

The Roles of Diffusion Kurtosis Imaging and Intravoxel Incoherent Motion Diffusion-Weighted Imaging Parameters in Preoperative Evaluation of Pathological Grades and Microvascular Invasion in Hepatocellular Carcinoma

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Reviewed by:

Xinming Zhao, The Fourth Hospital of Hebei Medical University, China Wei Zhang, Beijing Hospital, China

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Specialty section:

This article was submitted to Gastrointestinal Cancers: Hepato Pancreatic Biliary Cancers, a section of the journal Frontiers in Oncology

> Received: 27 February 2022 Accepted: 31 March 2022 Published: 11 May 2022

Citation:

Wang F, Yan Cy, Wang Ch, Yang Y and Zhang D (2022) The Roles of Diffusion Kurtosis Imaging and Intravoxel Incoherent Motion Diffusion-Weighted Imaging Parameters in Preoperative Evaluation of Pathological Grades and Microvascular Invasion in Hepatocellular Carcinoma. Front. Oncol. 12:884854. doi: 10.3389/fonc.2022.884854 Fei Wang^{1,2}, Chun yue Yan³, Cai hong Wang², Yan Yang² and Dong Zhang^{2*}

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Background: Currently, there are disputes about the parameters of diffusion kurtosis imaging (DKI), intravoxel incoherent motion (IVIM), and diffusion-weighted imaging (DWI) in predicting pathological grades and microvascular invasion (MVI) in hepatocellular carcinoma (HCC). The aim of our study was to investigate and compare the predictive power of DKI and IVIM-DWI parameters for preoperative evaluation of pathological grades and MVI in HCC.

Methods: PubMed, Web of Science, and Embase databases were searched for relevant studies published from inception to October 2021. Review Manager 5.3 was used to summarize standardized mean differences (SMDs) of mean kurtosis (MK), mean diffusivity (MD), tissue diffusivity (D), pseudo diffusivity (D*), perfusion fraction (f), mean apparent diffusion coefficient (ADCmean), and minimum apparent diffusion coefficient (ADCmin). Stata12.0 was used to pool the sensitivity, specificity, and area under the curve (AUC). Overall, 42 up-to-standard studies with 3,807 cases of HCC were included in the meta-analysis.

Results: The SMDs of ADCmean, ADCmin, and D values, but not those of D* and f values, significantly differed between well, moderately, and poorly differentiated HCC (P < 0.01). The sensitivity, specificity, and AUC of the MK, D, ADCmean, and ADCmin for preoperative prediction of poorly differentiated HCC were 69%/94%/0.89, 87%/80%/ 0.89, 82%/75%/0.86, and 83%/64%/0.81, respectively. In addition, the sensitivity, specificity, and ADC mean for preoperative prediction of well-differentiated HCC were 87%/83%/0.92 and 82%/88%/0.90, respectively. The SMDs of ADCmean, ADCmin, D, MD, and MK values, but not f values, showed significant differences (P < 0.01) between MVI-positive (MVI+) and MVI-negative (MVI-) HCC. The

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sensitivity and specificity of D and ADCmean for preoperative prediction of MVI+ were 80%/80% and 74%/71%, respectively; the AUC of the D (0.87) was significantly higher than that of ADCmean (0.78) (Z = -2.208, P = 0.027). Sensitivity analysis showed that the results of the above parameters were stable and reliable, and subgroup analysis confirmed a good prediction effect.

Conclusion: DKI parameters (MD and MK) and IVIM-DWI parameters (D value, ADCmean, and ADCmin) can be used as a noninvasive and simple preoperative examination method to predict the grade and MVI in HCC. Compared with ADCmean and ADCmin, MD and D values have higher diagnostic efficacy in predicting the grades of HCC, and D value has superior diagnostic efficacy to ADCmean in predicting MVI+ in HCC. However, f value cannot predict the grade or MVI in HCC.

Keywords: hepatocellular carcinoma, microvascular invasion, grade, diffusion-weighted imaging, intravoxel incoherent motion, diffusion kurtosis imaging, meta-analysis

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common malignant tumor in the world and also one of the main causes of cancerrelated death (1). Considering the specific pathogenic mechanism and epidemiological and pathological basis of the occurrence and development of HCC, early diagnosis of HCC is difficult (2). Previous studies (3, 4) have indicated that the pathological grade of HCC is closely related to patients' prognosis; specifically, the postoperative survival rate of patients with well- and moderately differentiated HCC is significantly higher than that of patients with poorly differentiated HCC, and the 5-year postoperative recurrence rate of poorly differentiated HCC is as high as 70%. Similarly, several studies (5–7) have suggested that microvascular invasion (MVI) is an independent risk factor for recurrence and metastasis of HCC after treatment and is the most characteristic malignant biological behavior of HCC. Moreover, the postoperative recurrence rate of MVI-positive (MVI+) patients is 4.4 times higher than that of MVI-negative (MVI-) patients (8). For patients with MVI, a larger surgical resection range or ablation zone has to be employed in combination with systemic adjuvant therapy (9).

However, determination of the pathological grade and MVI of HCC mainly depends on postoperative pathological diagnosis, so there is a certain time lag. Therefore, it is extremely important to explore a noninvasive preoperative examination method to predict the pathological grade and MVI in patients with HCC. In recent years, a number of studies (10-51) have suggested that diffusion kurtosis imaging (DKI) parameters of mean kurtosis (MK) and mean diffusivity (MD) and intravoxel incoherent motion diffusion-weighted imaging (IVIM-DWI) parameters of tissue diffusivity (D), pseudo diffusivity (D*), perfusion fraction (f), mean apparent diffusion coefficient (ADCmean), and minimum apparent diffusion coefficient (ADCmin) could be used for preoperative prediction of the pathological grade or MVI in individuals with HCC. However, there are still differences and controversies as to whether these parameters can distinguish the HCC pathological grade or MVI before

surgery; moreover, the preoperative prediction efficacy in previous studies was different, with large differences in each effective index and small sample size.

In 2020, a meta-analysis (52) summarized the diagnostic efficacy of ADC value (six studies, 693 HCCs) for welldifferentiated HCC, and D (four studies, 304 HCCs) was better than ADC value (13 studies, 1,239 HCCs) in differentiating poorly differentiated HCC (Z = -2.718, P = 0.007). However, some studies (15, 25, 31, 33–35, 38, 40, 42, 49–51) were not included in that meta-analysis. Moreover, that meta-analysis did not summarize the diagnostic efficacy of IVIM-DWI parameters for MVI and did not analyze whether D*, f, MK, and MD could predict the pathological grade and MVI in individuals with HCC. In addition, it remains controversial whether D*, f, MK, and MD values could detect the HCC pathological grade or MVI before surgery (22, 25, 34, 35, 39, 46, 47).

Therefore, the aim of our meta-analysis was to comprehensively investigate whether DKI or IVIM-DWI parameters could predict the pathological grade or MVI in patients with HCC and to compare the predictive power of these parameters for the diagnosis of pathological grades and MVI+ in individuals with HCC.

MATERIALS AND METHODS

Data Acquisition

PubMed, Web of Science, and Embase databases were searched for relevant articles published from inception to October 2021. The following search strategy was used: (a) DKI OR diffusion kurtosis imaging OR IVIM OR intravoxel incoherent motion OR DWI OR diffusion-weighted imaging OR apparent diffusion coefficient OR ADC mean value OR ADC minimum value AND hepatocellular carcinoma AND histological grade OR histopathological grade AND grading; (b) DKI OR diffusion kurtosis imaging OR IVIM OR intravoxel incoherent motion OR DWI OR diffusion weighted imaging OR apparent diffusion coefficient OR ADC mean value OR ADC minimum value AND hepatocellular carcinoma OR HCC and microvascular invasion OR microvessel invasion.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (a) evaluation of the diagnostic performance of DKI or IVIM or DWI for determining the presence of MVI or tumor grading in individuals with HCC using the MD and/or MK and/or D and/or D* and/or f and/or ADCmean and/or ADCmin parameters; (b) total sample not less than 20 cases; (c) available information regarding the mean/standard deviation or sensitivity/specificity of parameters for diagnosis of HCC grade or MVI; (d) the Edmondson–Steiner (ES) grade of one indicated well differentiated HCC (wdHCC), the ES grade of two indicated moderately differentiated HCC (mdHCC), and the ES grade greater than or equal to three indicated poorly differentiated HCC (pdHCC) (52). Duplicate articles, review articles, experimental animal studies, and case reports, as well as non-English publications, were excluded.

