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Original Article

Value of intravoxel incoherent motion diffusion-weighted MR imaging in differentiating malignant from benign pulmonary lesions: a meta analysis

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Abstract: Previous studies have indicated that intravoxel incoherent motion model (IVIM)of magnetic resonance imaging (MRI) shows great potential to differentiate malignant from benign lung lesions using various parameters such as pure diffusion coefficient (D), pseudo-diffusion coefficient (D*) and perfusion fraction (f). However, these studies showed inconsistent results. The aim of this meta-analysis was to evaluate the overall diagnostic value of the IVIM model in distinguishing malignant from benign lung lesions. A literature search was conducted in Pubmed, Web of Science, CNKI and Wanfang Data to identify relevant available studies. We compared IVIM parameters between malignant and benign lung lesions and determined sensitivities and specificities across studies and constructed summary receiver operating characteristic SROC) curves. The pooled sensitivities were 0.78 (0.68-0.86), 0.74 (0.65-0.82) and 0.84 (0.74-0.91) for ADC, f and D, respectively. The pooled specificities were 0.83 (0.70-0.93), 0.52 (0.39-0.65) and 0.60 (0.46-0.73) for ADC, f and D, respectively. The AUCs of the SROC were 0.8748, 0.6774 and 0.7868 for ADC, f and D, respectively. The combined weighted mean difference (WMD) suggested the mean values of ADC, D and f in lung cancer were significantly lower than in benign lung diseases. However, there were no significant differences between lung cancer and benign lung diseases for D* value. The IVIM model may be helpful to discriminate malignant from benign lung lesions. Large-scale randomized controlled trials regarding IVIM in characterizing focal pulmonary lesions are still required to be conducted.

Keywords: Lung cancer, magnetic resonance imaging, intravoxel incoherent motion, pulmonary lesions, differentiation, meta-analysis

Introduction

Lung cancer is the most common malignancy worldwide. Focal lung lesions are the most common radiological manifestations of lung cancer. However, not only lung cancer presented focal pulmonary lesions but also many benign conditions such as infection, granuloma, tuberculoma showed pulmonary nodules in chest imaging [1-3]. Diagnostic evaluation of focal pulmonary lesions is crucial to choose appropriate treatment for malignant tumors or benign diseases. Generally, lung cancer was confirmed by percutaneous transthoracic biopsy or bronchoscopic biopsy. How to noninvasively differentiate malignant pulmonary nodules from benign diseases has become a hotspot of clinical research. A variety of imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography and computed tomography (PET/CT) are used to distinguish malignant from benign lung diseases. CT is commonly used for focal lung lesions examination. However, CT is based on morphologic criteria to differentiate malignant and benign lesions and there are considerably overlapping morphological features between malignant and benign lesions. Therefore, CT has some limitations in assessing focal lung lesions [4, 5]. MRI has been limited for examining lung disease owing to low proton density and numerous air-

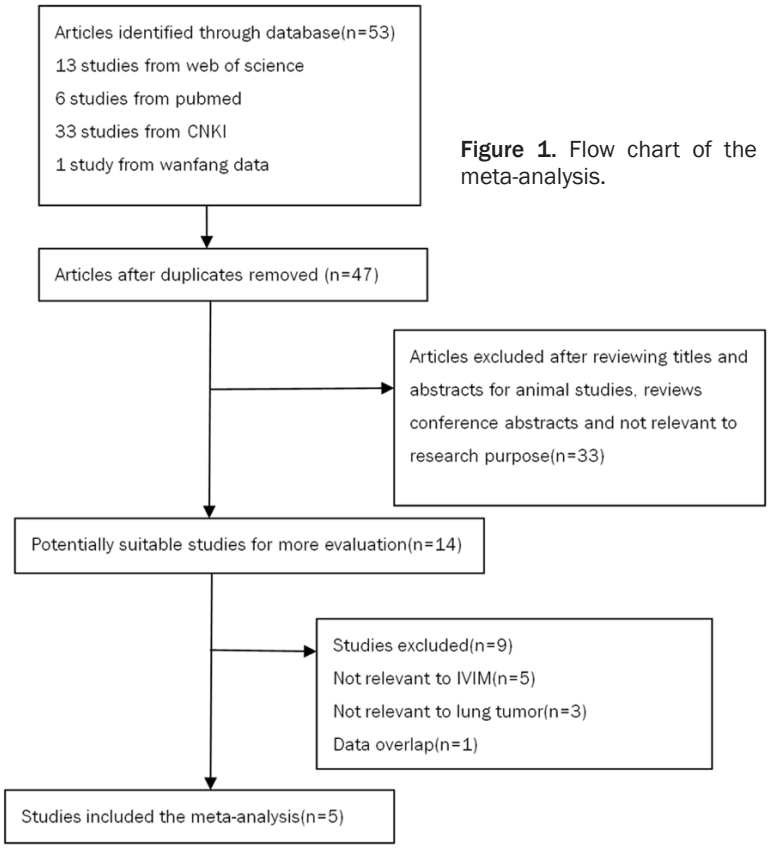

Figure 1. Flow chart of the meta-analysis.

