the pooled diagnostic indexes to comprehensively evaluate the value of IVIM in detecting and staging LF.

Therefore, with more eligible studies and patients included, the purpose of this meta-analysis was to investigate the diagnostic performance of IVIM in different LF stages with histology as reference.

MATERIALS AND METHODS

Literature search

Two independent investigators conducted a comprehensive literature search of the Cochrane Library, Ovid MEDLINE, Web of Science, EMBASE and Google Scholar databases to identify relevant publications (literature retrieval until December 2019). The following keywords and search strategy were used: "IVIM OR intravoxel incoherent motion OR biexponential DWI OR diffusion magnetic resonance imaging" AND "liver/hepatic fibrosis OR liver/hepatic cirrhosis." The search was limited to articles in the English language.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) IVIM was performed for LF detection and staging; (2) Hepatic histological analysis was used as the reference standard for all LF patients; and (3) Sufficient data were provided to calculate the values of true-positive (TP), false-positive (FP), false-negative (FN), and true-negative (TN). The studies were excluded if they were: (1) Reviews, letters, editorials, comments, case reports, or guidelines; (2) Duplicate publications; and (3) *ex vivo*, phantom, or animal research.

Data extraction and quality assessment

The following information were extracted from each study: author, publication year, country, study design (prospectively or retrospectively), study population, patient baseline characteristics (sex ratio, mean age, disease spectrum), reference standard, histopathological characteristics, blinding procedure, detailed MRI protocol (scanner, field strength, trigger methods, b-values, scan time) and time intervals between MRI examination and reference test. Meanwhile, the best diagnostic parameter and its diagnostic threshold as well as TP, FP, FN, TN were recorded. For detecting and staging LF, we respectively extracted diagnostic data and 2 × 2 contingency tables in four subgroups, which were LF ≥ F1 (F0 *vs* F1-F4, detecting LF from normal liver), LF ≥ F2 (F0-F1 *vs* F2-F4, differentiating moderate LF), LF ≥ F3 (F0-F2 *vs* F3-F4, differentiating severe LF) and LF = F4 (F0-F3 *vs* F4, detecting liver cirrhosis). The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) scale[17] was used to evaluate the quality of included studies. The other two investigators independently performed data extraction and quality assessment and reached to consensus by discussion or by consulting a senior abdominal radiologist if opinions differed.

Statistical analysis

The pooled sensitivities, specificities, positive likelihood ratio, negative likelihood ratio and diagnostic odds ratio with corresponding 95% confidence interval (CI) were calculated by using random-effects coefficient binary regression model[18]. The summary receiver operating characteristic (SROC) curves analysis were constructed in each LF group, and the areas under the curves (AUCs) were also calculated[19]. Heterogeneity among included studies was evaluated by using Q statistic of the χ^2 test and the inconsistency index (I^2), with I^2 = 25%-50% indicating low heterogeneity, I^2 = 51%-75% indicating moderate heterogeneity and I^2 > 75% indicating substantial heterogeneity[20]. To explore the potential sources of heterogeneity, the threshold effect was firstly examined by computing Spearman correlation coefficient between the logit of sensitivity and the logit of (1-specificity), and a significant strong positive correlation (P < 0.05) would suggest the presence of threshold effect[21]. Meta regression or subgroup analysis (depending on the number of included studies) was performed to find the possible sources other than threshold effect of heterogeneity[22]. Sensitivity analyses were also conducted to evaluate the stability and reliability of the summary results. To evaluate potential publication bias of the included studies, Deeks' funnel plot asymmetry test was conducted, and a P value higher than 0.05 in linear regression test indicated that there was no publication bias[23]. All statistical analyses were performed using Meta-Disc (version 1.4), Stata (version 12.0) and Reviewer Manager (version 5.3).

RESULTS

Literature search

A total of 890 studies were initially identified in the databases. After removing the duplicates, the remaining 655 studies were assessed by title, abstract and full paper. Finally, 12 studies with 923 subjects were included in this meta-analysis. The flowchart of studies inclusion and exclusion are shown in Figure 1.

Study characteristics and quality assessment

The baseline, methodological, and imaging protocol characteristics of the included studies are shown in Table 1 and Table 2. Of these 12 studies, there were 5 studies (n = 465) for LF ≥ F1[24-28], 9 studies (n = 757) for LF ≥ F2[25-27,29-34], 4 studies (n = 413) for LF ≥ F3[25-27,35] and 6 studies (n = 562) for LF = F4[25-27,29,31,33]. The best IVIM index, diagnostic threshold as well as reporting TP, FP, FN, TN, sensitivity and specificity in four LF groups were displayed in Table 3. The quality of included studies was good according to the QUADAS-2 scale (Figure 2).