Data Extraction

The study complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The retrieved literature was imported into EndNote X9 (Thomas Reuters, New York, NY, USA). After removing the duplicates, FW, CYY, and CHW extracted the basic characteristics and diagnostic parameters of the included articles in strict accordance with the inclusion and exclusion criteria, and the obtained data were reviewed three times.

Quality Assessment

The Review Manager 5.3 software (The Cochrane Collaboration, 2014) was used to evaluate the quality of the studies, referring to the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) (53). CYY and CHW independently evaluated the risk of bias and the clinical applicability of the studies in terms of patient selection, index tests, reference standards, and flow and timing. When there was a difference in opinions, the two investigators discussed the issue and reached a consensus.

Statistical Processing

The meta-analysis was conducted using Review Manager 5.3 and Stata version 12.0 (StataCorp, College Station, TX, USA). First of all, heterogeneity was determined by means of the inconsistency index I² (54, 55). A random-effects model was used when the I² was above 50% or P was <0.05, which indicated high heterogeneity between the studies; otherwise, a fixed-effects model was applied. Second, Egger's test or Begg's test was used to visually and quantitatively assess the publication bias for the continuous variables, whereas Deek's test was used to assess the publication bias of the diagnostic study. Finally, Review Manager 5.3 was used to summarize the standardized mean difference (SMD) and 95% confidence intervals (CIs) of the parameters, and Stata12.0 was used to pool the sensitivity, specificity, and area under the curve (AUC). The sensitivity analysis and subgroup analysis were used to explore the source of heterogeneity.

RESULTS

Basic Characteristics of the Study

Finally, 42 up-to-standard studies (10–51) with 3,807 cases of HCC were included. There were 27 studies on grading (2,172 HCCs), 11 studies on MVI (1,220 HCCs), and four studies on grading and MVI (415 HCCs). The literature screening process is shown in **Figure 1**. The basic characteristics of the included studies are shown in **Table 1**, and some parameters of diagnostic studies are shown in **Supplementary Table S1**.

Quality Evaluation

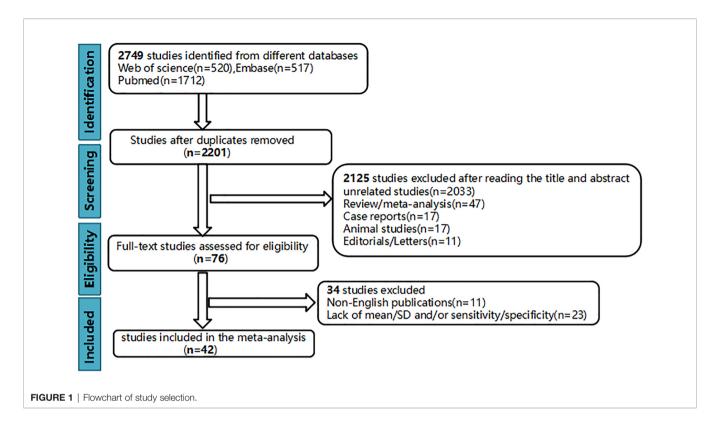
Figure 2 shows the quality assessment based on the QUADAS-2 scale. The overall quality of the studies was acceptable. In the patient selection domain, there was an unclear risk of bias in 18 studies because the inclusion and exclusion criteria had not been clearly reported. Eleven studies had an unclear concern, and one study had a high concern due to different inspection methods. In the index test domain, there was an unclear risk of bias in 18 studies because the information about blinding test had not been provided. Similarly, 23 studies had no information about blinding to the index test in the reference standard domain. Meanwhile, three studies had a high risk of bias in the flow and timing domain.

Diffusion-Weighted Imaging Parameters Used for the Evaluation of Grade/Microvascular Invasion in Hepatocellular Carcinoma Role of the Mean Apparent Diffusion Coefficient in the Evaluation of Grade/Microvascular Invasion in Hepatocellular Carcinoma

In 26 studies (n = 2,504), ADCmean was used to distinguish between HCC grades. There was high heterogeneity ($I^2 > 75\%$), so we used the random-effects model. As shown in the forest plot in **Figures 3A-C**, ADCmean positively correlated with the differentiation degree of HCC (P < 0.05). Egger's test suggested no publication bias (P = 0.238, P = 0.777, P = 0.699). Similarly, 15 studies (n = 1,752) reported that ADCmean was used for detecting MVI. There was no significant heterogeneity ($I^2 = 45\%$), so the fixed-effects model was used. **Figure 3D** shows that ADCmean of MVI- HCC was significantly higher than that of MVI+ HCC (P < 0.01). Egger's test suggested no publication bias (P = 0.958).

Role of the Minimum Apparent Diffusion Coefficient in the Evaluation of Grade/Microvascular Invasion in Hepatocellular Carcinoma

In five studies (n = 586), ADCmin was used for distinguishing grades. The studies (wdHCC vs. mdHCC, wdHCC vs. pdHCC) showed no significant heterogeneity ($I^2 = 0\%$), and the fixed-effects model was used. In contrast, the studies of mdHCC vs. pdHCC showed high heterogeneity ($I^2 = 53\%$), so the random-effects model was applied. As shown in **Figures 4A–C**, the ADCmin positively correlated with the differentiation degree of HCC (P < 0.01). Egger's test suggested no



publication bias (P = 0.981, P = 0.644, P = 0.614). Similarly, four studies (n = 672) reported that ADCmin was used for distinguishing MVI. These four studies had high heterogeneity ($I^2 = 79\%$), and the random-effects model was used. **Figure 4D** indicates that the ADCmin of MVI- HCC was significantly higher than that of MVI+ HCC (P < 0.01). Egger's test suggested no publication bias (P = 0.699).

Intravoxel Incoherent Motion Parameters Used for the Evaluation of Grade/Microvascular Invasion in Hepatocellular Carcinoma

Role of the Tissue Diffusivity Values in the Evaluation of Grade/Microvascular Invasion in Hepatocellular Carcinoma

In seven studies (n = 711), D was used for distinguishing grades. The studies had high heterogeneity (I² > 75%), and the randomeffects model was used. **Figures 5A–C** show that D positively correlated with the differentiation degree of HCC (P < 0.05). Egger's test (wdHCC vs. mdHCC, wdHCC vs. pdHCC) suggested no publication bias (P = 0.389, P = 0.232), and the Begg's test of mdHCC vs. pdHCC suggested no publication bias (P = 0.283). Four studies (n = 672) reported that D was used for distinguishing MVI; they did not show significant heterogeneity (I² = 22%), so the fixed-effects model was used. As shown in **Figure 5D**, D value of MVI- HCC was significantly higher than that of MVI+ HCC (P < 0.01). Egger's test suggested no publication bias (P = 0.652).

Role of the Pseudo Diffusivity Values in the Evaluation of Grade/Microvascular Invasion in Hepatocellular Carcinoma

In six studies (n = 593), D* was used for distinguishing grades. The studies (wdHCC vs. mdHCC, wdHCC vs. pdHCC) had no significant heterogeneity ($I^2 < 50\%$), so the fixed-effects model was used. The studies of mdHCC vs. pdHCC showed high heterogeneity ($I^2 = 65\%$), so the random-effects model was applied. As shown in **Figures 6A–C**, there was no significant difference for pathology grading in HCC (P > 0.05). Egger's test suggested no publication bias (P = 0.510, P = 0.325, P = 0.062). Three studies (n = 227) reported that D* was used for distinguishing MVI; there was no significant heterogeneity ($I^2 = 0\%$), so we used the fixed-effects model. **Figure 6D** shows that D* of MVI- HCC was higher than that of MVI+ HCC (P < 0.05). Egger's test suggested no publication bias (P = 0.560).

