Diffusion-Weighted Imaging Reflects Tumor Grading and Microvascular Invasion in Hepatocellular Carcinoma

Alexey Surov[a]   Maciej Pech[a]   Jazan Omari[a]   Frank Fischbach[a]   Robert Damm[a]
Katharina Fischbach[a]   Maciej Powerski[a]   Borna Relja[a]   Andreas Wienke[b]

[a]Department of Radiology and Nuclear Medicine University of Magdeburg, Magdeburg, Germany; [b]Institute of Medical Epidemiology, Biostatistics, and Informatics, Martin-Luther-University Halle-Wittenberg, Halle, Germany

Abstract

Background: To date, there are inconsistent data about relationships between diffusion-weighted imaging (DWI) and tumor grading/microvascular invasion (MVI) in hepatocellular carcinoma (HCC). Our purpose was to systematize the reported results regarding the role of DWI in prediction of tumor grading/MVI in HCC. *Method:* MEDLINE library, Scopus, and Embase data bases were screened up to December 2019. Overall, 29 studies with 2,715 tumors were included into the analysis. There were 20 studies regarding DWI and tumor grading, 8 studies about DWI and MVI, and 1 study investigated DWI, tumor grading, and MVI in HCC. *Results:* In 21 studies (1,799 tumors), mean apparent diffusion coefficient (ADC) values (ADC_{mean}) were used for distinguishing HCCs. ADC_{mean} of G1–3 lesions overlapped significantly. In 4 studies (461 lesions), minimum ADC (ADC_{min}) was used. ADC_{min} values in G1/2 lesions were over 0.80×10^{-3} mm^2/s and in G3 tumors below 0.80×10^{-3} mm^2/s. In 4 studies (241 tumors), true diffusion (D) was reported. A significant overlapping of D values between G1, G2, and G3 groups was found. ADC_{mean} and MVI were analyzed in 9 studies (1,059 HCCs). ADC_{mean} values of MIV+/MVI– lesions overlapped significantly. ADC_{min} was used in 4 studies (672 lesions). ADC_{min} values of MVI+ tumors were in the area under 1.00×10^{-3} mm^2/s. In 3 studies (227 tumors), D was used. Also, D values of MVI+ lesions were predominantly in the area under 1.00×10^{-3} mm^2/s. *Conclusion:* ADC_{min} reflects tumor grading, and ADC_{min} and D predict MVI in HCC. Therefore, these DWI parameters should be estimated for every HCC lesion for pretreatment tumor stratification. ADC_{mean} cannot predict tumor grading/MVI in HCC.

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignant neoplasm of the liver [1]. Histologically, HCCs are classified according to the Edmondson-Steiner classification into 4 grades [2]. The pathological grade of HCC is associated with the prognosis [2]. Poorly differentiated HCC has higher recurrence rate and poorer prognosis after surgical resection in comparison with well- and moderately differentiated tumors [3].
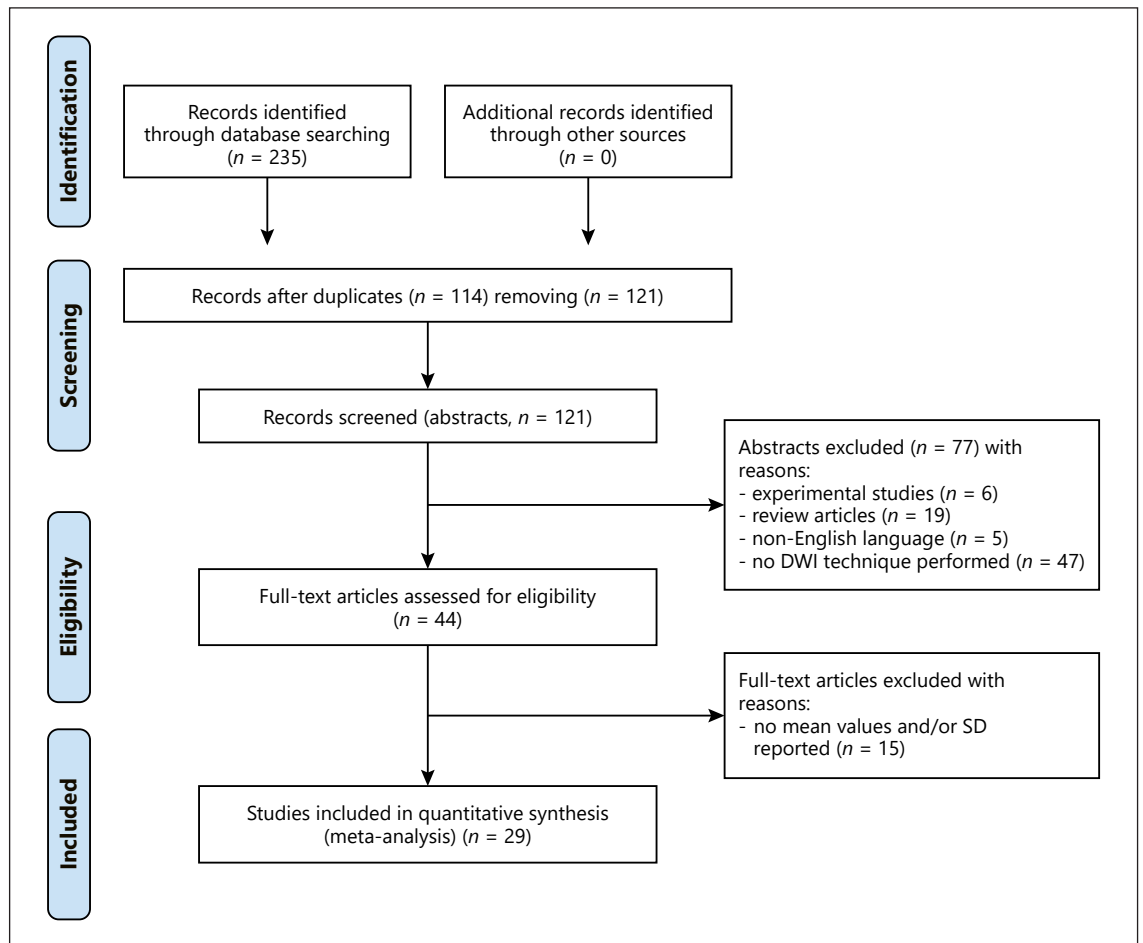
Alexey Surov
Department of Radiology and Nuclear Medicine
Ott-Von-Guericke University Magdeburg
Leipziger St., 44, DE–39112 Magdeburg (Germany)
alexey.surov@medizin.uni-leipzig.de

Fig. 1. PRISMA flowchart of the data acquisition. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement; DWI, diffusion-weighted imaging.

Similarly, microvascular invasion (MVI) is another important histopathological feature in HCC. MVI correlates with early recurrence and worse outcomes [4]. Therefore, prediction of the histological grade and/or MVI would provide great benefit in preoperative treatment planning. These tumor factors can be obtained only by histopathological examination. However, preoperative biopsy is not indicated for HCC. First, HCCs have typical radiological features on computed tomography (CT) and/or magnetic resonance imaging (MRI). Second, biopsy is an invasive approach. According to the current guidelines, for example, according to the American Association for the Study of Liver Diseases, biopsy is not needed for tumors with typical MRI or CT findings [5, 6]. Therefore, accurate pretreatment prediction of histological grade and MVI of HCCs based on MR images is very important.

However, it is difficult to define accurate preoperative grade of HCC using routine imaging modalities. Typical HCC features on MRI after administration of gadolinium-based contrast agents are already used in clinical practice to differentiate HCC from benign findings. However, contrast-enhancing MRI cannot provide histological information.

Some reports analyzed the role of diffusion-weighted imaging (DWI) as a predictor of histopathological features in HCC [7, 8]. DWI is an imaging modality, which characterizes random water movement or diffusion in tissues [9, 10]. Water diffusion can be quantified by apparent diffusion coefficient (ADC) [10]. Different ADC values such as mean ADC (ADC_{mean}), minimal ADC (ADC_{min}), maximal ADC (ADC_{max}), and so-called true diffusion (D) can be calculated [11]. Most frequently, ADC_{mean} is used. According to the literature, ADC can
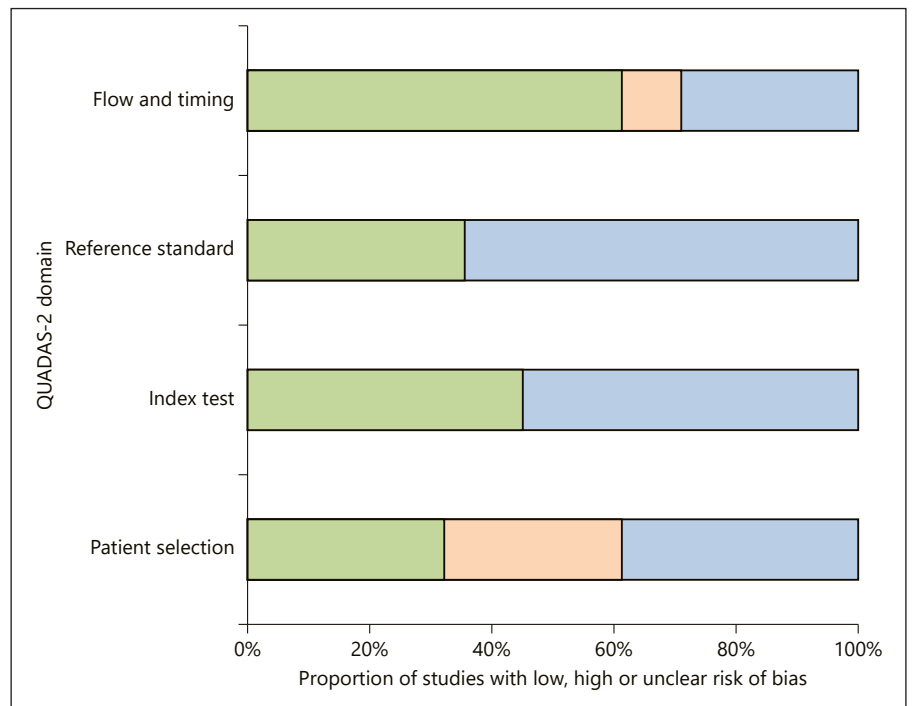
Fig. 2. QUADAS-2 quality assessment of the included studies. QUADAS, Quality Assessment of Diagnostic Studies.