Pooled diagnostic performance

The summarized diagnostic estimates are shown in Table 4. Pooled sensitivities and pooled specificities were estimated to be 0.78 (0.73-0.82) and 0.81 (0.74-0.86) for LF ≥ F1, 0.82 (0.79-0.86) and 0.80 (0.75-0.84) for LF ≥ F2, 0.85(0.79-0.90) and 0.83 (0.77-0.87) for LF ≥ F3, and 0.90 (0.84-0.94) and 0.75 (0.70-0.79) for LF = F4, respectively. According to SROC analysis, the AUCs were 0.862 (0.811-0.914), 0.883 (0.856-0.909), 0.886 (0.865-0.907) and 0.899 (0.866-0.932) for LF ≥ F1, F2, F3 and F4, respectively. SROC curves of four LF groups are demonstrated in Figure 3. Forest plots of sensitivity and specificity are shown Supplementary materials part 1.

Assessment of heterogeneity

There were moderate to substantial heterogeneity in our meta-analysis with I^2 ranging from 0% to 77.9% in pooled sensitivity and pooled specificity Supplementary materials part 1materials part 1). Threshold effect was eliminated by visual assessment of ROC plane, which showed no evidence of "shoulder-arm" shape, and the Spearman correlation coefficient, reporting 0.10 (P = 0.87), 0.47 (P = 0.21), -0.20 (P = 0.80) and 0.66 (P = 0.16) for LF ≥ F1, F2, F3 and F4, respectively. According to Cochrane handbook, meta regression was generally not considered when there were fewer than ten studies, so we conducted subgroup analysis to explore the potential contributors of heterogeneity in LF ≥ F2 group. The eligible studies for LF ≥ F1, F3 and F4 were too limited to perform meta-regression and subgroup analysis, and thus sensitivity analyses were conducted to test the robustness of results, which suggested our results were reliable (Supplementary materials part 2).

Subgroup analysis

We performed subgroup analysis to evaluate the possible sources of heterogeneity in LF ≥ F2 group in terms of study design, blindness manner, field strength, number of low b-values and IVIM trigger methods. The retrospective and double-blinded studies showed slightly higher AUC than prospective and unclear blinded studies. And the AUCs of studies using 3.0 T, more low-b-values and non-respiratory-triggered (RT) IVIM protocol were higher than those of studies with 1.5 T, less low-b-values and RT protocol. The detailed results of subgroup analysis are shown in Table 4.

Publication bias

The P values in Deeks' tests were 0.18 for LF ≥ F1, 0.28 for LF ≥ F2, and 0.20 for LF ≥ F3, and 0.84 for LF = F4, respectively, which suggested the absence of notable publication bias (Supplementary materials part 3).

DISCUSSION

With the accumulation of extracellular matrix (especially the collagen) in the fibrotic liver, the molecular water diffusion would be restricted, and the changes of fibrosis severity would be reflected in the diffusion parameters[36,37]. However, due to the relatively high hepatic blood volume fraction, perfusion-related diffusion, which was caused by incoherent motion of blood in pseudorandom capillary network, can contribute significantly to the true diffusion measurements, thus affecting the accuracy of traditional ADC in DWI[13]. Therefore, Le Bihan *et al*[10] proposed IVIM theory to capture the information of tissue diffusivity and microcapillary perfusion separately. In this meta-analysis, we included 12 eligible studies, and summarized the results based on a systematic and extensive statistical analysis, providing the pooled

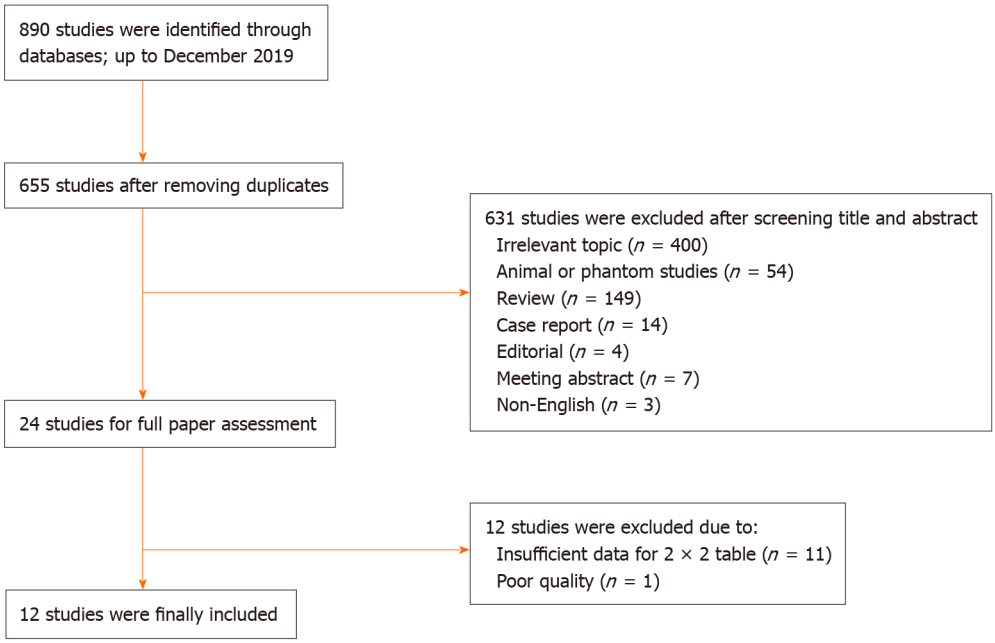

Figure 1 Flowchart of study inclusion and exclusion.