Role of the Perfusion Fraction Values in the Evaluation of Grade/Microvascular Invasion in Hepatocellular Carcinoma

In six studies (n = 593), f was used for distinguishing grades. The studies had high heterogeneity ($I^2 > 75\%$), so we used the random-effects model. As shown in **Figures 7A–C**, there was no significant difference for pathology grading in HCC (P > 0.05). Egger's test suggested no publication bias (P = 0.713, P = 0.100, P = 0.967). Three studies (n = 227) reported that f was used for distinguishing MVI. They had no significant heterogeneity ($I^2 = 0\%$), so the fixed-effects model was used. As shown in **Figure 7D**, f did not distinguish MVI+ HCC from

TABLE 1 | The basic characteristics of the studies.

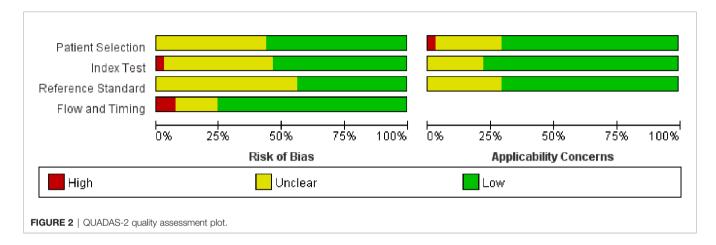
Author	Published year	Country	Study design	Sample size	Research direction	Machine type	Parameters	b-values (s/mm ²)
Muhi et al. (10)	2009	Japan	Retrospective	98	Grade	GE1.5	ADCmean	500, 1,000
Heo et al. (11)	2010	Korea	Retrospective	27	Grade	GE1.5	ADCmean	0, 1,000
Nishie et al. (12)	2011	Japan	Retrospective	52	Grade	Philips1.5	ADCmean	0, 500, 1,000
Nakanishi et al. (13)	2012	Japan	Retrospective	50	Grade	Siemens1.5	ADCmean/	500, 1,000
							ADCmin	
Saito et al. (14)	2012	Japan	Retrospective	42	Grade	Siemens1.5		100, 800
Sandrasegaran et al. (15)	2013	USA	Retrospective	57	Grade	Siemens1.5	ADCmean	0, 50, 400, 500, 800
Chang et al. (16)	2014	China	Retrospective	141	Grade	GE1.5	ADCmean	0, 500
_e moigne et al. (17)	2014	France	Prospective	62	Grade	Siemens1.5		50, 400, 800
Noo et al. (18)	2014	Korea	Retrospective	42	Grade	Siemens3.0	ADCmean/	0, 25, 50, 75, 100, 200, 500, 800
							D/D*/f	-,,,,,,,
Guo et al. (19)	2015	China	Prospective	27	Grade	GE3.0	ADCmean	0, 600
Fang et al. (20)	2016	China	Retrospective	74	Grade	GE3.0	ADCmean	0, 800
wasa et al. (21)	2016	Japan	Retrospective	42	Grade	GE1.5	ADCmean	0, 1,500
Granata et al. (22)	2016	Italy	Retrospective	62	Grade	Siemens1.5	ADCmean/	0, 50, 100, 200, 400, 600, 800
							D/D*/f	
Shankar et al. (23)	2016	India	Prospective	20	Grade	Siemens3.0	ADCmean	0, 100, 500, 1,000
i et al. (24)	2016	China	Retrospective	241	Grade	GE1.5	ADCmean/	0, 800
							ADCmin	
Shan et al. (25)	2017	China	Retrospective	109	Grade	GE3.0	ADCmean/ D/D*/f	0, 30, 50, 100, 150, 200, 300, 500, 800, 1,000, 1,500
ling at al. (OC)	0017	China	Detrespective	054	Crada			
Jing et al. (26)	2017	China	Retrospective	254	Grade	GE1.5	ADCmean/	0, 600
A_{crit} is at al (07)	0017	lonon	Detrespective	FC	Crada	Ciamana1 E	ADCmin	100,800
Aoriya et al. (27)	2017	Japan	Retrospective	56	Grade	Siemens1.5		100, 800
Dgihara et al. (28)	2018	Japan	Retrospective	42	Grade	GE1.5/3.0	ADCmean	0, 800, 1,000
Park et al. (29)	2018	Korea	Retrospective	141	Grade	Siemens1.5		50, 800
Zhu et al. (30)	2018	China	Retrospective	62	Grade	GE3.0	ADCmean/	10, 20, 40, 80, 100, 150, 200, 400,
		_					D/D*/f	600, 800, 1,000, 1,200
Sokmen et al. (31)	2019	Turkey	Retrospective	42	Grade	Siemens1.5	ADCmean/D	0, 50, 100, 150, 200, 300, 400, 500, 600, 700, 800, 900, 1,000, 1,100, 1,200, 1,300
Wang et al. (32)	2020	China	Retrospective	128	Grade	Siemens3.0	MD/MK/ ADCmean	0, 800
Shi et al. (33)	2020	China	Prospective	52	Grade	GE3.0	D	0, 10, 20, 30, 40, 60, 80, 100, 200, 500, 800
Wu et al. (34)	2020	China	Prospective	88	Grade	GE3.0	MD/MK/ ADCmean/ D/D*/f	0, 20, 40, 80, 160, 200, 400, 600, 800 1,000
Zhou et al. (35)	2021	China	Retrospective	70	Grade	GE3.0	ADCmean/ D/D*/f	Unclear
_ee et al. (36)	2018	Korea	Retrospective	114	Grade/MVI	Philips3.0	ADCmean/ ADCmin	0, 100, 800
Kim et al. (37)	2019	Korea	Retrospective	143	Grade/MVI	Philips3.0	ADCmean/ ADCmin	0, 100, 800
Cao et al. (38)	2019	China	Retrospective	74	Grade/MVI	Siemens3.0	MD/MK/ ADCmean	0, 200, 700, 1,400, 2,100
Nei et al. (39)	2019	China	Prospective	91	Grade	GE3.0	ADCmean/ D/D*/f	0, 10, 20, 40, 80, 100, 150, 200, 400 600, 800, 1,000, 1,200
Wang et al. (40)	2019	China	Retrospective	84	Grade/MVI	Siemens1.5	MD/MK/ ADCmean	0, 200, 500, 1,000, 1,500, 2,000
(u et al. (41)	2014	China	Retrospective	92	MVI	Siemens1.5	ADCmean	0, 500
Dkamura et al. (42)	2016	Japan	Retrospective	75	MVI	Siemens1.5	ADCmean	0, 1,000
luang et al. (43)	2016	China	Retrospective	51	MVI	Siemens1.5	ADCmean	0, 500
ee et al. (44)	2017	Korea	Retrospective	197	MVI	Philips3.0	ADCmean	0, 100, 800
Zhao et al. (45)	2017	China	Retrospective	318	MVI	GE1.5	ADCmean/	0, 800
i et al. (46)	2018	China	Prospective	41	MVI	Philips3.0	ADCmin ADCmean/	0, 10, 20, 40, 80, 200, 400, 600, 1,00
Zhao et al. (47)	2018	China	Retrospective	51	MVI	GE3.0	D/D*/f ADCmean/ D/D*/f	0, 10, 20, 30, 40, 50, 60, 70, 80, 90,
Chuang et al. (48)	2019	China	Retrospective	97	MVI	GE1.5	D/D^/f ADCmean/ ADCmin	100, 200, 300, 400, 500, 1,000 0, 400

(Continued)

TABLE 1 | Continued

Author	Published year	Country	Study design	Sample size	Research direction	Machine type	Parameters	b-values (s/mm²)
Chen et al. (49)	2021	China	Prospective	63	MVI	uMR 770.3.0	ADCmean/D	0, 20, 40, 50, 100, 200, 500, 800, 1,500, 2,000
Wang et al. (50)	2021	China	Retrospective	100	MVI	Philips3.0/ GE3.0	ADCmean	0, 100, 600
Wei et al. (51)	2019	China	Prospective	135	MVI	GE3.0	ADCmean/ D/D*/f	0, 10, 20, 40, 80, 100, 150, 200, 400, 600, 800, 1,000, 1,200

ADCmean, mean apparent diffusion coefficient; ADCmin, minimum apparent diffusion coefficient; D, tissue diffusivity; D*, pseudo diffusivity; f, perfusion fraction; MVI, microvascular invasion.