tissue interfaces in lung [6]. Nevertheless, MRI also has advantages over CT in providing integrating anatomical and functional information. Hence, MRI is increasingly being used to examine patients with solitary pulmonary nodules [7]. Diffusion-weighted imaging (DWI) is a functional MRI technique that yields tissue diffusion properties and provides information on biophysical properties of tissues such as cell organization, cell density, microstructure and microcirculation [8, 9]. Apparent diffusion coefficient (ADC) is a quantitative parameter calculated from DWI-MRI to measure the water diffusion motion [10]. ADC has been proved to be a technically feasible tool in distinguishing malignant and benign tumors such as pulmonary masses [11], renal tumors [9]. Yet, ADC measures the combined effects of the molecular diffusion of water and microcapillary perfusion [12-14]. The IVIM model of MRI analysis shows great potential to further separate images of tissue diffusivity and tissue microcapillary perfusion using high-quality multiple b-value DWI [15-17]. Therefore, IVIM model may help to distinguish malignant and benign tumors using various parameters such as pure diffusion coefficient (D), pseudo-diffusion coefficient (D*) and perfusion fraction (f). IVIM was initially applied to neuroimaging and subsequently was used to differentiate various cancers and benign diseases [18-20]. In recent years, several articles have reported the diagnostic performance of IVIM parameters in distinguishing lung cancer from benign diseases [21-25]. However, the results varied widely among these studies and there are some inconclusive in differentiating malignant from benign pulmonary lesions by IVIM parameters. So we performed this meta-analysis to evaluate the value of IVIM model in distinguishing malignant and benign lung tumors.

Materials and methods

Search strategy

A literature search was performed in PubMed, Web of Science, CNKI and Wanfang Data to identify available studies published before November 2015. A search strategy was used for the following terms: (lung OR pulmonary) and (nodule OR lesions OR cancer OR tumor OR neoplasms) AND (IVIM OR intravoxel incoherent motion). There were no language restrictions. In addition, references of each article were reviewed carefully to identify other relevant articles.

Eligibility criteria

Eligible studies were required to meet the following criteria: (1) IVIM parameters were used to detect malignant and benign lung lesions. (2) Values of IVIM parameters could be obtained. (3) Sufficient information were presented to calculate true-positive (TP), false positive (FP), false-negative (FN) and true-negative (TN). (4) Histopathologic analysis or clinical follow-up were applied as the reference standard; Exclusion criteria were as follows: (1) The research purpose was unrelated to differentiate lung cancer from benign diseases using IVIM model of MRI. (2) For duplicate publications, only the most complete study was included.

Table 1. Basic characteristics of included studies in this meta-analysis

Author	Year	Country	Study design	MRI machine type	No. of malignant tumors	No. of benign tumors	IVIM parameters	Cutoff values	2×2 table				Se	Sp	AUC
									TP	FP	FN	TN			
Wang LL [21]	2014	China	Prospective study	Siemens 1.5 T	31	31	ADC	1.409×10^{-3} mm^2/s	28	1	3	30	90.3%	96.8%	0.950
							D	0.980×10^{-3} mm^2/s	27	11	4	20	87.1%	66.5%	0.763
							f	24.925%	25	15	6	16	80.6%	54.8%	0.762
Wang XH [22]	2014	China	Prospective study	GE 3. 0 T	23	15	D	≤0.90×10^{-3} mm^2/s	22	3	1	12	95.7%	80. 0%	0.839
							D*	>3.70×10^{-3} mm^2/s	19	6	4	9	82.6%	60.0%	0.683
							f	≤39.3%	12	6	11	9	52.1%	80.0%	0.639
Koyama [25]	2015	Japan	Prospective study	Philips 1.5 T	27	9	ADC	0.9×10^{-3} mm^2/s	19	6	8	3	70.4%	33.3%	N
							D	0.6×10^{-3} mm^2/s	19	8	8	1	70.4%	11.1%	N
							f	15%	21	7	6	2	77.8%	22.2%	N
Yuan [24]	2015	China	Prospective study	Siemens 3.0 T	48	48	ADC	≤1.31×10^{-3} mm^2/s	N	N	N	N	81.2 (67.4-91)%	81.2 (67.4-91)%	N
							D	≤1.44×10^{-3} mm^2/s	N	N	N	N	91.3 (79.2-97.5)%	38.5 (20.3-59.4)	N
							D*	>12.71×10^{-3} mm^2/s	N	N	N	N	47.8 (32.9-63.1)%	69.2 (48.2-85.6)%	N
							f	<18.36%	N	N	N	N	60.9 (45.4-74.9)%	69.2 (48.2-85.6)%	N
Deng [23]	2015	China	Prospective study	Philips 3.0 T	30	8	ADC	1.0224×10^{-3} mm^2/s	22	1	8	7	73.3%	87.5%	0.833
							f	37.4309%	24	2	6	6	80.0%	75.0%	0.829