reflect cell count and proliferation activity in different tumors [12, 13]. However, published data regarding the role of DWI in prediction of tumor grade and/or MVI in HCC were inconsistent. Furthermore, the number of investigated patients/tumors in the studies was relatively small. Therefore, the aim of the present meta-analysis was to systematize the reported data regarding associations between DWI and clinically relevant histopathological parameters such as tumor grading and MVI in HCC.

Materials and Methods

Data Acquisition
MEDLINE library, Embase data base, and Scopus data base were screened for associations between DWI and tumor grading and MVI up to December 2019 (Fig. 1).

For data acquisition, the following search criteria were used:
- DWI and tumor grading: DWI OR diffusion weighted imaging OR diffusion OR magnetic resonance imaging OR ADC or apparent diffusion coefficient AND grading OR grade AND hepatocellular carcinoma
- DWI and MVI: DWI OR diffusion weighted imaging OR diffusion OR magnetic resonance imaging OR ADC or apparent diffusion coefficient AND microvessel invasion OR microvascular invasion AND hepatocellular carcinoma

After the primary search, secondary references were also analyzed. Duplicate articles, review articles, experimental animal and in vitro studies, case reports, and non-English publications were excluded. In the next step, articles without statistical data regard-ing DWI parameters (mean values and/or standard deviation [SD]) were also excluded. Overall, 29 studies with 2,715 tumors were included into the analysis [14–42]. There were 20 studies regarding DWI and tumor grading, 8 studies about DWI and MVI, and 1 study investigated DWI, tumor grading, and MVI in HCC.

The following data were extracted from the literature: authors, year of publication, number of HCC lesions, tumor grade, presence of MVI, and mean and standard deviation of the reported DWI parameters. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) was used for the research [43].

Meta-Analysis
The methodological quality of the acquired studies was checked by 1 observer (A.S.) using the Quality Assessment of Diagnostic Studies (QUADAS) instrument [44]. Figure 2 displays the results of QUADAS proving.

The meta-analysis was undertaken by using RevMan 5.3 (computer program, version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Heterogeneity was calculated by means of the inconsistency index I^2 [45, 46]. Also, DerSimonian and Laird [47] random-effects models with inverse-variance weights were performed without any further correction. Finally, heterogeneity between studies was evaluated by the I^2 statistic, which describes the percentage of variation across studies that is due to heterogeneity rather than chance [48].

Results

The acquired 29 studies comprised 2,715 tumors. Of the included 29 studies, 5 were prospective and 24 were retrospective (Table 1). Different 3.0T scanners were used

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Fischbach/Powerski/Relja/Wienke

Table 1. Overview of the involved studies

Author	Study design	Lesions, n	Analyzed histopathological features	Analyzed DWI parameters
Chang et al. [14]	Retrospective	141	Tumor grade	ADC_{mean}
Granata et al. [15]	Retrospective	62	Tumor grade	ADC_{mean}, D
Guo et al. [16]	Prospective	27	Tumor grade	ADC_{mean}
Heo et al. [17]	Retrospective	27	Tumor grade	ADC_{mean}
Iwasa et al. [18]	Retrospective	42	Tumor grade	ADC_{mean}
Jiang et al. [19]	Retrospective	254	Tumor grade	ADC_{mean}
Lee et al. [20]	Retrospective	114	Tumor grade, MVI	ADC_{mean}, ADC_{min}
Le Moigne et al. [21]	Prospective	62	Tumor grade	ADC_{mean}
Li et al. [22]	Retrospective	241	Tumor grade	ADC_{mean}, ADC_{min}
Moriya et al. [23]	Retrospective	56	Tumor grade	ADC_{mean}, ADC_{min}
Muhi et al. [24]	Retrospective	98	Tumor grade	ADC_{mean}
Nakanishi et al. [25]	Retrospective	50	Tumor grade	ADC_{min}
Nasu et al. [26]	Retrospective	125	Tumor grade	ADC_{mean}
Nishie et al. [27]	Retrospective	52	Tumor grade	ADC_{mean}
Ogihara et al. [28]	Retrospective	42	Tumor grade	ADC_{mean}
Park et al. [29]	Retrospective	141	Tumor grade	ADC_{mean}
Saito et al. [30]	Retrospective	42	Tumor grade	ADC_{mean}
Shankar et al. [31]	Prospective	20	Tumor grade	ADC_{mean}
Tang et al. [32]	Retrospective	74	Tumor grade	ADC_{mean}
Woo et al. [33]	Retrospective	38	Tumor grade	ADC_{mean}, D
Zhu et al. [34]	Retrospective	62	Tumor grade	ADC_{mean}, D
Chuang et al. [35]	Retrospective	97	MVI	ADC_{mean}, ADC_{min}
Huang et al. [36]	Retrospective	51	MVI	ADC_{mean}
Kim et al. [37]	Retrospective	143	MVI	ADC_{mean}, ADC_{min}
Li et al. [38]	Prospective	41	MVI	ADC_{mean}, D
Wei et al. [39]	Prospective	135	MVI, tumor grade	ADC_{mean}, D
Xu et al. [40]	Retrospective	109	MVI	ADC_{mean}
Zhao J et al. [41]	Retrospective	318	MVI	ADC_{mean}, ADC_{min}
Zhao W et al. [42]	Retrospective	51	MVI	ADC_{mean}, D

MVI, microvascular invasion; ADC, apparent diffusion coefficient; D, true diffusion.

in 10 studies and diverse 1.5T scanners in 18 reports. In 1 study, both scanners (1.5T and 3.0T) were used. In all studies, DWI was performed by using a single-shot echo-planar imaging (EPI) sequence. Technical DWI parameters varied among the studies (Table 2). The collected studies investigated different DWI parameters such as mean ADC (ADC_{mean}), minimum ADC (ADC_{min}), and D. The funnel plots (Fig. 3a–c) show no evidence for publication bias regarding the analyzed DWI parameters.

DWI versus Tumor Grade

In 21 studies (1,799 tumors), mean ADC values (ADC_{mean}) were used for distinguishing different HCC lesions. ADC_{mean} values ($\times 10^{-3}$ mm^2/s) of the lesions were as follows: grade 1 (G1, $n = 364$): 1.28, 95% CI: 1.14–1.41; grade 2 (G2, $n = 1,063$): 1.16, 95% CI: 1.09–1.24; and grade 3 (G3, $n = 360$): 1.09, 95% CI: 0.74–1.43 (Fig. 4a–c).

Figure 4d shows the distribution of ADC_{mean} values in different tumor grades. The ADC_{mean} values of the groups overlapped significantly.

Furthermore, in 4 studies (461 lesions), minimum ADC values (ADC_{min}) were estimated and used for the differentiation of HCCs. The distribution of ADC_{min} ($\times 10^{-3}$ mm^2/s) in dependency on tumor grade was as follows: G1 ($n = 52$): 0.92, 95% CI: 0.72–1.13; G2 ($n = 351$): 0.81, 95% CI: 0.64–0.98; and G3 ($n = 58$): 0.59, 95% CI 0.29–0.88 (Fig. 5a–c). ADC_{min} values of G1 and G2 lesions overlapped significantly (Fig. 5d). Predominantly, G1 and G2 lesions did not have ADC_{min} values under 1.00 $\times 10^{-3}$ mm^2/s. ADC_{min} values in G3 HCCs were below the threshold of 0.80×10^{-3} mm^2/s.