MVI- HCC (P > 0.05). Begg's test suggested no publication bias (P = 0.999).

Diffusion Kurtosis Imaging Parameters Used for the Evaluation of Grade/ Microvascular Invasion in Hepatocellular Carcinoma

Role of the Mean Diffusivity Values in the Evaluation of Grade/Microvascular Invasion in Hepatocellular Carcinoma

In three studies (n = 388), MD was used for distinguishing grades. There was no significant heterogeneity ($I^2 = 0\%$), so we used the fixed-effects model. **Figure 8A** shows that the MD value of pdHCC was significantly lower than that of non-pdHCC (P < 0.01). Egger's test suggested no publication bias (P = 0.582). Two studies (n = 258) reported that MD was used for distinguishing MVI; they did not show significant heterogeneity ($I^2 = 0\%$), and the fixed-effects model was used. **Figure 8B** shows that the MD of MVI- HCC was significantly higher than that of MVI+ HCC (P < 0.01). Egger's test suggested no publication bias (P = 0.870).

Role of the Mean Kurtosis Values in the Evaluation of Grade/Microvascular Invasion in Hepatocellular Carcinoma

In three studies (n = 388), the MK was used for distinguishing grades. There was highly significant heterogeneity ($I^2 > 75\%$), so we used the random-effects model. **Figure 9A** shows that the MK value of non-pdHCC was significantly lower than that of pdHCC (P < 0.01). Begg's test suggested no publication bias (P = 0.308).

Two studies (n = 258) reported that the MK was used to distinguish MVI. These studies did not show significant heterogeneity ($I^2 = 0\%$), so the fixed-effects model was used. **Figure 9B** shows that the MK of MVI- HCC was significantly lower than that of MVI+ HCC (P < 0.01). Egger's test suggested no publication bias (P = 0.179).

Sensitivity Analysis

Sensitivity Analysis of the Parameters for Distinguishing Microvascular Invasion in Hepatocellular Carcinoma

First, the SMDs of each parameter for distinguishing MVI changed little after the combination of transformation random-effects model and fixed-effects model. Moreover, after excluding each study one by one, the results of the sensitivity analysis (**Supplementary Figures S1A–G**) suggested that the studies of ADCmean, D value, D* value, f value, MD value, and MK value, but not ADCmin value, were stable and reliable to identify MVI- HCC vs. MVI+ HCC. After removing the study by Kim et al. (37), the result of ADCmin in discriminating MVI- vs. MVI+ HCC was stable and reliable (SMD = 0.87, *P* < 0.00001, **Supplementary Figure S2**). The I² decreased from 79% to 1%, which suggested that the excluded study was likely the source of heterogeneity.

Sensitivity Analysis of the Parameters for Distinguishing Grades in Hepatocellular Carcinoma

After excluding each study one by one, the results of the sensitivity analysis (**Supplementary Figures S3A–C–S7A–C**) suggested that