IVIM: Intravoxel incoherent motion; ADC: Apparent diffusion coefficient; D: true diffusion coefficients; D*: perfusion-related diffusion coefficient; f: perfusion fraction; Note: N = not mentioned; TP: True positive; TN: true negative; FP: false positive; FN: false negative.

Table 2. Quality assessment of included studies in this meta-analysis

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Wang LL [21]	UN	LR	LR	LR	HR	LR	LR
Wang XH [22]	UN	LR	LR	LR	UN	LR	LR
Koyama [25]	LR	LR	LR	HR	UN	LR	LR
Yuan [24]	UN	LR	LR	HR	HR	LR	LR
Deng [23]	LR	LR	LR	LR	LR	LR	LR

LR: low risk; HR: high risk; UN: unclear.

Data extraction and quality assessment

Two investigators (XD Zhang and XL Chen) independently extracted data from qualified studies. The following data were collected from each study: first author, year of publication, country, MRI machine type, No of malignant and benign tumors, IVIM parameters, cutoff values, the values of TP, FN, FP and TN. Quality evaluation of included studies in the meta analysis was performed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2). QUADAS-2 is a tool to evaluate the risk of bias and applicability of diagnostic accuracy studies, which included 4 domains: patient selection, index test, reference standard and flow and timing. Each domain is evaluated according to the risk of bias and the first three domains are also evaluated according to concerns about applicability [26].

Statistical analyses

Meta-Disc 1.4 was used to summarize the pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) and corresponding 95% confidence interval (CI). Additionally, summary receiver operating characteristic (SROC) curves were plotted for the aggregate data. The area under the curve (AUC) and Q* index were also calculated to assess the overall performance of the diagnostic test accuracy [27]. Heterogeneity among studies were identified using Cochran's Q-statistic (a *P* value <0.05 was considered statistically significant) and the inconsistency index (I^2) test (I^2>50% indicated significant heterogeneity). When heterogeneity was considered to be significant, the random-effects model (the Mantel-Haenszel method) was used; While there was no significant heterogeneity (I^2<50%), the fixed-effects model (the Der-Simonian and Laird method) was used. Review Manager 5.3 was used to summarize mean values of IVIM parameters with 95% confidence intervals of malignant and benign pulmonary lesions. Q-statistics and I^2 was also used to determine the heterogeneity among studies. The random effects model and fixed effects model were also used accordingly. The association between IVIM parameters and lung lesions was assessed by weighted mean difference (WMD) with 95% confidence intervals (CI) by the Z test. A two-sided *p* value of <0.05 was considered to indicate statistical significance.

Result

Study selection and characteristics of included studies

A total of 53 potentially relevant studies including 13 studies from web of science, 6 studies from pubmed, 33 studies from CNKI and 1 study from wanfang data were retrieved based on the search terms. After screening the title and abstract, 6 duplicates were removed, then 33 articles were excluded for animal studies, reviews, conference abstracts and unrelated to research purpose. After reviewed full texts of the remaining 14 articles, We also excluded 9 articles for the following reasons: the studies were not relevant to IVIM (n=5), were not relevant to lung tumor (n=3) and data was presented in another article (n=1). Finally, 5 eligible studies were included in the meta-analysis [21-25]. The flow chart of articles selection in the meta-analysis is illustrated in **Figure 1**. All studies included in this meta-analysis were published between 2014 and 2015. ALL studies [21-25] are prospective studies. Among the 5 studies included in the meta analysis, 4 studies [21-24] were from China, 1 study [25] from Japan. In total, all articles included 159 malignant lung lesions and 111 benign lesions. The two studies [21, 24] used Siemens 1.5 T and 3.0 T MRI scanner respectively, while one study [22] used GE 3.0 T scanner and the other 2 studies [23, 25] used Philips 1.5 T and 3.0 T MRI scanner respectively. Four studies [21-23, 25] provide information on the value TP, FP, FN