In 4 studies (241 tumors), D was reported. D values ($\times 10^{-3}$ mm^2/s) of the lesions were as follows: G1 ($n = 47$): 1.20, 95% CI: 0.80–1.61; G2 ($n = 115$): 1.04, 95% CI: 0.86–

Table 2. DWI techniques in the included studies

Author	Tesla strength, T	DWI sequence	TR/TE, ms	b values, s/mm^2	Matrix	Slice thickness, mm	Field of view, cm	Respiratory triggering
Chang et al. [14]	1.5	EPI	2,000/57.5	0, 500	128×128	6	42×42	+
Granata et al. [15]	1.5	EPI	7,500/91	0, 50, 100, 200, 400, 600, 800	192×192	3	nr	+
Guo et al. [16]	3.0	EPI	1,400/72.3	0, 600	128×128	7	38×38	+
Heo et al. [17]	1.5	EPI	8,000/92	0, 1,000	128×128	5	34×34	−
Iwasa et al. [18]	1.5	EPI	11,250/81.3	0, 1,500	256×256	7	35×35	+
Jiang et al. [19]	1.5	EPI	1,200/62.9	0, 600	128×128	4	36×36	+
Lee et al. [20]	3.0	EPI	1,600/70	0, 100, 800	112×108	5	32×38	+
Le Moigne et al. [21]	1.5	EPI	2,336–7,216/79	50, 400, 800	192×115	6	30×40	+
Li et al. [22]	1.5	EPI	4,225/61.4	0, 800	128×128	8	38×40	+
Moriya et al. [23]	1.5	EPI	1,600/66	100, 800	128×124	5	40×44.7	+
Muhi et al. [24]	1.5	EPI	8,000–10,000/73.2–73.4	500, 1,000	128×128	4–6	40×40	+
Nakanishi et al. [25]	1.5	EPI	3,000/69	50, 1,000	128×98	8	45×36	+
Nasu et al. [26]	1.5	EPI	800–3,000/73	0, 500	256×97	7	35×28	+
Nishie et al. [27]	1.5	EPI	1,542–2,386/71–72	0, 500, 1,000	128×70–81	7–8	36×30.4–32.6	+
Ogihara et al. [28]*	1.5 3.0	nr	4,500/76.3 1,198.3–1,336.7/73 2,319–5,000/69 6,250/65 5,500/72.5 13,800/68	0, 800 0, 1,000	256×256 384×384 256×168	6–11	40×40 35×35 35×40 36×36 38×38	+
Park et al. [29]	1.5	EPI	3,900/75	50, 800	156×192	6	nr	+
Saito et al. [30]	1.5	EPI	3,000/71	100, 800	128×128	6	40×40	+
Shankar et al. [31]	3.0	EPI	6,600–8,400/92	0, 100, 500, 1,000	320×320	6	38×38	+
Tang et al. [32]	3.0	EPI	2,500/64.8	0, 800	128×128	7	36×42	+
Woo et al. [33]	3.0	EPI	5,000/52	0, 25, 50, 75, 100, 200, 500, 800	136×136	7	38×38	+
Zhu et al. [34]	3.0	EPI	4,286/61.2	0, 10, 20, 40, 80, 100, 150, 200, 400, 600, 800, 1,000, 1,200	128×128	7	38×28.5	+
Chuang et al. [35]	1.5	EPI	2,400/44	0, 400	80×128	5	nr	nr
Huang et al. [36]	1.5	EPI	2,600/66	0, 500	128×128	7	38–40×30–32	nr
Kim et al. [37]	3.0	EPI	1,444/55	0, 100, 800	112×108	5	nr	+
Li et al. [38]	3.0	EPI	1,973/57	0, 10, 20, 40, 80, 200, 400, 600, 1,000	32×114	5	37.5×30.2	+
Wei et al. [39]	3.0	EPI	9,230/84.7	0, 10, 20, 40, 80, 100, 150, 200, 400, 600, 800, 1,000, and 1,200	80×128	6	40×30	+
Xu et al. [40]	1.5	EPI	2,400/66	0, 500	128×112	7	nr	+
Zhao et al. [41]	1.5	EPI	4,225/61.4	0, 800	128×129	8	38–40	+
Zhao et al. [42]	3.0	EPI	5,714/65.5	0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 1,000	96×130	6	38×38	+

DWI, diffusion-weighted imaging; EPI, echo-planar imaging. * Authors used different DWI techniques.

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Fischbach/Powerski/Relja/Wienke
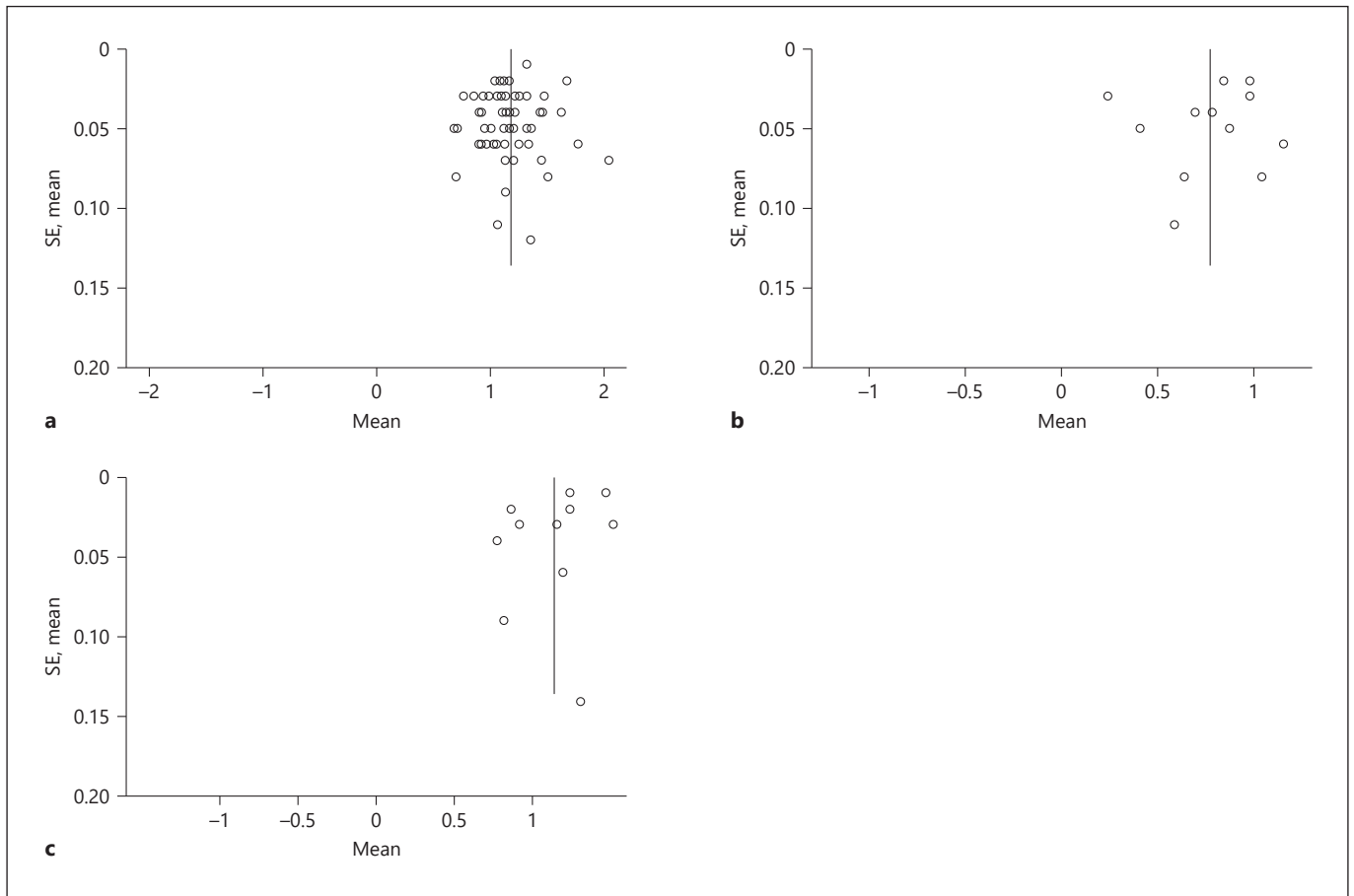
Fig. 3. Funnel plots show no evidence for publication bias. **a** Funnel plot for publications regarding ADC_{mean}. **b** Funnel plot for publications regarding ADC_{min}. **c** Funnel plot for publications regarding D. ADC, apparent diffusion coefficient; D, true diffusion.

1.21; G3 ($n = 79$): 1.17, 95% CI: 0.92–1.41 (Fig. 6a–c). A significant overlapping of D values between the groups was shown (Fig. 6d).

DWI versus MVI

Associations between ADC_{mean} and MVI were investigated in 9 studies (1,059 HCCs). MVI-positive ($n = 494$) and MVI-negative ($n = 565$) tumors had comparable ADC_{mean} values: 1.20 (95% CI: 1.11–1.30) and 1.35 (95% CI: 1.41–1.46), respectively. The ADC_{mean} values of the groups overlapped significantly (Fig. 7a–c).

Relationships between ADC_{min} and MVI were reported in 4 studies (672 lesions). MVI-positive tumors ($n = 335$) showed lower ADC_{min} values, 0.81 (95% CI: 0.69–0.93), than MVI-negative tumors, 1.02 (95% CI: 0.91–1.13). Furthermore, ADC_{min} values of MVI-positive tumors were in the area under 1.00×10^{-3} mm²/s (Fig. 8a–c)

In 3 studies (227 tumors), D was used for distinguishing different HCC lesions. MVI-positive tumors ($n = 94$) had lower D values, 0.84 (95% CI: 0.74–0.94), than MVI-negative tumors, 1.09 (95% CI: 0.97–1.21). D values of MVI-negative lesions were predominantly in the area over 1.00×10^{-3} mm²/s, and D values of MVI-positive lesions were under 1.00×10^{-3} mm²/s (Fig. 9a–c).