Chang WC2014	wd-HCC Mean SD	Total Mean		otal W	leight	td. Mean Difference IV, Random, 95% Cl	Std. Mean Difference IV, Random, 95% Cl
Granata V2016	2.04 0.41 0.94 0.12	34 1.62 14 1.03	0.3 0.31	64 30	3.9% 3.5%	1.22 [0.77, 1.67] -0.33 [-0.97, 0.31]	—
Guo W2015 Heo SH2010	1.43 0.09 1.2 0.22	6 1.34 9 1.1	0.19		2.7% 2.9%	0.53 [-0.51, 1.56] 0.56 [-0.39, 1.50]	
Iwasa Y2016 Jiang T2017	1.1 0.14 1.67 0.13	14 1.14 39 1.31	0.28	18	3.4% 4.0%	-0.17 [-0.87, 0.53] 2.31 [1.90, 2.72]	
Kim JG2019	1.14 0.37	9 1.01		122	3.5%	0.50 [-0.18, 1.18]	<u></u>
Le moigne F2014 Lee S2018	1.119 0.233	14 1.081	0.202	75	3.7%	0.34 [-0.17, 0.84] 0.18 [-0.39, 0.75]	- -
Li X2016 Moriya T2017	1.13 0.32 1.051 0.203	20 1.12 12 0.999	0.163	35	3.9% 3.5%	0.04 [-0.42, 0.50] 0.29 [-0.36, 0.95]	
Muhi A2009 Nishie A2011	0.91 0.25	39 0.71 5 1.134	0.26 0.228	54	3.9% 2.9%	0.78 [0.30, 1.26] 0.34 [-0.58, 1.26]	
Ogihara Y 2018 Ogihara Y2018	1.08 0.15 1.33 0.19	8 1.19 10 1.2	0.23	31	3.2% 3.2%	-0.50 [-1.28, 0.29] 0.62 [-0.16, 1.40]	
Park IK2018	1.11 0.18	16 1.16	0.21	83	3.8%	-0.24 [-0.78, 0.29]	
Saito K2012 Shan QG2017	1.25 0.25 1.19 0.34	17 1.12 18 1.07	0.22 1.32	66	3.5% 3.8%	0.54 [-0.14, 1.22] 0.10 [-0.42, 0.62]	
Shankar S2016 Tang YH2016	0.924 0.165	8 0.866 10 1.13	0.1 0.18		2.9% 3.4%	0.42 [-0.53, 1.36] 1.07 [0.36, 1.77]	
Wang GZ2020 Wei Y 2019	1.46 0.31 1.46 0.28	22 1.28 15 1.12	0.18 0.21	37 41	3.7% 3.5%	0.75 [0.21, 1.30] 1.46 [0.80, 2.11]	
Wei Y20 19	1.56 0.26 1.77 0.29	15 1.24	0.15	41	3.5%	1.71 [1.03, 2.38]	
Wei Y2019 Woo S2014	1.35 0.25	4 1.22	0.15	20	2.6%	1.38 [0.73, 2.03] 0.75 [-0.35, 1.85] 1.15 [0.53, 1.77]	
Wu B2020 Zhou Y2021	1.7 0.32 1.35 0.17	19 1.41 15 1.16	0.19 0.17	46	3.6% 3.6%	1.10 [0.49, 1.72]	
Zhu SC 2018 Zhu SC2018	1.496 0.312 1.503 0.306	14 1.21 14 1.214	0.186 0.186		3.4% 3.4%	1.17 [0.45, 1.89] 1.20 [0.48, 1.91]	
Total (95% CI)		472		443 10	0.0%	0.67 [0.40, 0.95]	•
Heterogeneity: Tau* Test for overall effect	= 0.44; Chi ² = 149	9.14, df = 28 (P	< 0.00001); l ² = 8	1%	,	
	t: Z = 4.85 (P < 0.1	00001)					Favours [experimental] Favours [control]
	wd-HCC		pd -HCC		s	itd. Mean Difference	Std. Mean Difference
Study or Subgroup Chang WC2014	Mean SD 2.04 0.41	Total Mean 34 1.26	SD To 0.21	43 4	eight	IV, Random, 95% Cl 2.46 [1.86, 3.06]	IV. Random, 95% Cl
Granata V2016 Guo W2015	0.94 0.12	14 2.44	0.04	18 I 11 :	4.1% 0.7% · 3.2%	-17.30 [-21.87, -12.72] 1.82 [0.61, 3.04]	·
Heo SH2010	1.2 0.22	9 0.9	0.13	9 3	3.4%	1.58 [0.49, 2.67]	
Iwasa Y2016 Jiang T2017	1.1 0.14 1.67 0.13	14 0.9 39 1.08	0.2 0.11	29 3	3.7% 3.6%	1.16 [0.27, 2.04] 4.78 [3.83, 5.74]	→
Kim JG2019 Lee S2018	1.14 0.37 1.119 0.233	9 1.02 14 0.947	0.28 0.131	7 3	3.7% 3.6%	0.36 [-0.51, 1.23] 0.80 [-0.15, 1.75]	<u>+-</u>
Li X2016 Moriya T2017	1.13 0.32 1.051 0.203	20 0.92	0.17	23	4.0%	0.82 [0.20, 1.45] 0.44 [-0.43, 1.32]	<u> </u>
Muhi A2009 Nishie A2011	0.91 0.25	39 0.68 5 0.902	0.19	14 4	4.0% 3.4%	0.96 [0.32, 1.60] 1.92 [0.84, 3.01]	<u> </u>
Ogihara Y 2018	1.08 0.15	8 1.01	0.19	19 3	3.8%	0.38 [-0.46, 1.21]	+
Ogihara Y2018 Park IK2018	1.33 0.19 1.11 0.18	10 1.06 16 1.05	0.39 0.16	42 4	3.7% 4.1%	0.82 [-0.06, 1.70] 0.36 [-0.22, 0.94]	-
Saito K2012 Shan QG2017	1.25 0.25 1.19 0.34	17 1.13 18 0.855	0.23 0.56	7 25	3.7% 4.0%	0.47 [-0.42, 1.37] 0.68 [0.06, 1.31]	
Shankar S2016 Tang YH2016	0.924 0.165	8 0.695 10 0.92	0.122 0.21	2 3	2.5% 3.4%	1.29 [-0.42, 3.00] 2.07 [1.01, 3.12]	<u>+</u>
Wang GZ2020 Wei Y 2019	1.46 0.31 1.46 0.28	22 1.1 15 1.03	0.13	69 4	4.1% 3.8%	1.89 [1.34, 2.45] 1.80 [1.02, 2.57]	
Wei Y20 19 Wei Y2019	1.56 0.26	15 1.16	0.2	23 3	3.8%	1.74 [0.97, 2.51]	
Woo S2014	1.77 0.29 1.35 0.25	15 1.31 4 1.02	0.14 0.13	14 3	3.8% 3.0%	2.13 [1.31, 2.95] 1.97 [0.64, 3.30]	<u> </u>
Wu B2020 Zhou Y2021	1.7 0.32 1.35 0.17	19 1.31 15 0.98	0.27		4.0% 3.5%	1.32 [0.67, 1.96] 1.93 [0.91, 2.94]	
Zhu SC 2018 Zhu SC 2018	1.496 0.312 1.503 0.306	14 1.003 14 1.001	0.247 0.236	24 3	3.8% 3.8%	1.77 [0.99, 2.55] 1.87 [1.07, 2.66]	
Total (95% CI)	1.303 0.300	435		568 10		1.32 [0.91, 1.74]	
Heterogeneity: Tau ^a	= 1.02; Chi ^a = 184	4.55, df = 27 (P				1.32 [0.91, 1.74]	-4 -2 0 2 4
	t: Z = 6.23 (P < 0.1	00001)					Favours [experimental] Favours [control]
	t: Z = 6.23 (P < 0.1 md-l-		pd-HCC		5	Std. Mean Difference	
Study or Subgroup	md-F Mean SD	ICC Total Mean	pd-HCC SD Tr	otal W	leight	Std. Mean Difference IV. Random, 95% CI 1.34 (0.91, 1.76)	Favours (experimental) Favours (control) Std. Mean Difference IV. Random, 95% Cl
Study or Subgroup Chang WC2014 Granata V2016	md-I- Mean SD 1.62 0.3 1.03 0.31	ICC Total Mean 64 1.26 30 2.44	<u>SD T</u> 0.21 0.04	43 18	4.0% 2.1%	IV, Random, 95% CI 1.34 [0.91, 1.76]	Std. Mean Difference
Study or Subgroup Chang WC2014 Granata V2016 Guo W2015 Heo SH2010	md.J- Mean SD 1.62 0.3 1.03 0.31 1.34 0.19 1.1 0.1	ICC <u>Total Mean</u> 64 1.26 30 2.44 10 1.16 9 0.9	SD T 0.21 0.04 0.16 0.13	43 18 11 9	4.0% 2.1% 2.9% 2.5%	V, Random, 95% CI 1.34 [0.91, 1.76] -5.61 [-6.92, -4.30] 0.99 [0.07, 1.91] 1.64 [0.54, 2.75]	Std. Mean Difference