Table 3. Summarized diagnostic accuracy of IVIM parameters

IVIM parameters	Se (95% CI)	Sp (95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)	AUC	Q*
ADC [21, 23, 25]	0.78 (0.68-0.86)	0.83 (0.70-0.93)	5.21 (0.23-119.45)	0.30 (0.1-0.94)	17.10 (0.66-441.30)	0.8748	0.8053
F [21-23, 25]	0.74 (0.65-0.82)	0.52 (0.39-0.65)	1.41 (0.93-2.14)	0.50 (0.28-0.92)	3.05 (1.64-5.68)	0.6774	0.6350
D [21, 22, 25]	0.84 (0.74-0.91)	0.60 (0.46-0.73)	2.00 (0.56-7.15)	0.29 (0.05-1.910	6.91 (0.40-119.03)	0.7868	0.7224

IVIM: Intravoxel Incoherent Motion; Se: sensitivity; Sp: specificity; PLR: positive likelihood ratio; NLR: Negative likelihood ratio; DOR: diagnostic odds ratio; AUC: area under the curve; Q*: an index defined by the point on the SROC curve where the sensitivity and specificity are equal, which is the point closest to the top-left corner of the ROC space.

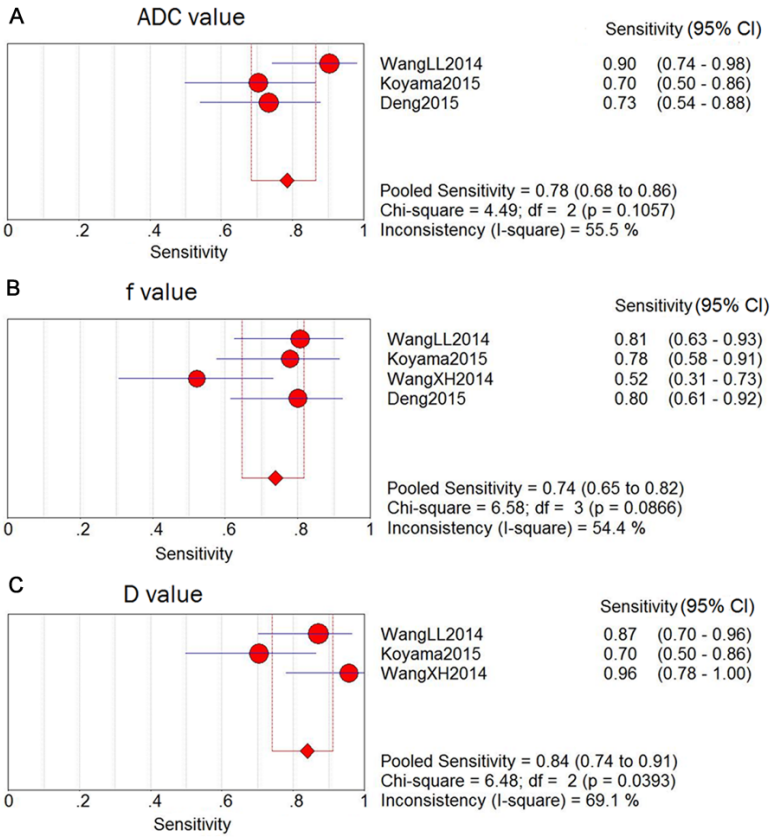

Figure 2. The pooled sensitivity of IVIM parameters in distinguishing malignant from benign pulmonary lesions.

and TN, while one study [24] did not provide the relevant information. In addition, information on IVIM parameters of the five studies included in the meta-analysis are listed in **Table 1**.

Quality assessment

The quality and bias of 5 papers were assessed according to QUADAS-2. Only 2 studies [23, 25] were at low risk of selection bias, while the others studies did not explicitly explain a consecutive or random sample of patients enrolled. All studies were low risk of index test and reference standard bias. One study [24] was regarded as being at high risk of flow and timing bias due to patients enrolled omitting from 2×2 table of results. Concerns regarding applicability, one studie [21] was at high risk of patient selection for patients with lung cancer and obstructive consolidations was selected, While another study [24] were at high risk of patient selection because patients received anti-inflammatory therapies before MRI scan. In addition, all studies were at low risk of index test and reference standard. The evaluation of studies included in this meta-analysis according to QUADAS-2 is shown in **Table 2**.