Discussion

To the best of our knowledge, this is the first meta-analysis regarding associations between DWI and tumor grade/MVI in HCC based on a large sample. DWI shows a great diagnostic potential and is widely used in oncological MRI. DWI, namely, ADC_{mean}, can differentiate

DWI Reflects Histopathology in HCC

| a | | | Weight, | Mean | Mean |
Study or subgroup	Mean	SE	%	IV, random, 95% CI	IV, random, 95% CI
Chang, 2014	2.04	0.07	4.7	2.04 [1.90, 2.13]	
Granata, 2016	0.94	0.03	4.9	0.94 [0.33, 1.00]	
Guo, 2015	1.43	0.04	4.9	1.43 [1.35, 1.51]	
Heo, 2010	1.2	0.07	4.7	1.20 [1.06, 1.34]	
Iwasa, 2016	1.1	0.04	4.9	1.10 [1.02, 1.18]	
Jiang, 2017	1.67	0.02	4.9	1.67 [1.63, 1.71]	
Le Moigne, 2014	1.05	0.03	4.9	1.05 [0.99, 1.11]	
Lee, 2019	1.12	0.06	4.3	1.12 [1.00, 1.24]	
Li, 2016	1.13	0.07	4.7	1.13 [0.99, 1.27]	
Morya, 2017	1.05	0.06	4.3	1.05 [0.93, 1.17]	
Muhi, 2009	0.91	0.04	4.9	0.91 [0.33, 0.99]	
Nasu, 2009	1.45	0.07	4.7	1.45 [1.31, 1.59]	
Nishie, 2011	1.21	0.05	4.3	1.21 [1.11, 1.31]	
Ogihara, 2013	1.33	0.06	4.3	1.33 [1.21, 1.45]	
Park, 2013	1.11	0.05	4.3	1.11 [1.01, 1.21]	
Saito, 2012	1.25	0.06	4.3	1.25 [1.13, 1.37]	
Shankar, 2016	0.92	0.06	4.3	0.92 [0.30, 1.04]	
Tang, 2016	1.32	0.05	4.3	1.32 [1.22, 1.42]	
Wei, 2019	1.77	0.06	4.3	1.77 [1.65, 1.39]	
Woo, 2014	1.35	0.12	4.3	1.35 [1.11, 1.59]	
Zhu, 2013	1.5	0.03	4.6	1.50 [1.34, 1.66]	
Total (95% CI)			**100.0**	**1.28 [1.14, 1.41]**	

Heterogeneity: $\tau^2 = 0.10$, $\chi^2 = 962.99$, df = 20 ($p < 0.00001$); $I^2 = 93\%$
Test for overall effect: $Z = 13.21$ ($p < 0.00001$)

| b | | | Weight, | Mean | Mean |
Study or subgroup	Mean	SE	%	IV, random, 95% CI	IV, random, 95% CI
Chang, 2014	1.62	0.04	4.8	1.62 [1.54, 1.70]	
Granata, 2016	1.03	0.06	4.5	1.03 [0.91, 1.15]	
Guo, 2015	1.34	0.06	4.5	1.34 [1.22, 1.46]	
Heo, 2010	1.1	0.03	4.9	1.10 [1.04, 1.16]	
Iwasa, 2016	1.14	0.07	4.3	1.14 [1.00, 1.28]	
Jiang, 2017	1.31	0.01	5.0	1.31 [1.29, 1.33]	
Le Moigne, 2014	0.99	0.03	4.9	0.99 [0.93, 1.05]	
Lee, 2019	1.08	0.02	4.9	1.08 [1.04, 1.12]	
Li, 2016	1.12	0.02	4.9	1.12 [1.08, 1.16]	
Morrya, 2017	0.99	0.03	4.9	0.99 [0.93, 1.05]	
Muhi, 2009	0.71	0.05	4.6	0.71 [0.61, 0.81]	
Nasu, 2009	1.46	0.04	4.8	1.46 [1.38, 1.54]	
Nishie, 2011	1.14	0.04	4.8	1.14 [1.06, 1.22]	
Ogihara, 2018	1.2	0.05	4.6	1.20 [1.10, 1.30]	
Park, 2018	1.16	0.02	4.9	1.16 [1.12, 1.20]	
Saito, 2012	1.12	0.05	4.6	1.12 [1.02, 1.22]	
Shankar, 2016	0.86	0.03	4.9	0.86 [0.80, 0.92]	
Tang, 2016	1.13	0.03	4.9	1.13 [1.07, 1.19]	
Wei, 2019	1.47	0.03	4.9	1.47 [1.41, 1.53]	
Woo, 2014	1.22	0.03	4.9	1.22 [1.16, 1.28]	
Zhu, 2018,	1.21	0.04	4.8	1.21 [1.13, 1.29]	
Total (95% CI)			**100.0**	**1.16 [1.09, 1.24]**	

Heterogeneity: $\tau^2 = 0.03$, $\chi^2 = 768.92$, df = 20 ($p < 0.00001$); $I^2 = 97\%$
Test for overall effect: $Z = 30.22$ ($p < 0.00001$)

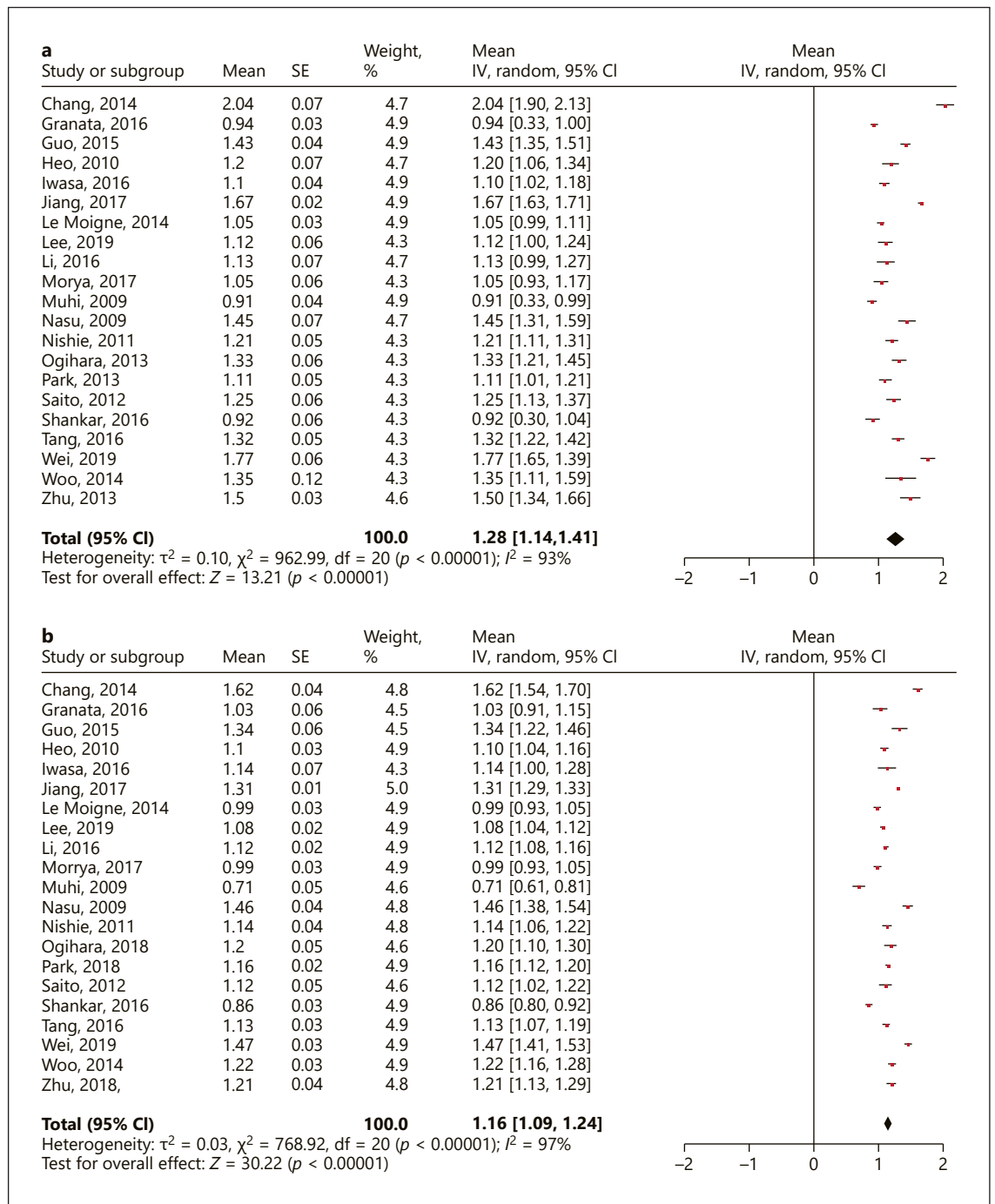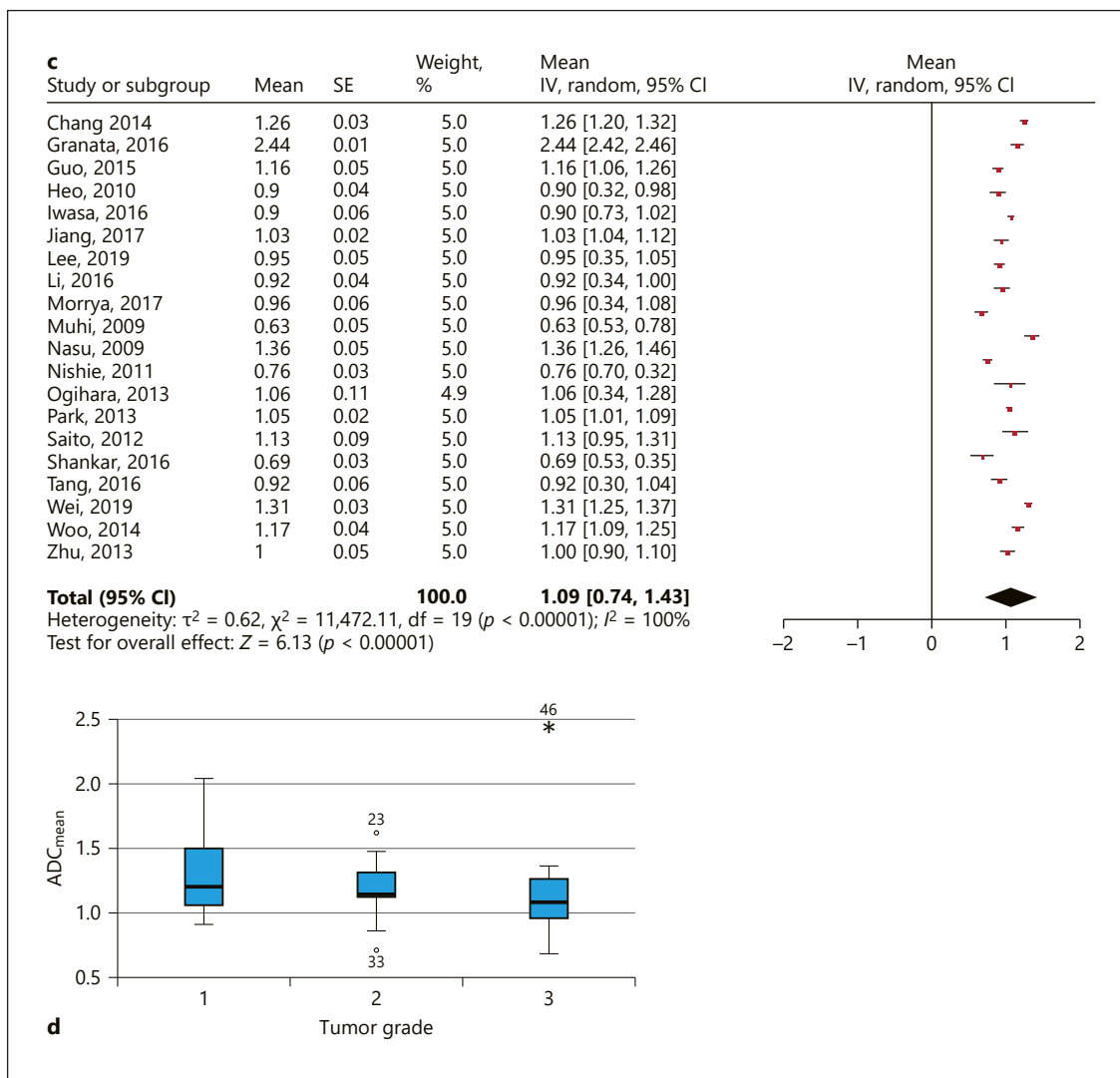**Fig. 4. a** Forrest plots of ADC_{mean} values reported for grade 1 HCC lesions. **b** Forrest plots of ADC_{mean} values reported for grade 2 HCC lesions. **c** Forrest plots of ADC_{mean} values reported for grade 3 HCC lesions. **d** Comparison of ADC_{mean} values between grade 1, 2, and 3 HCCs. ADC, apparent diffusion coefficient; HCC, hepatocellular carcinoma.