diagnostic estimates to simulate a large sample study and trying to overcome the limitations that previous studies have mentioned. According to our results, IVIM showed good but not perfect diagnostic accuracy in detecting and staging LF with AUCs ranging from 0.862 (0.811-0.914) to 0.899 (0.866-0.932).

There are three diagnostic parameters in IVIM model: $S_b/S_0 = (1\text{-}f)\cdot\exp(-bD_t) + f\cdot\exp[-b(D_t + D^*)]$.

Where D_t is true diffusion coefficient, which was free from perfusion effects; D^* is pseudo-diffusion coefficient or perfusion-related diffusion and f stands for the fraction of the perfusion component[11]. In most studies, D^* was reported to decrease significantly with the progression of LF and considered as the best diagnostic parameter in detecting and staging LF, probably because of the architectural disruption and underlying hemodynamics changes of arterial and portal blood flow in fibrotic liver[29,38]. However, in this meta-analysis, there were one or two studies suggesting D_t or f as the best diagnostic index in each LF group[25,34,35], as demonstrated in Table 3, which may be attributed to the different b value distributions in those studies and the relatively large variability of D^*[39]. Although we have validated good reliability of our results by conducting sensitivity analyses in terms of different diagnostic parameters, further investigations are needed to explore the optimal IVIM parameter and its threshold in LF detection and staging.

LF ≥ F2 is considered as the clinically significant fibrosis and is a crucial time point for anti-fibrotic treatment[3]. In this meta-analysis, substantial heterogeneity was detected in LF ≥ F2 group; therefore we performed subgroup analyses to explore the possible contributors. To our knowledge, there is no clear consensus on the number and distribution of b-values in IVIM protocol so far. Theoretically, four b-values would be sufficient for fitting a biexponential model; however, including more b-values would provide added robustness to the fit process, and low b-values is particularly important in fitting pseudo-diffusion constant[40]. In subgroup analysis, our results revealed that including three or more low b-values ($0 < b < 50$ s/mm^2) would obtain a slightly higher diagnostic performance in detecting F2 fibrosis (AUC: 0.877 *vs* 0.890), which were in accordance with Cohen *et al*[41] who recommended including at least two low b-values to ensure the accuracy when conducting liver IVIM research. Previous studies have tried to figure out the optimized b-values number and distribution in different clinical scenarios, however, the conclusions varied in those studies[42,43], and investigators have to balance the parameter estimation quality with the acquisition time during this process.

Apart from b-values, IVIM triggering methods is another key factor in acquisition time. Typically, scanning time of free-breathing (FB) IVIM is predetermined and often less than 5 min, while the time of RT IVIM is unpredictable, usually longer (5-10 min) and highly depends on subjects' respiratory condition[44]. It is known that the RT

Table 1 Baseline characteristics of the included studies and subjects

Ref.	Year	Country	Study design	Sample size	Sex ratio, M/F	mean ± SD age in yr	Patient spectrum (*n*)
Yoon *et al*[30]	2019	South Korea	Retro	106	81/25	55.4 ± 11.6	HBV (82), HCV (9), non-B non-C cirrhosis (3), ALD (10), PBC (2)
Fu *et al*[25]	2019	China	Pros	125	71/54	37.6 ± 9.3 (patients), 31.5 ± 12.9 (volunteers)	HBV (81), HCV (8), NAFLD (3), DIH (2), AIH (6)
Zawada *et al*[34]	2019	Poland	Pros	40	10/30	22-75	HCV (40)
Sandrasegaran *et al*[32]	2018	United States	Retro	49	35/14	56.6 (range: 32–73)	HBV (3), HCV (35), ALD (24), AIH (4), Other (7)[1]
Seo *et al*[31]	2018	South Korea	Retro	95	70/25	59.5 ± 9.5	HBV (44), HCV (7), ALD (14), no underlying liver disease (30)
Hu *et al*[29]	2017	China	Retro	56	14/42	47.48 (range: 15–76)	HBV (5), NAFLD (14), ASH (1), PSC (8), AIH (10), overlap syndrome of AIH (5), and DIH (13)
Chung *et al*[35]	2015	South Korea	Retro	57	35/22	58.7 (range: 32–89)	HBV (34), HCV (1), ALD (2), Other (20)
Wu *et al*[27]	2015	China (Taiwan)	Pros	49	36/13	62.4 (range: 38–85)	HBV (17), HVC (10), non-B non-C carriers (17), both hepatitis B and C carriers (5)
Ichikawa *et al*[26]	2015	Japan	Retro	182	127/55	66.4 ± 11.6	HBV (18), HCV (62), ASH (12), NASH (3), AIH (1), PBC (2), unidentified liver disease with an elevated liver enzyme level (12)
Parente *et al*[28]	2015	Brazil	Pros	59	10/49	54 ± 9	Type 2 diabetic subjects (59)
Chen *et al*[24]	2014	China	Pros	50	37/13	43.7 ± 1.2 (patients), 38.9 ± 1.3 (volunteers)	HBV (15), HCV (1), ALD (1), unidentified liver disease with an elevated liver enzyme level (8)
Yoon *et al*[33]	2014	South Korea	Retro	55	42/13	53.9 (range: 18–78)	HBV (45), HCV (1), ALD (1), Other (8)