Study or Subgroup Chang WC2014 Granata V2016 Guo W2015 Heo SH2010 Iwasa Y2016 Jiang T2017	md-l- Mean SD 1.62 0.3 1.03 0.31 1.34 0.19 1.1 0.18 1.31 0.16	ICC <u>Total Mean</u> 64 1.26 30 2.44 10 1.16 9 0.9 18 0.9 18 1.08	SD T 0.21 0.04 0.16 0.13 0.2 0.11	43 18 11 9 10 29	4.0% 2.1% 2.9% 2.5% 3.1% 4.0%	V, Random, 95% Cl 1.34 [0.91, 1.76] -5.61 [-6.92, -4.30] 0.99 [0.07, 1.91] 1.64 [0.54, 2.75] 0.91 [0.10, 1.73] 1.48 [1.07, 1.90]	Std. Mean Difference
Study of Subgroup Chang WC2014 Granata V2016 Guo W2015 Heo SH2010 Mwasa Y2016 Jiang T2017 Kim JG2019 Lee S2018	Mean SD 1.62 0.3 1.03 0.31 1.34 0.19 1.1 0.1 1.14 0.28 1.31 0.16 1.01 0.25 1.081 0.202	ICC Total Mean 64 1.26 30 2.44 10 1.16 9 0.9 18 0.9 18 1.08 122 1.02 75 0.947	SD T 0.21 0.04 0.16 0.13 0.2 0.11 0.28 0.131	43 18 11 9 10 29 12 7	4.0% 2.1% 2.9% 2.5% 3.1% 4.0% 3.6% 3.2%	<u>N. Random, 95% Cl</u> 1.34 [0.91, 1.76] -5.61 [-6.92, -4.30] 0.99 [0.07, 1.91] 1.64 [0.54, 2.75] 0.91 [0.10, 1.73] 1.48 [1.07, 1.90] -0.04 [-0.63, 0.55] 0.67 [-0.11, 1.45]	Std. Mean Difference
Study or Subgroup Chang WC 2014 Granata V2016 Guo W2015 Heo SH2010 Iwasa Y2016 Jiang T2017 Kim JG 2019 Lee S2018 Li X2016	md.l Mean SD 1.62 0.3 1.03 0.31 1.34 0.19 1.1 0.1 1.31 0.16 1.03 0.31 1.14 0.28 1.31 0.16 1.021 0.25 1.081 0.202 1.12 0.23	ICC Total Mean 64 1.26 30 2.44 10 1.16 9 0.9 18 0.9 186 1.08 122 1.02 75 0.947 198 0.92	SD T 0.21 0.04 0.16 0.13 0.2 0.11 0.28 0.131 0.17	43 18 11 9 10 29 12 7 23	teight 4.0% 2.1% 2.9% 2.5% 3.1% 4.0% 3.6% 3.2% 4.0%	<u>IV. Random, 95% CI.</u> 1.34 [0.91, 1.76] -5.61 [-6.92, -4.30] 0.99 [0.07, 1.91] 1.64 [0.54, 2.75] 0.91 [0.10, 1.73] 1.48 [1.07, 1.90] -0.04 [-0.63, 0.55] 0.67 [-0.11, 1.45] 0.89 [0.45, 1.33]	Std. Mean Difference
Study of Subgroup Chang WC2014 Granata V2016 Guo W2015 Heo SH2010 Iwasa Y2016 Jiang T2017 Kim JG2019 Lee S2018 Li X2018 Moriya T2017 Muhi A2009	md-1 Mean SD 1.62 0.3 1.03 0.31 1.34 0.19 1.14 0.28 1.31 0.16 1.01 0.25 1.081 0.202 1.12 0.23 0.999 0.163 0.71 0.26	ACC Total Mean 64 1.26 30 2.44 10 1.16 9 0.9 18 0.9 18 1.09 186 1.08 122 1.02 75 0.947 198 0.92 35 0.964 33 0.68	SD T 0.21 0.04 0.16 0.13 0.2 0.11 0.28 0.131 0.17 0.167 0.167 0.19	43 18 11 9 10 29 12 7 23 9 14	leight 4.0% 2.1% 2.9% 2.5% 3.1% 4.0% 3.6% 3.2% 4.0% 3.3% 3.3% 3.6%	V. Random, 95% C1 1.34 (0.91, 1.76) 5.61 [+6.92, -4.30] 0.99 [0.07, 1.91] 1.64 (0.54, 2.75] 0.91 [0.10, 1.73] 1.48 [1.07, 1.90] -0.04 [-0.63, 0.55] 0.67 [-0.11, 1.45] 0.89 [0.45, 1.33] 0.21 [-0.52, 0.94] 0.12 [-0.50, 0.75]	Std. Mean Difference
Study or Subaroup Chang Wc2014 Granata V2016 Guo W2015 Heo SH2010 Iwasa V2016 Jiang T2017 Kim J02019 Lee S2018 Li X2018 Moriya T2017 Muh A2009 Nakanishi M2012	md.F Mean SD 1.62 0.3 1.33 0.31 1.34 0.19 1.11 0.11 1.14 0.28 1.31 0.16 1.01 0.25 1.081 0.202 1.12 0.23 0.999 0.163 0.71 0.26 1.134 0.228	ACC Total Mean 64 1.26 30 2.44 10 1.16 9 0.9 18 0.9 186 1.08 122 1.02 75 0.947 198 0.92 35 0.964 33 0.68 29 1.07 54 0.902	SD T- 0.21 0.04 0.16 0.13 0.2 0.11 0.28 0.131 0.17 0.167 0.167 0.15 0.162	43 18 11 9 10 29 12 7 23 9 14 18 26	leight 4.0% 2.1% 2.9% 2.5% 3.1% 4.0% 3.6% 3.3% 3.6% 3.6% 3.6% 3.9%	W. Random, 95% CI 1.34 [0.91, 1.76] 5.61 [+6.92, -4.30] 0.99 [0.07, 1.91] 1.64 [0.54, 2.75] 0.91 [0.10, 1.73] 1.48 [1.07, 1.90] -0.04 [-0.63, 0.55] 0.67 [-0.11, 1.45] 0.89 [0.45, 1.33] 0.21 [-0.52, 0.94] 0.12 [-0.50, 0.75] 1.14 [0.51, 1.78] 1.10 [0.60, 1.60]	Std. Mean Difference
Study or Subgroup Chang WC2014 Granata V2015 Out W2015 Heo SH2010 Mexaa Y2016 Jiang T2017 Kim J62019 Lee S2018 Lix2016 Moriya T2017 Muhi A2009 Nakanishi M2012 Ojiahara Y2018	md-l- Mean SD 1.62 0.3 1.03 0.31 1.34 0.19 1.1 0.11 1.14 0.28 1.33 0.31 1.34 0.28 1.31 0.16 1.021 0.23 0.999 0.163 0.71 0.26 1.124 0.228 1.134 0.228 1.19 0.23	ACC Total Mean 64 1.26 30 2.44 10 1.16 9 0.9 18 0.9 18 1.02 75 0.947 198 0.92 35 0.964 33 0.68 29 1.07 54 0.902 31 1.01 20 1.06	SD T/ 0.21 0.04 0.13 0.2 0.13 0.2 0.11 0.2 0.11 0.13 0.13 0.13 0.167 0.19 0.15 0.162 0.39	43 18 11 9 10 29 12 7 23 9 14 18 26 19 12	leight 4.0% 2.1% 2.9% 2.5% 3.1% 4.0% 3.6% 3.6% 3.6% 3.6% 3.6% 3.9% 3.6% 3.9% 3.6% 3.3%	M. Random, 95% CI 1.34 [0 91, 1.76] 5.61 [6.92, -4.30] 0.99 [0.07, 1.91] 1.64 [0.54, 2.75] 0.91 [0.10, 1.73] 1.48 [10,7, 1.90] -0.04 [-0.63, 0.55] 0.67 [-0.11, 1.45] 0.89 [0.45, 1.33] 0.21 [-0.52, 0.94] 0.12 [-0.50, 0.75] 1.14 [0.61, 1.60] 0.82 [0.23, 1.42] 0.47 [-0.25, 1.20] 0.47 [-0.25, 1.20]	Std. Mean Difference