Diagnostic accuracy of IVIM parameters

Table 3 show the pooled sensitivities, specificities, PLR, NLR, DOR with 95% CIs of IVIM parameters for lung cancer diagnosis. The pooled sensitivities in distinguishing malignant from benign lung lesions were 0.78 (0.68-0.86), 0.74 (0.65-0.82) and 0.84 (0.74-0.91) for ADC, f and D, respectively (**Figure 2**). The pooled specificities were 0.83 (0.70-0.93), 0.52 (0.39-0.65) and 0.60 (0.46-0.73) for ADC, f and D, respectively (**Figure 3**). The AUCs were 0.8748, 0.6774 and 0.7868 for ADC, f and D, respectively (**Figure 4**)

Meta-analysis of IVIM parameters value in lung cancer diagnosis

In this meta-analysis, 4 studies [21, 23-25] reported the values of ADC, D and f for malignant and benign lung lesions, while 3 studies

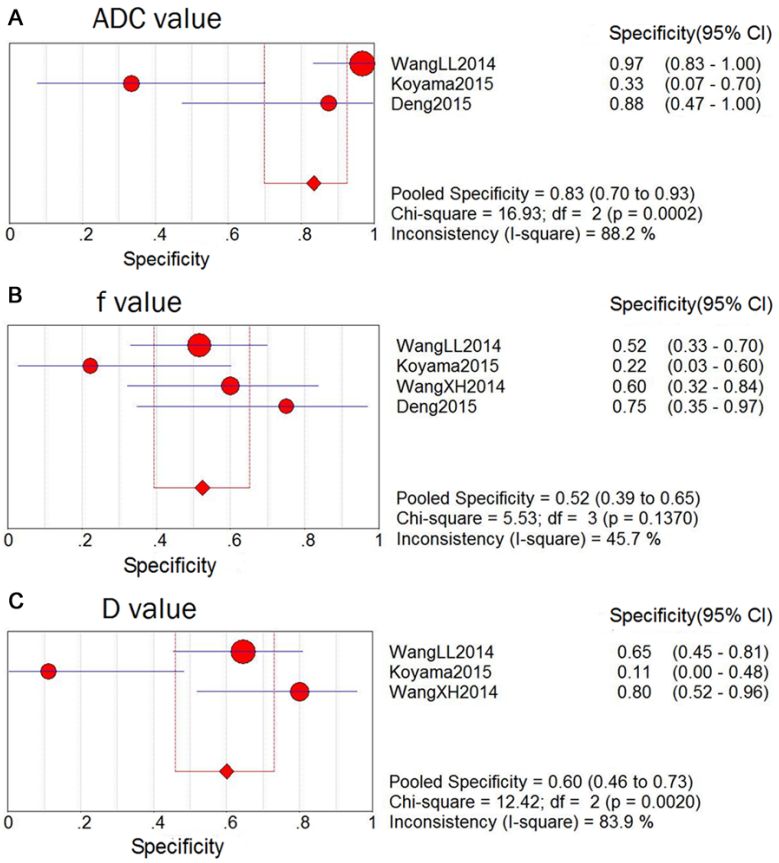

Figure 3. The pooled specificity of IVIM parameters in distinguishing malignant from benign pulmonary lesions.

[21, 23, 24] reported the D* values for malignant and benign lung lesions. The results of meta-analysis indicated that the mean ADC, D and f values of lung cancer was significantly lower than those of benign lung diseases. (ADC: WMD=-0.28, 95% CI: -0.38~-0.17, P<0.00001; D: WMD=-0.20, 95% CI: -0.35~-0.05, P=0.008; f: WMD=-8.48, 95% CI: -14.36~-2.60, P=0.005, respectively). However, there were not statistically significant differences between lung cancer and benign lung diseases for D* value (WMD=-0.96, 95% CI: -9.19~7.27, P=0.82) (**Figure 5**).