(Figure continued on next page.)

c

Study or subgroup	Mean	SE	Weight, %	Mean IV, random, 95% CI	Mean IV, random, 95% CI
Chang 2014	1.26	0.03	5.0	1.26 [1.20, 1.32]	
Granata, 2016	2.44	0.01	5.0	2.44 [2.42, 2.46]	
Guo, 2015	1.16	0.05	5.0	1.16 [1.06, 1.26]	
Heo, 2010	0.9	0.04	5.0	0.90 [0.32, 0.98]	
Iwasa, 2016	0.9	0.06	5.0	0.90 [0.73, 1.02]	
Jiang, 2017	1.03	0.02	5.0	1.03 [1.04, 1.12]	
Lee, 2019	0.95	0.05	5.0	0.95 [0.35, 1.05]	
Li, 2016	0.92	0.04	5.0	0.92 [0.34, 1.00]	
Morrya, 2017	0.96	0.06	5.0	0.96 [0.34, 1.08]	
Muhi, 2009	0.63	0.05	5.0	0.63 [0.53, 0.78]	
Nasu, 2009	1.36	0.05	5.0	1.36 [1.26, 1.46]	
Nishie, 2011	0.76	0.03	5.0	0.76 [0.70, 0.32]	
Ogihara, 2013	1.06	0.11	4.9	1.06 [0.34, 1.28]	
Park, 2013	1.05	0.02	5.0	1.05 [1.01, 1.09]	
Saito, 2012	1.13	0.09	5.0	1.13 [0.95, 1.31]	
Shankar, 2016	0.69	0.03	5.0	0.69 [0.53, 0.35]	
Tang, 2016	0.92	0.06	5.0	0.92 [0.30, 1.04]	
Wei, 2019	1.31	0.03	5.0	1.31 [1.25, 1.37]	
Woo, 2014	1.17	0.04	5.0	1.17 [1.09, 1.25]	
Zhu, 2013	1	0.05	5.0	1.00 [0.90, 1.10]	
Total (95% CI)			**100.0**	**1.09 [0.74, 1.43]**	

Heterogeneity: $\tau^2 = 0.62$, $\chi^2 = 11{,}472.11$, df = 19 ($p < 0.00001$); $I^2 = 100\%$
Test for overall effect: $Z = 6.13$ ($p < 0.00001$)

d

4

c

Study or subgroup	Mean	SE	Weight, %	Mean IV, random, 95% CI	Mean IV, random, 95% CI
Chang 2014	1.26	0.03	5.0	1.26 [1.20, 1.32]	
Granata, 2016	2.44	0.01	5.0	2.44 [2.42, 2.46]	
Guo, 2015	1.16	0.05	5.0	1.16 [1.06, 1.26]	
Heo, 2010	0.9	0.04	5.0	0.90 [0.32, 0.98]	
Iwasa, 2016	0.9	0.06	5.0	0.90 [0.73, 1.02]	
Jiang, 2017	1.03	0.02	5.0	1.03 [1.04, 1.12]	
Lee, 2019	0.95	0.05	5.0	0.95 [0.35, 1.05]	
Li, 2016	0.92	0.04	5.0	0.92 [0.34, 1.00]	
Morrya, 2017	0.96	0.06	5.0	0.96 [0.34, 1.08]	
Muhi, 2009	0.63	0.05	5.0	0.63 [0.53, 0.78]	
Nasu, 2009	1.36	0.05	5.0	1.36 [1.26, 1.46]	
Nishie, 2011	0.76	0.03	5.0	0.76 [0.70, 0.32]	
Ogihara, 2013	1.06	0.11	4.9	1.06 [0.34, 1.28]	
Park, 2013	1.05	0.02	5.0	1.05 [1.01, 1.09]	
Saito, 2012	1.13	0.09	5.0	1.13 [0.95, 1.31]	
Shankar, 2016	0.69	0.03	5.0	0.69 [0.53, 0.35]	
Tang, 2016	0.92	0.06	5.0	0.92 [0.30, 1.04]	
Wei, 2019	1.31	0.03	5.0	1.31 [1.25, 1.37]	
Woo, 2014	1.17	0.04	5.0	1.17 [1.09, 1.25]	
Zhu, 2013	1	0.05	5.0	1.00 [0.90, 1.10]	
Total (95% CI)			**100.0**	**1.09 [0.74, 1.43]**	

Heterogeneity: $\tau^2 = 0.62$, $\chi^2 = 11{,}472.11$, df = 19 ($p < 0.00001$); $I^2 = 100\%$
Test for overall effect: $Z = 6.13$ ($p < 0.00001$)

d

4

between malignant and benign lesions in different regions [49, 50]. Typically, malignant tumors have lower ADC_{mean} values in comparison to benign lesions [49, 50]. So far, recently, a large series showed that ADC_{mean} was lower with the threshold of 1.00 in breast cancer and higher in benign breast lesions [49]. Similar results were reported for liver lesions [50].

Furthermore, according to the literature, DWI is associated with tissue microstructure and can reflect several histopathological features [9, 10, 12, 13]. For example, it has been shown that ADC_{mean} and ADC_{min} correlated with cellularity and proliferation index Ki-67 in several malignant and benign tumors [12, 13]. Similar results were also reported for D values [11]. Some reports indicated that different DWI parameters can also reflect stromal fraction and nucleic size/nucleic-cytoplasmic ratio in tumors [9–11].