Study of Subaroup Chang Wc2014 Granata V2016 Guo W2015 Heo SH2010 hwasa Y2016 Jiang T2017 Kim J02019 Lee S2018 Lix2016 Monya T2017 Muhi A2009 Nishie A2011 Ogihara Y2018 Ogihara Y2018	md-I Mean SD 1.62 0.3 1.03 0.31 1.34 0.19 1.1 0.11 1.14 0.28 1.31 0.16 1.01 0.25 1.081 0.202 1.12 0.23 0.990 0.163 0.71 0.26 1.29 0.21 1.14 0.28 1.19 0.23	ACC Total Mean. 64 1.26 30 2.44 10 1.46 9 0.9 18 0.9 18 0.9 18 0.9 18 0.9 122 1.02 55 0.947 198 0.92 33 0.68 29 1.07 54 0.902 31 1.01 20 1.06 83 1.05	SD T/ 0.21 0.04 0.13 0.2 0.13 0.2 0.131 0.17 0.167 0.167 0.19 0.15 0.162 0.19	43 18 11 9 10 29 12 7 23 9 14 18 26 19 12 42	leight 4.0% 2.1% 2.9% 2.5% 3.1% 4.0% 3.6% 3.6% 3.6% 3.6% 3.6% 3.9% 3.6%	M. Random, 95% CI 31, 34 (0.31, 1.76) -5.61 [+6.82, -4.30) 0.99 [0.07, 1.91] 1.64 [0.54, 2.75] 0.91 [10.10, 1.73] 1.48 [1.07, 1.90] -0.04 [-0.53, 0.55] 0.67 [-0.11, 1.45] 0.89 [0.45, 1.33] 0.21 [-0.52, 0.94] 0.12 [-0.50, 0.75] 1.14 [[0.51, 1.78] 1.14 [[0.51, 1.78] 1.14 [[0.51, 1.78] 1.14 [[0.51, 1.78] 1.14 [[0.51, 1.78] 1.14 [[0.51, 1.78] 0.82 [[0.23, 1.42] 0.47 [[-0.25, 1.20] 0.56 [[0.18, 0.94]	Std. Mean Difference
Study or Subaroup Chang WC2014 Granata V2016 Guo W2015 Heo SH2010 Iwasa V2016 Jiang T2017 Kim J02019 Lee S2018 Li X2016 Morly A2019 Nishie A2011 Ogihara V2018 Ogihara V2018 Salb K2012 Salb K2012	md-1 1.62 0.3 1.03 0.31 1.34 0.19 1.1 0.1 1.14 0.28 1.33 0.16 1.14 0.28 1.31 0.16 1.14 0.28 1.14 0.28 1.29 0.21 1.29 0.21 1.29 0.21 1.14 0.28 1.29 0.21 1.20 0.21 1.14 0.228 1.29 0.21 1.12 0.21 1.12 0.22 1.16 0.21 1.17 0.22 1.12 0.22 1.12 0.22 1.12 0.22 1.12 0.22 1.12 0.22 1.12 0.22 1.12 0.22 1.12 0.23	ACC Total Meann 64 1.26 30 2.44 10 1.16 9 0.9 18 0.9 18 1.08 122 1.02 75 0.947 198 0.82 30 0.68 29 1.07 54 0.902 31 1.01 20 1.68 83 1.05 18 1.13 36 0.862	SD T 0.21 0.04 0.16 0.13 0.2 0.13 0.11 0.12 0.13 0.12 0.13 0.16 0.16 0.19 0.16 0.19 0.16 0.19 0.16 0.19 0.39 0.16 0.23 0.56	43 18 11 9 10 29 12 7 23 9 14 18 26 19 12 42 7 25	teight 4.0% 2.1% 2.9% 2.5% 3.1% 4.0% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6% 3.9% 3.6% 3.9%	$\begin{array}{c} \underline{N}, \underline{Random}, \underline{955}, \underline{C}\\ 1,34 (0 51, 1.76)\\ -5.61 (F 62, 2, 30)\\ 0.99 (0 7, 1 51)\\ 1.64 (0 54, 2.75)\\ 0.91 (0 10, 1.73)\\ 1.48 (1 0, 71, 205)\\ -0.61 (4 0, 52, 0.56)\\ 0.67 (-0 11, 1.45)\\ 0.88 (0, 45, 1.33)\\ 0.21 (-0.52, 0.54)\\ 0.21 (-0.52, 0.5$	Std. Mean Difference
Study of Subgroup Chang WC2014 Granata V2016 Guo W2015 Heo SH2016 Iwasa V2016 Iwasa V2016 Iwasa V2016 Iwasa V2019 Lee S2018 Lix2016 Moriya T2017 Nakanishi M2012 Nakanishi M2012 Nakanishi M2012 Ogihara Y2018 Shankar S2016 Shankar S2016	mel.1 Mean SD 1.62 0.3 1.33 0.31 1.34 0.19 1.1 0.1 1.1 0.1 1.1 0.1 1.1 0.20 1.11 0.20 1.12 0.23 0.71 0.76 1.19 0.23 1.19 0.23 1.16 0.21 1.16 0.21 1.12 0.22 1.13 0.18	NCC Total Mean 64 1.26 30 2.44 10 1.16 18 0.9 18 0.9 186 1.08 75 0.947 33 0.68 29 1.07 54 0.902 31 1.61 02 1.06 83 0.68 10 1.16 60 0.855 10 0.695 51 0.82	SD Tr 0.21 0.04 0.16 0.13 0.2 0.11 0.28 0.11 0.28 0.13 0.167 0.167 0.19 0.162 0.162 0.162 0.162 0.162 0.166 0.23 0.562 0.122 0.21 0.21	43 18 11 9 10 29 12 7 23 9 14 18 26 19 12 42 7 5 2 13	teight 4.0% 2.1% 2.5% 3.1% 4.0% 3.6% 3.6% 3.6% 3.6% 3.9% 3.6% 3.9% 3.6% 3.9% 3.6% 3.9% 3.6% 3.9% 3.6% 3.9% 3.6% 3.9% 3.6% 3.9% 3.6% 3.9% 3.6% 3.9% 3.6% 3.9% 3.6% 3.9% 3.6% 3.9% 3.6% 3.6% 3.9% 3.9% 3.6% 3.9% 3.9% 3.6% 3.9% 3.9% 3.6% 3.9% 3.5%	$\begin{array}{c} \underline{N}, \underline{Routen}, \underline{95}, \underline{C}, \underline{1}, \underline{3}, \underline{10}, \underline{91}, 1, 78\\ 1, 34 [0, 91, 1, 76]\\ 0, 99 [0, 07, 1, 91]\\ 1, 64 [0, 54, 2, 75]\\ 0, 91 [0, 10, 1, 73]\\ 1, 48 [1, 07, 1, 90]\\ 0, 54 [1, 033, 0, 55]\\ 0, 65 [7, 01, 1, 1, 45]\\ 0, 56 [1, 05, 0, 15]\\ 0, 56 [1, 05, 0, 15]\\ 1, 14 [0, 50, 1, 15]\\ 0, 58 [0, 64, 1, 33]\\ 0, 21 [1, 05, 0, 15]\\ 1, 14 [0, 50, 1, 16]\\ 0, 50 [1, 16]\\ 0, 17 [1, 16]\\ 0, 1$	Std. Mean Difference
Study of Subarous Chang WC2014 Granata V2016 Guo W2015 Heo SH2016 Juna V2017 Heo SH2016 Juna V2017 Heo SH2018 Juna V2018 Hom J2019 Lee S2018 Lix2016 Moriya T2017 Makanishi M2012 Ogihara Y2018 Park IK2018 Shahor S2016 Shahor S2016 Shahor S2016 Shahor S2016 Wang 02/2020 Wang 02/2019	md4, Mean SD 1 fc2 0.3 1 no 0.31 1 no 0.43 1 no 0.51 1 no 0.51 1 no 0.51 1 no 0.61 1 no 0.72 1 no 0.72 1 no 0.72 1 no 0.73 1 no 0.73 1 no 0.72 1 no 0.72 1 no 0.73 1 no 0.74	CC Total Mean. 64 1.26 30 2.44 9 0.9 186 1.08 122 1.02 75 0.947 198 0.92 33 0.68 29 1.07 54 0.902 33 0.68 29 1.07 54 0.902 11 1.01 20 1.065 18 1.13 16 0.885 51 0.685 51 0.685 51 0.823 7 1.1 41 1.13	SD Tr 0.21 0.04 0.16 0.13 0.11 0.2 0.11 0.28 0.137 0.167 0.162 0.115 0.162 0.199 0.166 0.239 0.122 0.21 0.122 0.21 0.122 0.21	43 18 11 9 10 29 12 7 23 9 14 18 26 19 12 42 7 25 2 13 69 23	teinth 4.0% 2.1% 2.9% 2.5% 3.1% 4.0% 3.6% 3.2% 4.0% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6% 3.9% 1.6% 3.5% 4.0% 3.5% 3.9% 3.5% 3.5% 3.9% 3.5% 3.8%	$\begin{array}{c} \underline{M}, \underline{Routen}, \underline{g}^{N}, \underline{C}\\ 1, 34 \ [0 91, 1, 76]\\ -5.61 \ [f, 9.2, -4.30]\\ 0.99 \ [0.07, 1.01]\\ 1.64 \ [0.54, 2.75]\\ 0.91 \ [0.10, 1, 73]\\ 1.48 \ [1.07, 1.00]\\ 0.56 \ [1.01, 1, 45]\\ 0.56 \ [1.01, 1, 45]\\ 0.56 \ [1.01, 1, 45]\\ 0.56 \ [1.01, 1, 45]\\ 0.56 \ [1.01, 1, 45]\\ 0.56 \ [1.01, 1, 14]\\ 0.56 \ [1.01, 1, 14]\\ 0.56 \ [1.01, 1, 14]\\ 0.56 \ [1.01, 1, 14]\\ 0.56 \ [1.01, 1, 14]\\ 0.56 \ [1.01, 1, 14]\\ 0.57 \ [1.01, 1, 14]\\ 0.57 \ [1.01, 1, 14]\\ 0.57 \ [1.01, 1, 14]\\ 0.57 \ [1.01, 1, 14]\\ 0.57 \ [1.01, 1, 14]\\ 0.57 \ [1.01, 14]\\ 0.57$	Std. Mean Difference