Discussion

In recent years, IVIM-MRI has been widely applied in distinguishing malignancy from benign diseases, such as breast tumors [28], hepatic focal lesions [19], pancreas carcinoma [29] and prostate cancer [30]. Several studies have already investigated the potential role of IVIM-MRI in differential diagnosis of pulmonary lesions, but the clinical effect remains controversial. Wang et al [21] showed that the ADC, D and f values were lower in lung cancer than obstructive pulmonary consolidations. However, Koyama et al [25] found that there was no significant difference for ADC, D and f values between malignant and benign pulmonary nodules. Several studies also showed inconsistent results [22, 23, 31]. In this meta-analysis, we assessed the clinical effect of IVIM-MRI in distinguishing malignant and benign pulmonary lesions. The results showed lung cancer had lower pooled ADC, D and f values than benign lung diseases. However, there were no significant difference for D* values between malignant and benign pulmonary lesions in this meta-analysis.

The D value was reflecting pure extravascular water diffusion and was mainly dependent on tissue cell density which restrict water diffusion. In general, malignant tumors have low D values due to high cellularity. Liu et al [32] indicated D value was significantly lower in breast malignant lesions compared with benign lesions. In this meta-analysis, the D value was significantly lower in lung cancer than benign lung lesions. The results suggested cell density is higher in lung cancer tissue than benign lesions.

D* value was perfusion-related diffusion coefficient and was determined by the blood microcirculation. Our results indicated no significant difference was observed for D* values in two patient groups, suggesting that it may not be a potential discriminating markers. However, several studies showed measurement of D* value may not be reliable using IVIM fitting method due to the low signal-to-noise ratio (SNR) and measurement instability [15, 23, 32]. *Further studies are needed* to assess D* value in distinguishing lung cancer and benign pulmonary

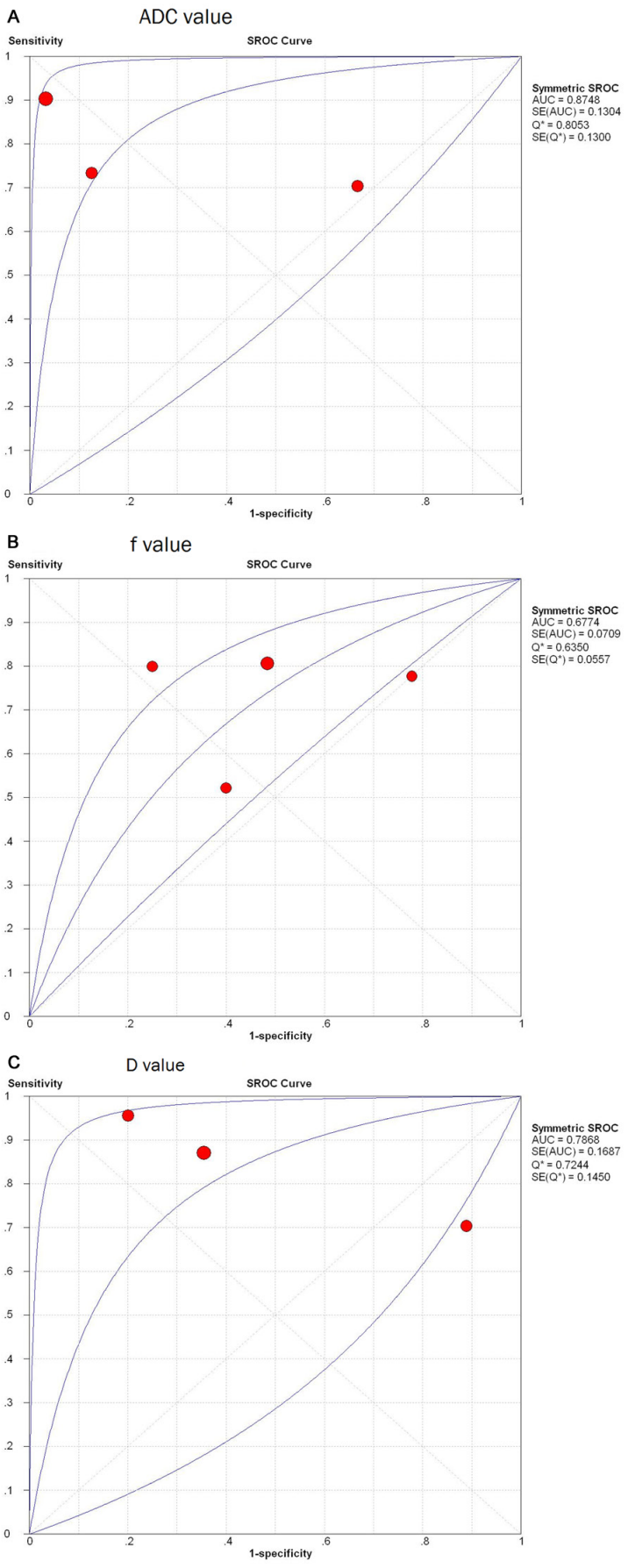

Figure 4. SROC curve of IVIM parameters in distinguishing malignant from benign pulmonary lesions.