Presumably, DWI may also be helpful to characterize HCC lesions, namely, tumor differentiation and MVI. Prediction of histopathological features based on imaging is of high clinical relevance. Previously, some studies investigated this question with contradictory results. So, Chang et al. [14] found that highly differentiated HCCs showed statistically significant higher ADC_{mean} values ($2.04 \pm 0.41 \times 10^{-3}$ mm^2/s) in comparison to moderately differentiated ($1.62 \pm 0.3 \times 10^{-3}$ mm^2/s) and poorly differentiated tumors ($1.26 \pm 0.21 \times 10^{-3}$ mm^2/s). Similar results were reported also in other studies [16, 21]. However, other authors did not find significant differences of ADC_{mean} values between G1, G2, and G3 lesions [26, 29].
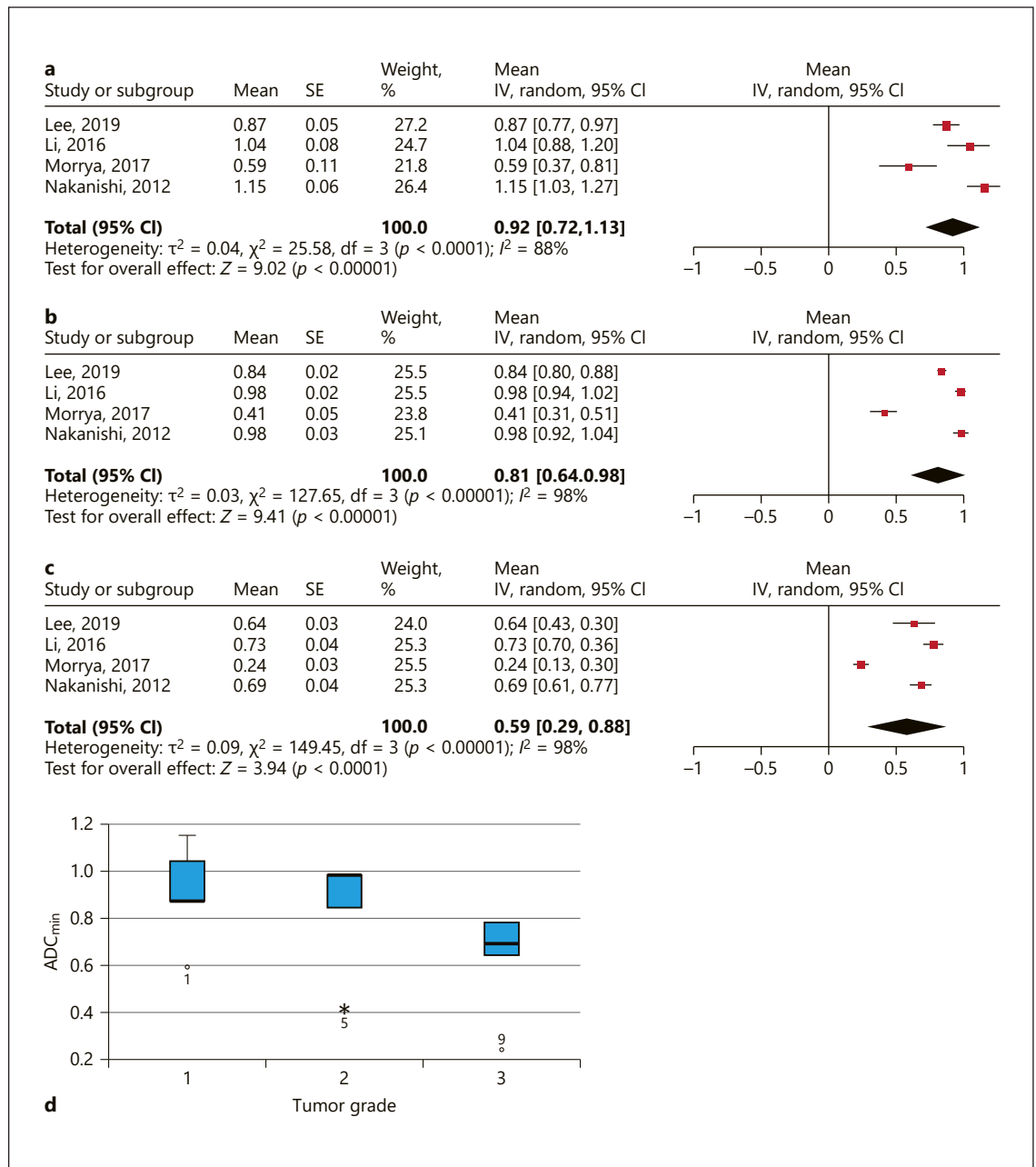
Fig. 5. a Forrest plots of ADC_{min} values reported for grade 1 HCC lesions. **b** Forrest plots of ADC_{min} values reported for grade 2 HCC lesions. **c** Forrest plots of ADC_{min} values reported for grade 3 HCC lesions. **d** Graphical distribution of ADC_{min} values between different tumor grades in HCC. ADC, apparent diffusion coefficient; HCC, hepatocellular carcinoma.

For example, according to Nasu et al. [26], ADC_{mean} values ($\times 10^{-3}$ mm²/s) were 1.45 ± 0.35 in G1, 1.46 ± 0.32 in G2, and 1.36 ± 0.29 in G3 tumors.

As already mentioned, DWI let retrieve different parameters. In most studies, ADC_{mean} was used. Less frequently, other DWI parameters, such as ADC_{min} and D, were analyzed. Presumably, different DWI parameters may reflect different histopathological features in HCC. In fact, the present results confirmed our hypothesis. As shown, ADC_{mean} and D cannot discriminate HCC with different
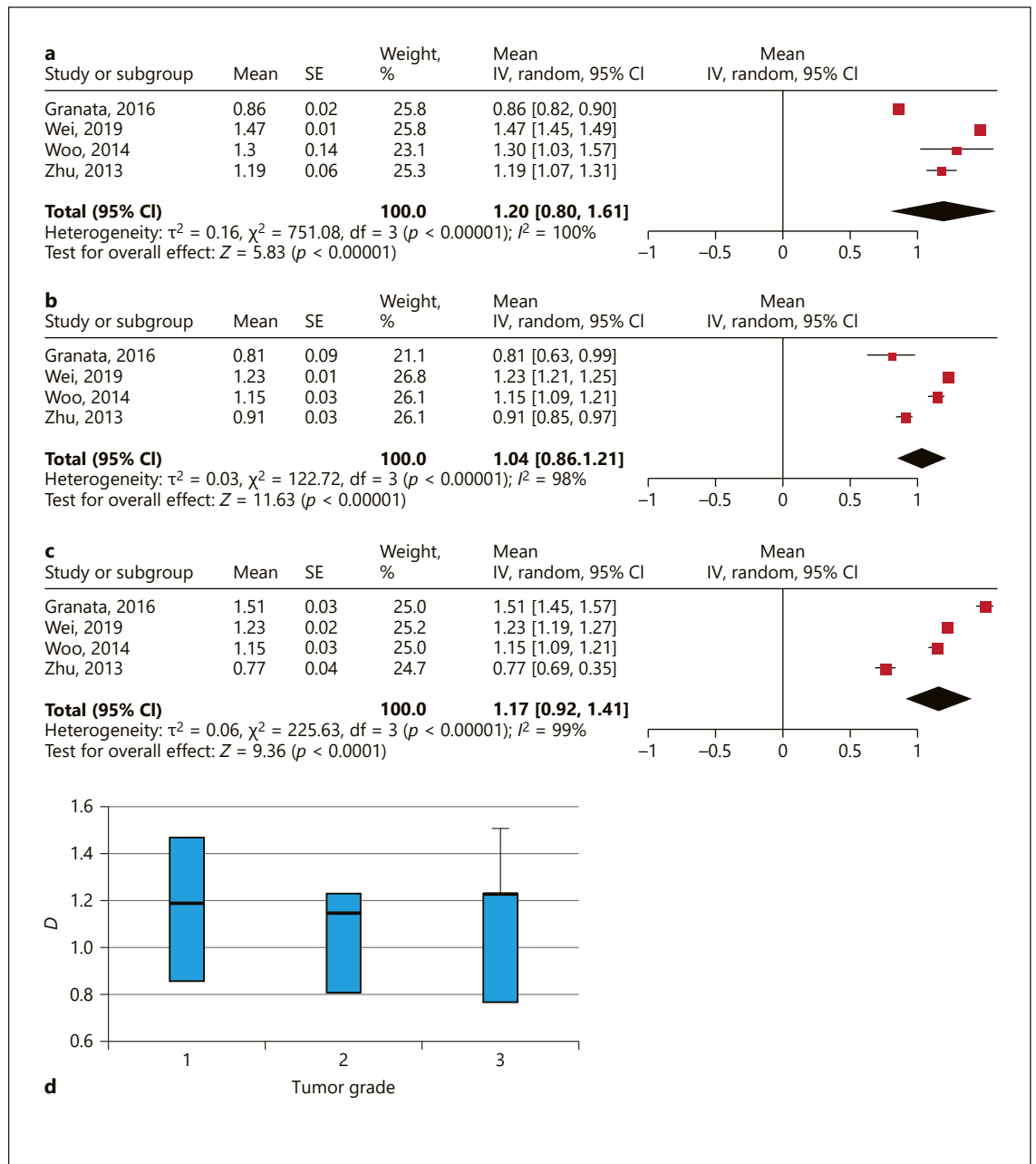
a Study or subgroup	Mean	SE	Weight, %	Mean IV, random, 95% CI	Mean IV, random, 95% CI
Granata, 2016	0.86	0.02	25.8	0.86 [0.82, 0.90]	
Wei, 2019	1.47	0.01	25.8	1.47 [1.45, 1.49]	
Woo, 2014	1.3	0.14	23.1	1.30 [1.03, 1.57]	
Zhu, 2013	1.19	0.06	25.3	1.19 [1.07, 1.31]	
Total (95% CI)			**100.0**	**1.20 [0.80, 1.61]**	