[1]Some patients had more than one etiology of liver disease. M/F: Male/female; SD: Standard deviation; Retro: Retrospective; Pros: Prospective; HBV: Hepatitis B virus; HCV: Hepatitis C virus; ALD: Alcoholic liver disease; PBC: Primary biliary cirrhosis; PSC: Primary sclerotic cholangitis; NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; DIH: Drug-induced hepatitis; AIH: Autoimmune hepatitis; ASH: Alcoholic steatohepatitis.

technique enables the reduction of motion-related blurring by tracking the movement from the respiratory cycle and acquiring data only in the same phase; however, patients' irregular breathing can decrease the time-efficiency of the acquisition or, in some cases, make the navigator tracking unusable[45,46]. In our study, results of subgroup analysis showed that diagnostic performance of IVIM was lower in five studies with RT method, compared with four studies with non-RT (FB or unclear) method (AUC: 0.867 *vs* 0.919). Although still controversial, our findings together with most previous studies indicated that RT method offers no advantage in fitting IVIM parameters and could be substituted by FB method, which is usually more comfortable for the patients[45-47]. In addition, Riexinger *et al*[48] recently found that

Table 2 Methodological and imaging protocol characteristics of included studies

Ref.	Reference standard	Scoring system	F0/F1/F2/F3/F4	Mean intervals	Double blindness	Scanner	FS	Trigger methods	b values	Scan time[1]
Yoon *et al*[30], 2019	S/B	METAVIR	13/6/19/18/50	6 (4-38) d	Yes	GE	1.5 T	FB	0, 15, 25.4, 42.9, 72.5, 122.5, 207, 350, 592, 1000	4.5
Fu *et al*[25], 2019	S/B	METAVIR	26/17/33/25/24	< 1 mo	Yes	GE	3.0 T	RT	0, 50, 100, 150, 200, 300, 500, 800, 1000, 1300, 1500, 1700, 2000	10
Zawada *et al*[34], 2019	B	Scheuer scale	7/17/10/2/2	NA	Unclear	GE	1.5 T	RT	0, 20, 50, 100, 200, 400, 600, 800, 1000	2.6
Sandrasegaran *et al*[32], 2018	B	METAVIR	4/8/2/9/26	< 3 mo	Unclear	Siemens	1.5 T	RT	0, 50, 100, 300, 600, 800	12-15
Seo *et al*[31], 2018	S/B/T	Batts-Ludwig	30/14/4/18/29	81.2 d	Yes	Philips	3.0 T	FB	0, 10, 25, 50, 75, 100, 200, 500, 800	4.25
Hu *et al*[29], 2017	B	METAVIR	6/19/13/8/10	6 d	Unclear	Siemens	3.0 T	NA	0, 25, 50, 75, 100, 150, 200, 500, 800	5
Chung *et al*[35], 2015	B/I	METAVIR	21/1/6/7/22	15.9 (2–43) d	Unclear	Siemens	1.5 T	RT	0, 30, 60, 100, 150, 200, 400, 600, 900	7
Wu *et al*[27], 2015	S	METAVIR	6/16/10/10/7	< 7 d	Unclear	Siemens	3.0 T	RT	0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 1000	< 7
Ichikawa *et al*[26], 2015	S/B	METAVIR	72/13/14/19/64	< 3 mo	Unclear	GE	3.0 T	RT	0, 10, 20, 30, 40, 50, 80, 100, 200, 500, 1000	2-3
Parente *et al*[28], 2015	B	METAVIR	43/9/5/1/1	< 3 mo	Unclear	Philips	3.0 T	RT	0, 10, 20, 40, 80, 160, 200, 400, 800, 1000	3
Chen *et al*[24], 2014	B	METAVIR	25/4/9/11/1	< 1 mo	Unclear	GE	3.0 T	RT	0, 50, 100, 200, 400, 600, 800	NA
Yoon *et al*[33], 2014	S/B/T	METAVIR	11/7/7/9/21	NA	Unclear	Siemens	3.0 T	FB	0, 25, 50, 75, 100, 200, 500, 800	6.5

[1]The unit of scan time is min. NA: Not available; S: Liver surgery; B: Percutaneous liver biopsy; T: Liver transplantation; I: Imaging findings; FS: Field strength; FB: Free breathing; RT: Respiratory triggered.