lesions. The ADC measurement was influenced by diffusion and perfusion which reflect pure extravascular water diffusion and microcirculation respectively. Our results showed ADC values were significantly lower in lung cancer than benign lung diseases, which was also consistent with previous meta-analysis. Shen et al [33] also demonstrated malignant pulmonary lesions have significantly lower ADC values than benign lesions. In general, malignant tumors have low ADC values due to high cellularity, cell density which restrict water diffusion [34]. However, the ADC value is high in normal tissues for low cellularity and better organization of tissue structure which contribute water molecules move freely [35]. Three studies included in this meta-analysis showed D values were lower in lung cancer compared with benign pulmonary lesions [21, 22, 31]. In the three studies, two studies [21, 31] also demonstrated ADC values were lower in lung cancer than benign lesions, while another study did not mention ADC value [22]. Therefore, we hypothesized that ADC values were mainly determined by the D values in pulmonary lesions and pure water molecular motion contribute to differentiate malignant from benign pulmonary lesions. In addition, our results also demonstrate that f values were significantly lower in lung cancers than benign lung lesions. IVIM studies in nasopharyngeal carcinoma [36] and pancreatic carcinoma [37] also indicated that f values were significantly higher in benign lesions compared with malignant carcinomas. However, IVIM studies in other malignant tumors were inconsistent with the current results. Several studies showed