Heterogeneity: $\tau^2 = 0.16$, $\chi^2 = 751.08$, df = 3 ($p < 0.00001$); $I^2 = 100\%$
Test for overall effect: $Z = 5.83$ ($p < 0.00001$)

b Study or subgroup	Mean	SE	Weight, %	Mean IV, random, 95% CI	Mean IV, random, 95% CI
Granata, 2016	0.81	0.09	21.1	0.81 [0.63, 0.99]	
Wei, 2019	1.23	0.01	26.8	1.23 [1.21, 1.25]	
Woo, 2014	1.15	0.03	26.1	1.15 [1.09, 1.21]	
Zhu, 2013	0.91	0.03	26.1	0.91 [0.85, 0.97]	
Total (95% CI)			**100.0**	**1.04 [0.86.1.21]**	

Heterogeneity: $\tau^2 = 0.03$, $\chi^2 = 122.72$, df = 3 ($p < 0.00001$); $I^2 = 98\%$
Test for overall effect: $Z = 11.63$ ($p < 0.00001$)

c Study or subgroup	Mean	SE	Weight, %	Mean IV, random, 95% CI	Mean IV, random, 95% CI
Granata, 2016	1.51	0.03	25.0	1.51 [1.45, 1.57]	
Wei, 2019	1.23	0.02	25.2	1.23 [1.19, 1.27]	
Woo, 2014	1.15	0.03	25.0	1.15 [1.09, 1.21]	
Zhu, 2013	0.77	0.04	24.7	0.77 [0.69, 0.35]	
Total (95% CI)			**100.0**	**1.17 [0.92, 1.41]**	

Heterogeneity: $\tau^2 = 0.06$, $\chi^2 = 225.63$, df = 3 ($p < 0.00001$); $I^2 = 99\%$
Test for overall effect: $Z = 9.36$ ($p < 0.0001$)

Fig. 6. a Forrest plots of D values reported for grade 1 HCC lesions. **b** Forrest plots of D values reported for grade 2 HCC lesions. **c** Forrest plots of D values reported for grade 3 HCC lesions. **d** Comparison of D values between grade 1, 2, and 3 HCCs. D, true diffusion; HCC, hepatocellular carcinoma.

tumor differentiation. Therefore, these DWI parameters cannot be used as a surrogate marker for tumor grading in HCC. However, our data showed that ADC_{min} can predict grade of HCC lesions. In fact, G1 and G2 HCCs had ADC_{min} values above 0.80×10^{-3} mm^2/s and G3 HCCs had ADC_{min} values in the area below 0.80×10^{-3} mm^2/s.

Only in 1 study, ADC_{min} values of G1 and G2 tumors were also in the area under the threshold of 0.80×10^{-3}[23]. In this study, all ADC values were lower in comparison to other reports, also ADC_{mean}. It may be explained by the measure method. In fact, ADC values were calculated in the study using three-dimensional histograms [23]. In
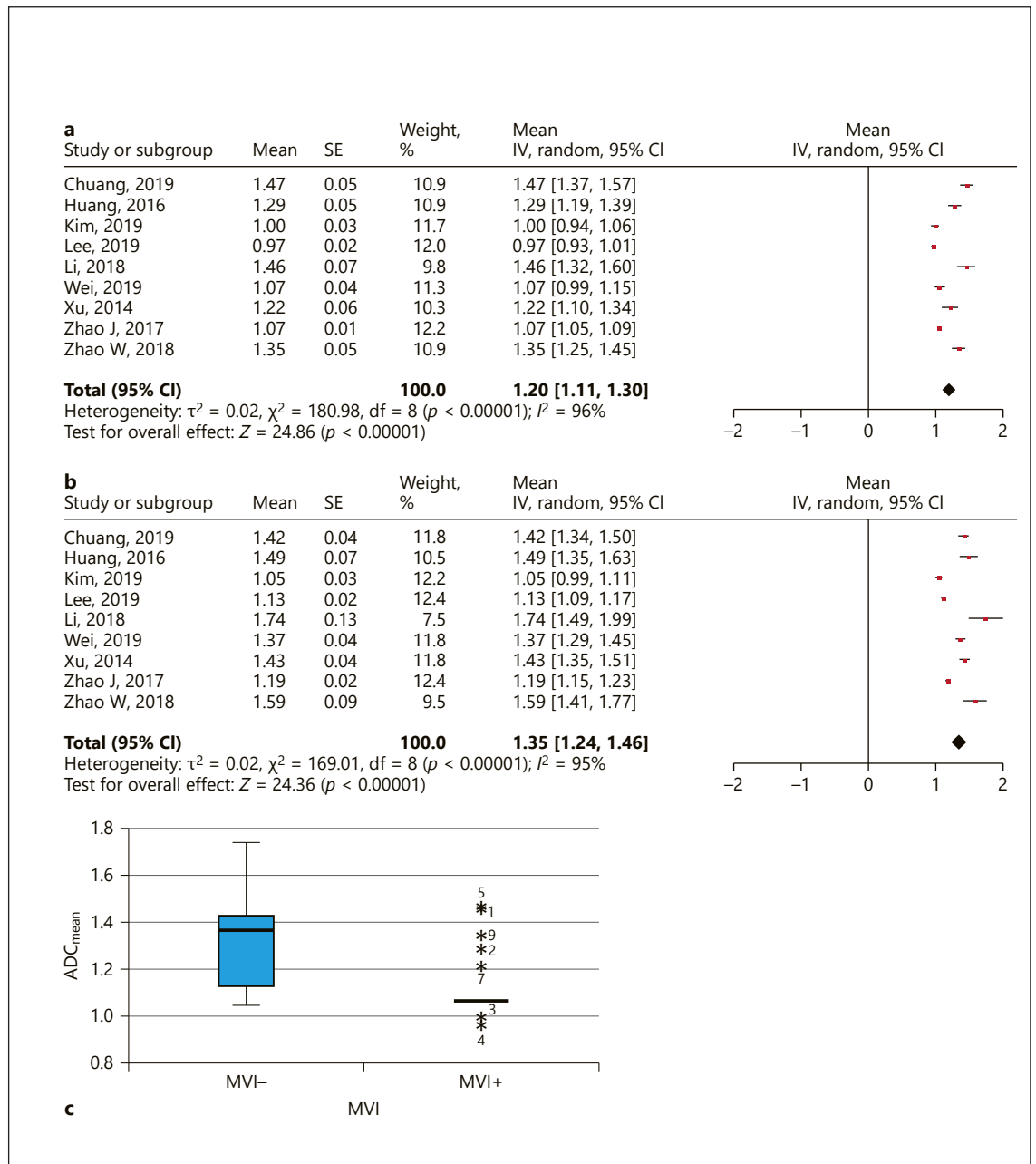
a

Study or subgroup	Mean	SE	Weight, %	Mean IV, random, 95% CI
Chuang, 2019	1.47	0.05	10.9	1.47 [1.37, 1.57]
Huang, 2016	1.29	0.05	10.9	1.29 [1.19, 1.39]
Kim, 2019	1.00	0.03	11.7	1.00 [0.94, 1.06]
Lee, 2019	0.97	0.02	12.0	0.97 [0.93, 1.01]
Li, 2018	1.46	0.07	9.8	1.46 [1.32, 1.60]
Wei, 2019	1.07	0.04	11.3	1.07 [0.99, 1.15]
Xu, 2014	1.22	0.06	10.3	1.22 [1.10, 1.34]
Zhao J, 2017	1.07	0.01	12.2	1.07 [1.05, 1.09]
Zhao W, 2018	1.35	0.05	10.9	1.35 [1.25, 1.45]
Total (95% CI)			**100.0**	**1.20 [1.11, 1.30]**

Heterogeneity: $\tau^2 = 0.02$, $\chi^2 = 180.98$, df = 8 ($p < 0.00001$); $I^2 = 96\%$
Test for overall effect: $Z = 24.86$ ($p < 0.00001$)

b

Study or subgroup	Mean	SE	Weight, %	Mean IV, random, 95% CI
Chuang, 2019	1.42	0.04	11.8	1.42 [1.34, 1.50]
Huang, 2016	1.49	0.07	10.5	1.49 [1.35, 1.63]
Kim, 2019	1.05	0.03	12.2	1.05 [0.99, 1.11]
Lee, 2019	1.13	0.02	12.4	1.13 [1.09, 1.17]
Li, 2018	1.74	0.13	7.5	1.74 [1.49, 1.99]
Wei, 2019	1.37	0.04	11.8	1.37 [1.29, 1.45]
Xu, 2014	1.43	0.04	11.8	1.43 [1.35, 1.51]
Zhao J, 2017	1.19	0.02	12.4	1.19 [1.15, 1.23]
Zhao W, 2018	1.59	0.09	9.5	1.59 [1.41, 1.77]
Total (95% CI)			**100.0**	**1.35 [1.24, 1.46]**