IVIM parameters of the liver showed a significant dependency on the applied field strength, hence we also conducted subgroup analysis in this regard. Commonly speaking, 3.0 T is much more sensitive to magnetic susceptibility induced artifacts and eddy current related distortion[37], however, our results indicated higher diagnostic performance of IVIM in 3.0 T scanners with AUC of 0.904, compared with 1.5 T scanners with AUC of 0.839. Cui *et al*[49] also reported the similar findings and concluded the improved signal-to-noise ratio in high filed strength may be the underlying reason. Therefore, the standardized and optimized IVIM protocols in different filed strength should be investigated in the future for better clinical practice.

Other sophisticated diffusion models were also considered feasible in detecting and staging LF, including diffusion kurtosis imaging (DKI)[50], diffusion tensor imaging (DTI)[51], tri-exponential IVIM model[52] and stretched exponential model[53]. However, except for the stretched exponential model, other diffusion models showed no added

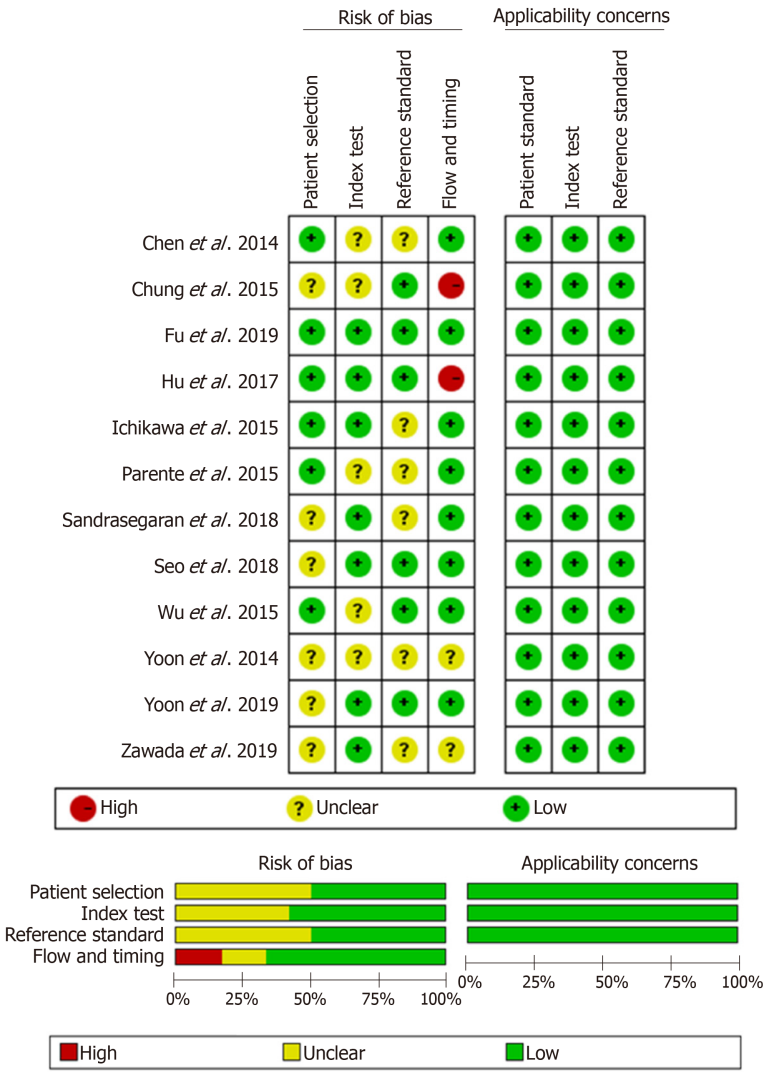

Figure 2 Quality assessment of included studies according to Quality Assessment of Diagnostic Accuracy Studies-2. The results showed that the quality of the included studies was good.

diagnostic value to conventional DWI or bi-exponential IVIM for LF detection and staging[50-52]. Recently, Seo *et al*[31] and Fu *et al*[25] both reported the higher diagnostic potential of distributed diffusion coefficient (DDC) in stretched exponential model, compared with DWI and IVIM, for staging LF greater than F2. These results may be credited to the ability of DDC in capturing a continuous distribution of diffusion coefficients from every diffusion compartment (decided by the "no tissue compartmentalization" assumption)[54,55]. Beside different diffusion techniques, magnetic resonance elastography (MRE) has also been utilized in many studies for LF staging[8,25,56]. Although MRE demonstrated excellent diagnostic ability, even greater than DWI or IVIM, it is currently not widely available around the world since it requires special equipment as well as technical expertise for data acquisition and image postprocessing. However, IVIM is an easy-to-perform and relatively informative technique, which is more widely used in current clinical work.