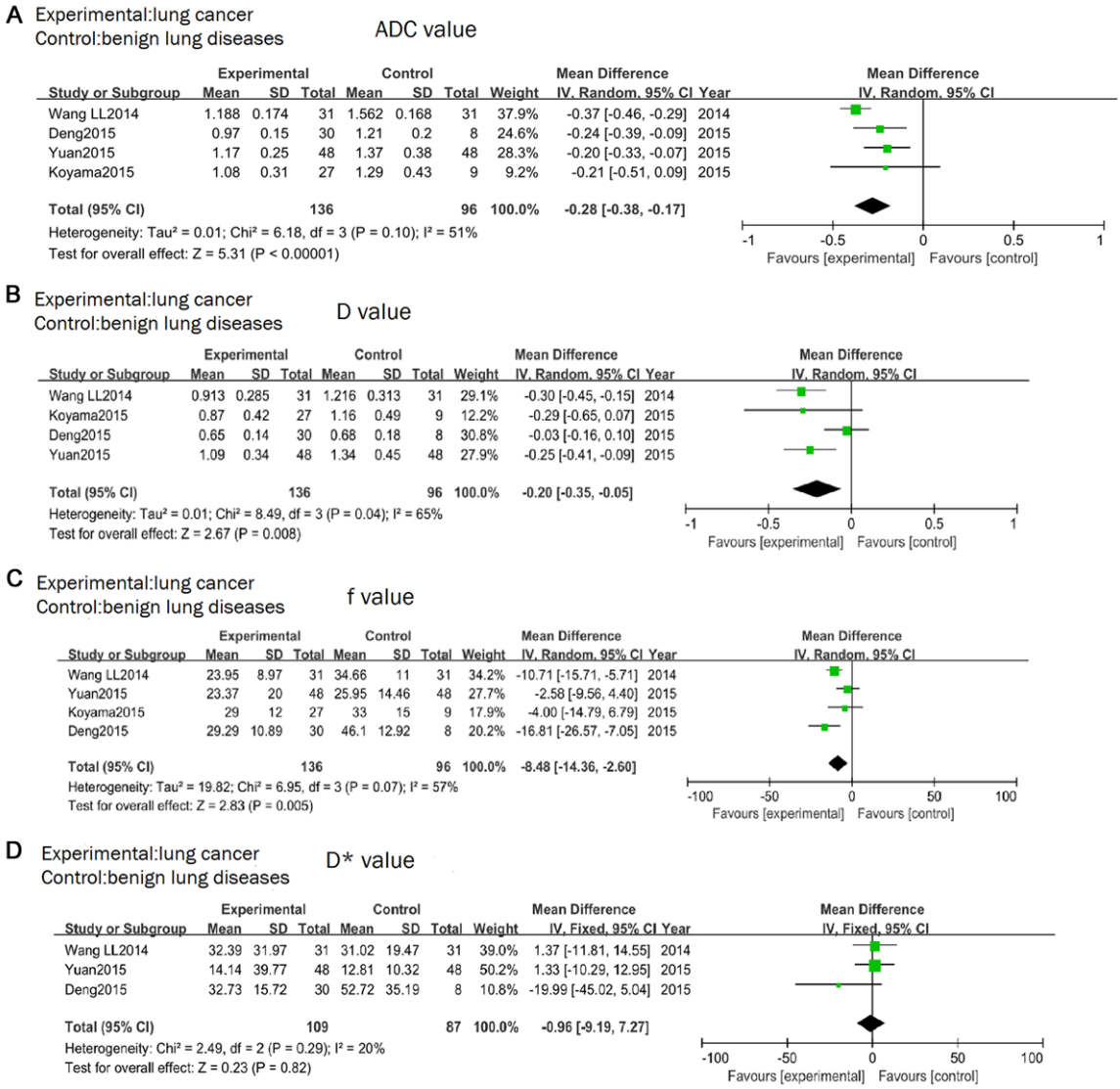

Figure 5. Forest plots of IVIM parameters in distinguishing malignant from benign pulmonary lesions. A: Comparison of ADC values between lung cancer and benign lung diseases; B: Comparison of D values between lung cancer and benign lung diseases; C: Comparison of f values between lung cancer and benign lung diseases; D: Comparison of D* values between lung cancer and benign lung diseases.

the f values were higher in breast cancers compared with benign breast tumors [28, 32, 38]. The f value was related to tissue microcirculation and reflected the ratio of vascular volume and tissues [32, 39]. Interestingly, two studies [21, 23] concerning lung cancer and focal inflammatory lesions showed f values were lower in lung cancer than inflammatory lesions, however, other studies [22, 25, 31] concerning lung cancer and benign solitary pulmonary lesions suggested there were no difference between the two groups. We hypothesized that neovascularization in malignant tumors increase f values, but the process of inflammation including vasodilation, increased permeability and increased blood flow also contribute to higher f values [23]. In addition, the study by Lemke et al [40] also demonstrated that f value was related not only blood flow but also echo time and f value increased closely with increasing echo time. The role of f value in distinguishing benign and malignant lung lesions needs further study.

In this study, we also assessed the diagnostic accuracy of IVIM in distinguishing malignant

from lung benign lesions. The results of this meta-analysis indicated D values showed higher sensitivity (0.84) in distinguishing malignant from benign lung lesions, however ADC values have higher specificity (0.83) in distinguishing malignant from benign lung lesions. In this study, the area under the sROC curve (AUC) and the Q* index were used to illustrate the overall significance of IVIM in distinguishing malignant from benign lung lesions. In general, an AUC of 0.97 or above is excellent accuracy; an AUC of 0.93 to 0.96 is very good; 0.75 to 0.92 is good; but an AUC less than 0.75 is considered poor accuracy [41]. In this meta-analysis, we observed that AUC for ADC, f and D value were 0.8748, 0.6774 and 0.7868, respectively, which indicated ADC and D values have good accuracy in differentiating lung cancer from benign lung lesions, but the diagnostic accuracy of f values were poor. Our studies showed that IVIM-MRI is potentially useful in differentiating lung cancer from benign lung lesions.

There are several limitations in this study. Firstly, the numbers of eligible studies included in this meta-analysis were relatively small and the sample size was limited in number, which may have affected our final conclusion. Secondly, number and magnitudes of b values used for the IVIM model are lack of consensus, which may result in the heterogeneity between studies included in this meta-analysis. Thirdly, the actual cut-off value of IVIM parameters for discriminating malignant from benign lung lesions is unclear which may influence the diagnostic accuracy. Finally, the benign lung lesions included focal organized pneumonia lesions, tubercular granulomas, fungal infections and Hamartoma may exhibit various values of IVIM parameters, therefore influenced the final conclusion.

Conclusion

In conclusion, our study has shown IVIM is potentially useful in differentiation of malignant and benign lung lesions. The values of ADC, D and f were helpful discriminating markers to distinguish lung cancer and benign lung lesions, but D* values were not so useful. ADC and D values have higher diagnostic performance than f value in differentiating lung cancer from benign lung lesions. However, the choice of number and magnitudes of b values and cut-off value are lack of consensus. Large-scale randomized controlled trials would be required to assess its clinical value and determine the optimal b values and cut-off value in IVIM model in the differentiation of lung cancer and benign lung lesions.

Disclosure of conflict of interest

None.

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