Heterogeneity: $\tau^2 = 0.02$, $\chi^2 = 169.01$, df = 8 ($p < 0.00001$); $I^2 = 95\%$
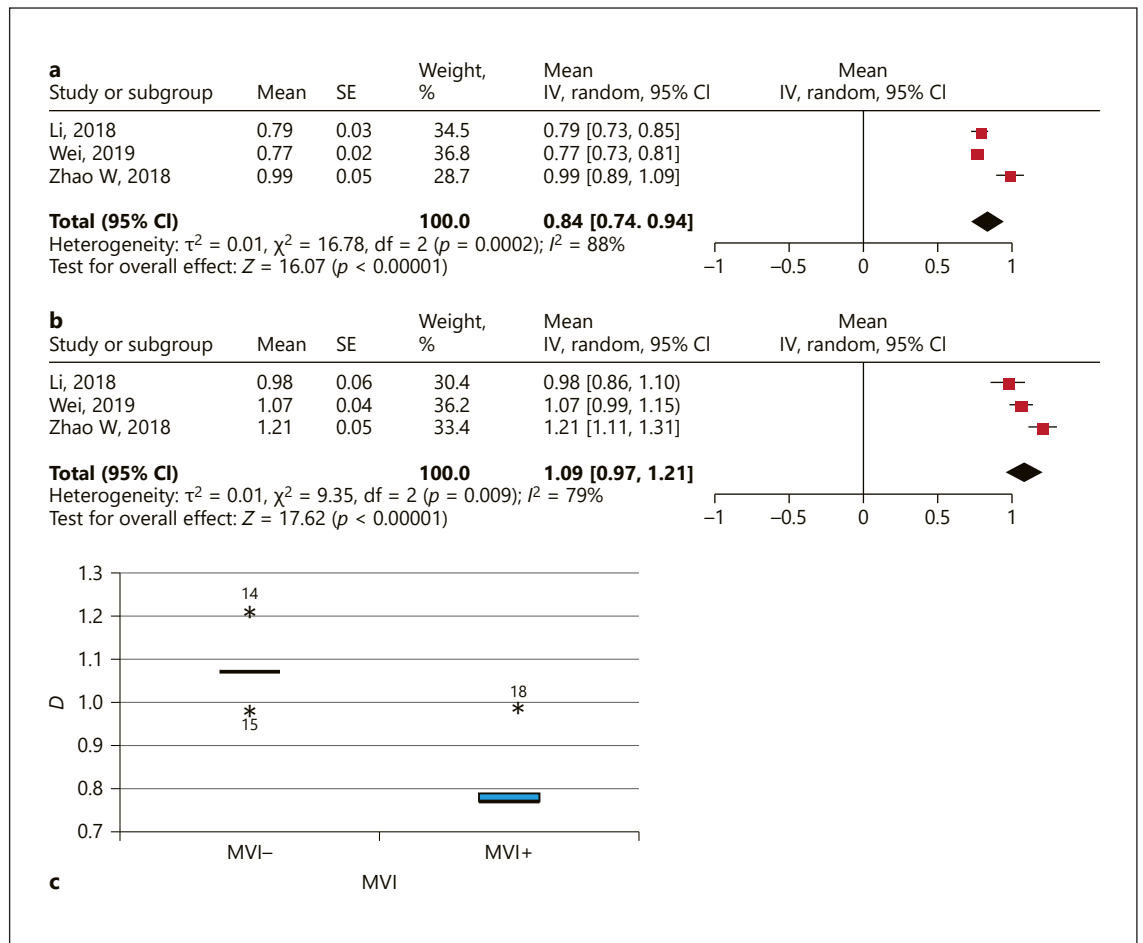Test for overall effect: $Z = 24.36$ ($p < 0.00001$)

Fig. 7. a Forrest plots of ADC_{mean} values reported for HCC lesions with MVI. **b** Forrest plots of ADC_{mean} values reported for HCC lesions without MVI. **c** Comparison of ADC_{mean} values between HCCs with and without MVI. ADC, apparent diffusion coefficient; HCC, hepatocellular carcinoma; MVI, microvascular invasion.

other studies, region-of-interest-based measurements were performed.

The indicated ADC_{min} value of 0.80×10^{-3} can be used as thresholds for estimation of tumor grading. This finding may be related to the fact that ADC_{min} is more sensitive to reflect tumor cell count. Furthermore, some reports suggested that different DWI parameters were associated with different histopathological findings [11]. For example, in meningiomas, ADC_{mean} correlated significantly with proliferation index Ki-67 and nucleic size/nucleic area of tumor cells, but not with cell count [11]. ADC_{min} and D correlated significantly with cell count and

Surov/Pech/Omari/Fischbach/Damm/
Fischbach/Powerski/Relja/Wienke

a

Study or subgroup	Mean	SE	Weight, %	Mean IV, random, 95% CI	Mean IV, random, 95% CI
Chuang, 2019	0.33	0.06	21.7	0.33 [0.71, 0.95]	
Kim, 2019	0.3	0.03	25.6	0.30 [0.74, 0.36]	
Lee, 2019	0.69	0.03	25.6	0.69 [0.63, 0.75]	
Zhao J, 2017	0.92	0.01	27.1	0.92 [0.90, 0.94]	
Total (95% CI)			**100.0**	**0.81 [0.09, 0.93]**	

Heterogeneity: $\tau^2 = 0.01$, $\chi^2 = 63.32$, df = 3 ($p < 0.00001$); $I^2 = 95\%$
Test for overall effect: $Z = 13.11$ ($p < 0.00001$)

b

Study or subgroup	Mean	SE	Weight, %	Mean IV, random, 95% CI	Mean IV, random, 95% CI
Chuang, 2019	1.03	0.03	24.5	1.03 [0.97, 1.09]	
Kim, 2019	0.85	0.03	24.5	0.85 [0.79, 0.91]	
Lee, 2019	1.13	0.02	25.5	1.13 [1.09, 1.17]	
Zhao J, 2017	1.06	0.02	25.5	1.06 [1.02, 1.10]	
Total (95% CI)			**100.0**	**1.02 [0.91, 1.13]**	

Heterogeneity: $\tau^2 = 0.01$, $\chi^2 = 61.09$, df = 3 ($p < 0.00001$); $I^2 = 95\%$
Test for overall effect: $Z = 18.67$ ($p < 0.00001$)

c

Fig. 8. a Forrest plots of ADC_{min} values reported for HCC lesions with MVI. **b** Forrest plots of ADC_{min} values reported for HCC lesions without MVI. **c** Comparison of ADC_{min} values between HCCs with and without MVI. ADC, apparent diffusion coefficient; HCC, hepatocellular carcinoma; MVI, microvascular invasion.

total nucleic area, but not with Ki-67 [11]. Tumor grading in HCC is based on the morphological features of tumor cells and nucleic content such as nucleic size. Grade 1 tumors have cells with abundant cytoplasm and minimal nuclear irregularity. Grade 2 lesions are characterized by greater nuclear irregularity and prominent nucleoli. Grade 3 HCCs show increased nuclear pleomorphism and angulation of the nuclei. In addition, tumor giant cells are also more commonly seen. Finally, grade 4 tumors are poorly differentiated lesions with marked nuclear pleomorphism, hyperchromatism, and anaplasia [2]. As shown, there are histopathological features which are associated with ADC_{min} but not with ADC_{mean}. Therefore, our finding that ADC_{min} is sensitive to discriminate different tumor grades in HCC is plausible.

Another important aspect of the present study is the fact that ADC_{min} and D can identify lesions with MVI. As shown, both parameters were in the area under 1.00×10^{-3} mm^2/s in MVI-positive tumors. Furthermore, our study identified that ADC_{mean} cannot predict MVI. Owing to the fact that pretreatment visualization of tumor MVI is very beneficial in clinical setting, ADC_{min} and/or D should be estimated in each HCC lesion to predict MVI and tumor prognosis.

The results of the present analysis are based on a large cohort and, therefore, provide evident data regarding associations between DWI and tumor grading/MVI in HCC. However, there are several limitations to address. First, most of the acquired studies were retrospective. Second, according the QUADAS criteria, some of the involved studies showed clinical review bias, patient selec-

Fig. 9. a Forrest plots of *D* values reported for HCC lesions with MVI. **b** Forrest plots of *D* values reported for HCC lesions without MVI. **c** Comparison of *D* values between HCCs with and without MVI. *D*, true diffusion; HCC, hepatocellular carcinoma; MVI, microvascular invasion.

tion bias, and diagnostic review bias. Third, different MR equipment, Tesla strength, DWI sequences, and *b* values were used in the collected studies. However, our data reflect a real clinical situation with different technical and other details.

Finally, our statement about use of ADC_{min} is based on 4 studies. Therefore, further studies and/or meta-analyses regarding some DWI parameters are needed to prove our results.

In conclusion, ADC_{min} reflects tumor grading in HCC. ADC_{min} and *D* can predict MVI in HCC. Therefore, these DWI parameters should be estimated for every HCC lesion for pretreatment tumor stratification. ADC_{mean} does not predict tumor grading and/or MVI in HCC.

Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The paper is exempt from ethical committee approval because it is a meta-analysis.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

Alexey Surov: study concept and design; acquisition, analysis, and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content. Maciej Pech: critical revision of the manuscript for important intellectual content; technical and material support; study supervision. Jazan Omari: acquisition of data; drafting of the manuscript; technical or material support. Frank Fischbach, Robert Damm, Katharina Fischbach, Maciej Powerski, and Borna Relja: drafting of the manuscript and technical or material support. Andreas Wienke: analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; study supervision.

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