We acknowledge some limitations in this study. First, although we used QUADAS-2 scale to ensure the high quality of included studies, there were still some studies with retrospective design and unclear blinding method in interpreting IVIM or pathological results, which may introduce inevitable bias and non-objective interpretation of results. Second, substantial heterogeneity was detected in the pooled estimates of LF ≥ F2, therefore we performed subgroup analysis in terms of study design, IVIM protocol *etc.* to explore the potential contributors and used random effects model to summarize our data. However, due to limited eligible studies (less than 10 studies), we did not perform meta-regression to find heterogeneity sources in a significant statistical way. Third, the number of included studies in LF ≥ F1, F3 and F4 was too limited to be further assessed, but the reliability of our results has been confirmed by sensitivity analyses and we believe that should be valuable in clinical

Table 3 Diagnostic raw data of intravoxel incoherent motion in each liver fibrosis group

Study	Index	Threshold[1]	TP	FP	FN	TN	SEN	SPE
LF ≥ F1								
Chen *et al*[24], 2014	D*	17.52	20	7	5	18	0.80	0.72
Fu *et al*[25], 2019	Dt	0.63	75	3	24	23	0.76	0.88
Ichikawa *et al*[26], 2015	D*	72.15	96	10	14	62	0.87	0.86
Parente *et al*[28], 2015	D*	37.75	10	13	6	30	0.63	0.70
Wu *et al*[27], 2015	D*	51.30	27	0	16	6	0.63	1.00
LF ≥ F2								
Fu *et al*[25], 2019	Dt	0.62	64	7	18	36	0.78	0.84
Hu *et al*[29], 2017	D*	32.10	30	8	1	17	0.97	0.68
Ichikawa *et al*[26], 2015	D*	71.72	91	14	6	71	0.94	0.84
Sandrasegaran *et al*[32], 2018	D*	23.40	31	4	6	8	0.84	0.67
Seo *et al*[31], 2018	D*	77.64	44	17	7	27	0.86	0.61
Wu *et al*[27], 2015	D*	40.90	16	3	11	19	0.59	0.86
Yoon *et al*[33], 2014	D*	43.33	31	0	6	18	0.84	1.00
Yoon *et al*[30], 2019	D*	70.70	67	2	20	17	0.77	0.89
Zawada *et al*[34], 2019	Dt	1.00	7	5	7	21	0.50	0.81
LF ≥ F3								
Chung *et al*[35], 2015	f	0.28	20	5	9	23	0.69	0.82
Fu *et al*[25], 2019	Dt	0.58	40	16	9	60	0.82	0.79
Ichikawa *et al*[26], 2015	D*	65.04	78	14	5	85	0.94	0.86
Wu *et al*[27], 2015	D*	40.90	13	6	4	26	0.76	0.81
LF = F4								
Fu *et al*[25], 2019	Dt	0.58	23	31	1	70	0.96	0.69
Hu *et al*[29], 2017	D*	14.44	8	3	2	43	0.80	0.93
Ichikawa *et al*[26], 2015	D*	61.97	58	24	6	94	0.91	0.80
Seo *et al*[31], 2018	D*	54.42	22	17	7	49	0.76	0.74
Wu *et al*[27], 2015	D*	40.30	7	15	0	27	1.00	0.64
Yoon *et al*[33], 2014	D*	44.17	21	12	0	22	1.00	0.65

[1]The unit of Dt and D* is 10^{-3} mm^2/s. LF: Liver fibrosis; TP: True positive; FP: False positive; FN: False negative; TN: True negative; SEN: Sensitivity; SPE: Specificity; Dt: True diffusion coefficient; D*: Pseudo-diffusion coefficient; f: Perfusion fraction.

practice. In the future, more studies are needed to update this meta-analysis for more comprehensive evaluation.

In conclusion, with a larger sample size and the comprehensive statistical analysis, our meta-analysis showed that IVIM is a good diagnostic tool in detecting and staging LF and may serve as a noninvasive substitute to liver biopsy. Moreover, establishing an optimized and standardized IVIM protocol for LF detection and staging would be one of the future directions for its widespread application in patient care.

Table 4 Summary diagnostic performance and subgroup analysis

Characteristics	No.	Sensitivity	Specificity	Positive LR	Negative LR	DOR	AUC
LF ≥ F1	5	0.78 (0.73-0.82)	0.81 (0.74-0.86)	3.93 (2.12-7.27)	0.30 (0.19-0.46)	15.37 (5.74-41.16)	0.862 (0.811-0.914)
LF ≥ F2	9	0.82 (0.79-0.86)	0.80 (0.75-0.84)	3.69 (2.53-5.37)	0.24 (0.16-0.37)	19.35 (9.51-39.34)	0.883 (0.856-0.909)
LF ≥ F3	4	0.85 (0.79-0.90)	0.83 (0.77-0.87)	4.70 (3.51-6.28)	0.21 (0.10-0.44)	22.61 (8.24-62.05)	0.886 (0.865-0.907)
LF = F4	6	0.90 (0.84-0.94)	0.75 (0.70-0.79)	3.36 (2.57-4.38)	0.16 (0.08-0.31)	26.99 (12.88-56.58)	0.899 (0.866-0.932)
Subgroup analysis in LF ≥ F2							
Study design							
Retrospective	6	0.86 (0.82-0.90)	0.78 (0.71-0.83)	3.73 (2.19-6.34)	0.17 (0.10-0.29)	29.82 (11.65-76.32)	0.921 (0.891-0.952)
Prospective	3	0.71 (0.62-0.79)	0.84 (0.74-0.90)	3.97 (2.42-6.52)	0.42 (0.25-0.69)	10.20 (4.30-24.16)	0.905 (0.862-0.948)
Double blindness							
Yes	3	0.80 (0.74-0.85)	0.75 (0.66-0.83)	3.75 (1.69-8.32)	0.25 (0.19-0.33)	15.46 (8.20-29.14)	0.874 (0.848-0.901)
Unclear	6	0.85 (0.80-0.89)	0.82 (0.76-0.87)	3.80 (2.47-5.84)	0.22 (0.10-0.49)	22.39 (6.91-72.51)	0.892 (0.855-0.930)
Field strength							
1.5 T	3	0.76 (0.68-0.83)	0.81 (0.68-0.90)	3.16 (1.67-5.99)	0.34 (0.18-0.64)	10.40 (3.51-30.87)	0.839 (0.758-0.919)
3.0 T	6	0.85 (0.81-0.89)	0.79 (0.74-0.84)	3.92 (2.42-6.37)	0.19 (0.10-0.36)	26.17 (10.81-63.36)	0.904 (0.872-0.935)
Low b-values (0-50 s/mm^2)							
< 2	5	0.81 (0.75-0.86)	0.81 (0.73-0.87)	3.40 (2.17-5.35)	0.26 (0.14-0.47)	17.12 (6.11-47.98)	0.877 (0.834-0.921)
≥ 2	4	0.83 (0.78-0.88)	0.79 (0.72-0.85)	4.11 (2.07-8.17)	0.22 (0.10-0.47)	21.73 (7.22-65.42)	0.890 (0.855-0.935)
Trigger method							
RT	5	0.82 (0.77-0.86)	0.79 (0.73-0.84)	3.66 (2.24-5.97)	0.27 (0.14-0.54)	15.05 (5.78-39.22)	0.867 (0.828-0.905)
Non-RT	4	0.83 (0.77-0.88)	0.81 (0.70-0.89)	4.02 (1.85-8.76)	0.21 (0.13-0.34)	29.43 (9.89-87.59)	0.919 (0.883-0.956)

No.: Number of studies; LR: Likelihood ratio; DOR: Diagnostic odds ratio; AUC: Area under summary receiver operating characteristic curves; RT: Respiratory triggered.

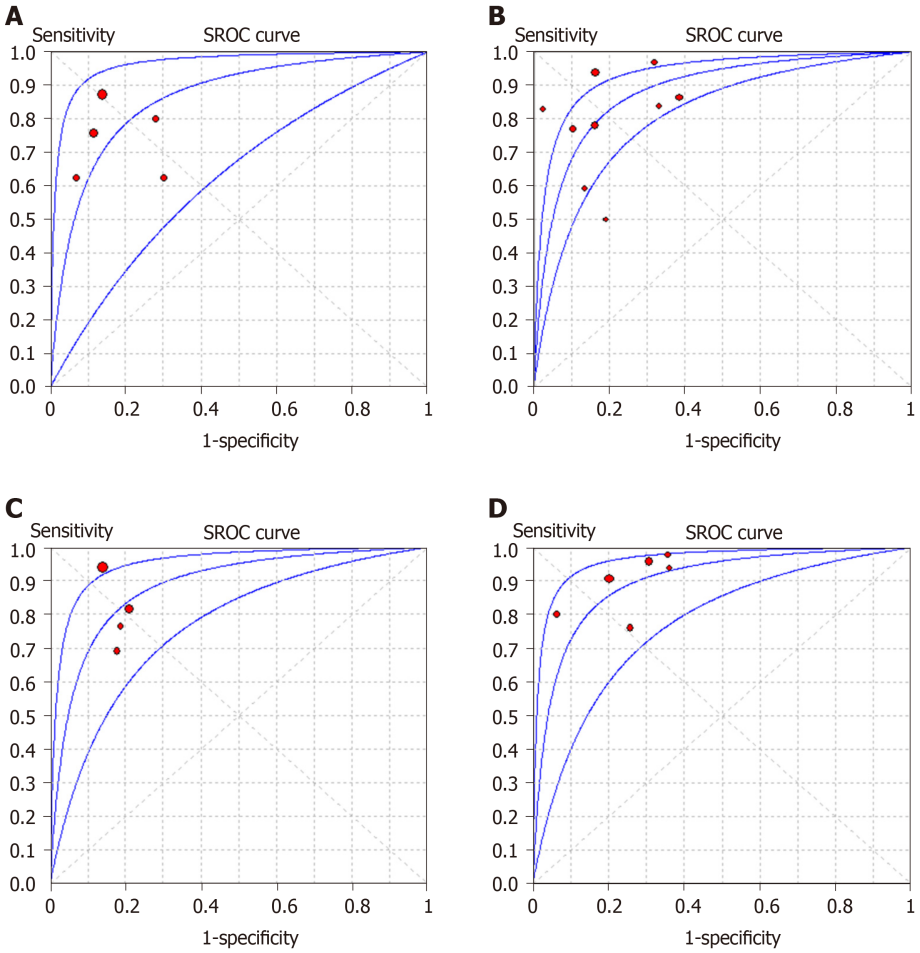

Figure 3 Summary receiver operating characteristic curves of intravoxel incoherent motion in detecting and staging liver fibrosis. A and B: The area under the curves are 0.862 for liver fibrosis (LF) ≥ F1 (A), B: 0.883 (0.856-0.909) for LF ≥ F2 (B); C and D: 0.886 (0.865-0.907) for LF ≥ F3 (C) and 0.899 (0.866-0.932) for LF = F4 (D), respectively. SROC: Summary receiver operating characteristic.

ARTICLE HIGHLIGHTS

Research background

Liver fibrosis (LF) is a common pathological feature of all chronic liver diseases. Liver biopsy is the current reference standard in detecting and staging LF. However, liver biopsy is invasive, observer dependent, and prone to sampling variability, all of which hampers its widespread use in clinical practice; thus, a noninvasive method to quantify LF is urgently needed. Recently, magnetic resonance imaging techniques have been increasingly applied to LF detection and staging and could possibly be the noninvasive alternative to liver biopsy. With the accumulation of extracellular matrix in the fibrotic liver, the true molecular water diffusion and perfusion-related diffusion would be restricted. Intravoxel incoherent motion (IVIM) could capture the information of tissue diffusivity and microcapillary perfusion separately and reflect the fibrotic severity with diffusion coefficients.

Research motivation

IVIM, a bi-exponential model based on diffusion-weighted imaging, allows for the separate evaluation of true molecular diffusion and perfusion-related diffusion. Although several recent studies focused on the diagnostic performances of IVIM in LF staging, the reported results were discrepant among studies

Research objectives

With more eligible studies and patients included, the purpose of this meta-analysis is to investigate the diagnostic performance of IVIM in different LF stages with histology as reference.

Research methods

A comprehensive literature search was conducted to identify studies on the diagnostic accuracy of IVIM for assessment of histology proven LF. The stages of LF were classified as F0 (no fibrosis), F1 (portal fibrosis without septa), F2 (periportal fibrosis with few septa), F3 (septal fibrosis) and F4 (cirrhosis), according to histopathological findings. Data were extracted to calculate the pooled sensitivity, specificity, positive and negative likelihood ratios and diagnostic

odds ratio, as well as the area under the summary receiver operating characteristic curve (AUC) in each group.

Research results

Twelve studies with 923 subjects were included in this meta-analysis with 5 studies (n = 465) for LF ≥ F1, 9 studies (n = 757) for LF ≥ F2, 4 studies (n = 413) for LF ≥ F3 and 6 studies (n = 562) for LF = F4. The pooled sensitivity and specificity were estimated to be 0.78 (95% confidence interval: 0.73-0.82) and 0.81 (0.74-0.86) for LF ≥ F1 detection with IVIM; 0.82 (0.79-0.86) and 0.80 (0.75-0.84) for staging F2 fibrosis; 0.85 (0.79-0.90) and 0.83 (0.77-0.87) for staging F3 fibrosis, and 0.90 (0.84-0.94) and 0.75 (0.70-0.79) for detecting F4 cirrhosis, respectively. The AUCs for LF ≥ F1, F2, F3, F4 detection were 0.862 (0.811-0.914), 0.883 (0.856-0.909), 0.886 (0.865-0.907) and 0.899 (0.866-0.932), respectively. Moderate to substantial heterogeneity was observed with inconsistency index (I^2) ranging from 0% to 77.9%. No publication bias was detected.

Research conclusions

IVIM is a noninvasive tool with good diagnostic performance in detecting and staging LF. Optimized and standardized IVIM protocols are needed for further improving its diagnostic accuracy in clinical practice.

Research perspectives

The results showed that IVIM is a valuable tool in noninvasively detecting and staging LF. However, field strength, the number and distribution of b-values, as well as the triggering methods would affect the diagnostic accuracy. There is still a need to establish an optimized and standardized IVIM protocol for LF diagnosis in clinical practice.

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