Study of Subaroou Chang WC2014 Chang WC2014 Chang WC2014 Heo SH2010 Wasa Y2016 Jang T2017 Kim J02019 LHX2016 Jang T2017 Muth A2009 Nakanish M2012 Nishie A2011 Oghara Y 2016 Jang T2017 Muth A2009 Nakanish M2012 Shan Go2017 Shan Go2017 Shankar S2016 Tang W12018 Shankar S2016 Tang W12018 Shankar S2016	md4, Mean SD 1 f22 0.3 1 02 0.31 1 03 0.31 1 103 0.16 1 11 1.1 1 14 0.29 1 13 0.16 1 001 0.25 1 14 0.28 1 15 0.18 0 099 0.163 0 17 0.26 1 14 0.28 1 14 0.23 1 15 0.29 0 16 0.20 1 16 0.21 0 17 0.26 1 16 0.21 1 16 0.21 1 17 0.12 0 186 0.11 1 13 0.18 1 12 0.21 1 12 0.21 1 14 0.15	CC Total Mean. 64 1.26 30 2.44 9 0.9 186 1.08 122 1.02 75 0.947 198 0.92 33 0.66 29 1.07 54 0.902 51 0.92 11.01 20 1.06 183 1.05 18 0.12 51 0.92 51	SD Tr 0.21 0.04 0.16 0.13 0.2 0.111 0.28 0.131 0.19 0.167 0.19 0.162 0.162 0.162 0.123 0.166 0.122 0.21 0.23 0.56 0.122 0.21 0.23 0.23 0.50 0.122 0.213 0.22 0.213 0.2 0.24 0.144	43 18 11 9 10 29 12 7 23 9 14 18 26 19 22 7 25 13 69 23 23 23	teinth 4.0% 2.1% 2.5% 3.1% 4.0% 3.6% 3.2% 4.0% 3.3% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6% 3.6% 3.3% 4.1% 3.0% 3.9% 1.6% 3.8%	$ \begin{array}{c} \underline{N}, \underline{Banden}, \underline{g}^{Sb}, \underline{C}\\ 1, 3 + [0, 0, 1, 76]\\ 0.3 \pm [0, 0, 7, 16]\\ 0.3 \pm [0, 0, 7, 16]\\ 1.5 \pm [0, 10, 1, 76]\\ 0.5 \pm [0, 10, 1, 76]\\ 0.5 \pm [0, 10, 1, 16]\\ 0.5 \pm [0, 10, 1, 16]\\ 0.5 \pm [0, 10, 10, 16]\\ 0.5 \pm [0, 10, 10, 16]\\ 0.5 \pm [0, 10, 10, 16]\\ 0.5 \pm [0, 10, 20, 16]\\ 0.5 \pm [0, 10, 10, 16]\\ 0.5 \pm [0, 10, 20, 16]\\ 0.5 \pm [0, 10, 10, 10, 10, 10]\\ 0.5 \pm [0, 10, 10, 10, 10]\\ 0.5 \pm [0, 10, 10, 10]\\ 0.5$	Std. Mean Difference
Stuth or Subaroom Charg Wc2014 Granab V2016 Granab V2016 Here Self-2010 Here Self-2010 Here Self-2010 Here Self-2010 Jang T2017 Kim J2019 Jang T2017 Kim J2019 Urg T2017 Here Self-2019 Here Self-2019 Granab V2019 Here Self-2019 Granab V2019 Here Self-2019 Self-2019 Here Self-2019 Here Self-2	md4, Mean SD 1.62 0.3 1.30 0.31 1.34 0.19 1.1 0.11 1.1 0.14 0.21 0.23 0.30 0.71 0.40 0.26 1.14 0.28 0.15 0.27 1.16 0.21 1.19 0.23 1.16 0.21 1.17 0.22 1.18 0.22 1.19 0.23 1.112 0.22 1.12 0.21 1.13 0.18 1.14 0.28 1.15 0.27 1.112 0.22 1.113 0.18 1.12 0.12 1.13 0.18 1.22 0.15 1.24 0.15 1.24 0.15 1.22 0.15	CC General Mean 64 1.26 30 2.44 0 2.44 1.26 30 2.44 0 0.47 1.16 116 116 116 112 1.02 1.02 1.02 1.03 0.86 29 1.07 54 0.902 31 0.84 1.03 0.86 83 1.05 1.01 0 1.06 83 1.05 1.01 0.855 51 0.925 51 0.925 51 0.925 51 1.03 7 1.1 1.1 1.03 1.04 1.03 1.04 1.03 1.04 1.03 1.04 1.03 1.04 1.03 1.04 1.03 1.04 1.03 1.04 1.03 1.1 1.1 1.03 1.05 1.04 1.03 1.05 1.01 1.03 1.05 1.01 1.03 1.05 1.01 1.03 1.05 1.01 1.03 1.01 1.01 1.03 1.02 1.	SD Tr 0.21 0.04 0.16 0.13 0.2 0.111 0.28 0.131 0.17 0.167 0.162 0.19 0.162 0.162 0.162 0.123 0.23 0.26 0.122 0.21 0.13 0.22 0.21 0.13	43 111 9 10 22 23 9 14 26 9 23 23 23 24 27 25 2 13 69 23 23 21 4	teinth 4,0% 2,1% 2,2% 2,5% 3,1% 4,0% 3,3% 4,0% 3,3% 4,0% 3,3% 4,0% 3,3% 4,1% 3,3% 4,1% 3,3% 4,1% 3,3% 4,1% 3,3% 3,3% 4,1% 3,3% 3,3% 4,0% 3,3% 3,3% 4,0% 3,3% 3,3% 4,0% 4,0% 3,3% 4,0% 3,3% 4,0% 3,3% 4,0% 3,3% 4,0% 3,3% 4,0% 3,3% 4,0% 3,3% 4,0% 3,3% 4,0% 3,3% 4,0% 3,3% 4,0% 3,3% 4,0% 3,3% 4,0% 3,3% 4,0% 3,3% 4,0% 4,0% 4,0% 4,0% 4,0% 4,0% 4,0% 4,0	$ \begin{array}{c} {\sf M}, {\sf Bandem}, {\sf gS} {\sf S}, {\sf C} \\ {\sf 1}, {\sf 3}4 [0, {\sf 9}1, {\sf 1}, {\sf 7}6 \\ {\sf 0}, {\sf 9}1, {\sf 0}, {\sf 0}, {\sf 1}, {\sf 0}1 \\ {\sf 0}, {\sf 9}9 [0, {\sf 0}, {\sf 1}, {\sf 0}1 \\ {\sf 0}, {\sf 9}9 [0, {\sf 0}, {\sf 1}, {\sf 0}1 \\ {\sf 0}, {\sf 1}9 [0, {\sf 0}, {\sf 1}, {\sf 0}1 \\ {\sf 0}, {\sf 1}9 [0, {\sf 0}, {\sf 1}, {\sf 0}1 \\ {\sf 0}, {\sf 1}9 [0, {\sf 1}, {\sf 1}3 \\ {\sf 0}, {\sf 1}9 [0, {\sf 1}, {\sf 1}3 \\ {\sf 0}, {\sf 1}9 [0, {\sf 1}, {\sf 1}3 \\ {\sf 0}, {\sf 1}9 [0, {\sf 1}, {\sf 1}3 \\ {\sf 0}, {\sf 2}7 [0, {\sf 1}, {\sf 1}, {\sf 1}4 \\ {\sf 0}, {\sf 1}2 {\sf 0}, {\sf 2}, {\sf 0}, {\sf 2}4 \\ {\sf 0}, {\sf 2}2 [0, {\sf 2}2, {\sf 0}, {\sf 2}4 \\ {\sf 0}, {\sf 2}2 [0, {\sf 2}3, {\sf 1}, {\sf 4}2 \\ {\sf 0}, {\sf 2}6 [0, {\sf 1}, {\sf 1}, {\sf 1}1 \\ {\sf 1}0 [0, {\sf 0}, {\sf 1}0 \\ {\sf 0}, {\sf 2}[{\sf 0}, {\sf 2}, {\sf 1}, {\sf 1}, {\sf 1}0 \\ {\sf 0}, {\sf 1}0 [0, {\sf 1}, {\sf 0}, {\sf 1}] \\ {\sf 0}, {\sf 0}, {\sf 6}[{\sf 0}, {\sf 1}, {\sf 0}, {\sf 1}] \\ {\sf 0}, {\sf 0}, {\sf 6}[{\sf 0}, {\sf 1}0, {\sf 0}, {\sf 1}0 \\ {\sf 0}, {\sf 1}] {\sf 0}, {\sf 0}, {\sf 0}, {\sf 0}, {\sf 1}0 \\ {\sf 0}, {\sf 1}1 {\sf 0}0 {\sf 0}, {\sf 1}0 \\ {\sf 0}, {\sf 1}1 {\sf 0}0 {\sf 1}, {\sf 0}0 \\ {\sf 1}1 {\sf 0}0 {\sf 1}0 {\sf 1}0 \\ {\sf 0}, {\sf 1}2 {\sf 0}0 {\sf 1}1 \\ {\sf 0}0 {\sf 1}1 {\sf 0}0 {\sf 1}0 \\ {\sf 0}, {\sf 1}2 {\sf 0}0 {\sf 1}1 \\ {\sf 0}0 {\sf 1}1 {\sf 0}0 {\sf 1}0 \\ {\sf 0}0 {\sf 1}0 {\sf 0}0 {\sf 1}1 \\ {\sf 0}0 {\sf 1}0 {\sf 0}0 {\sf 1}1 \\ {\sf 0}0 {\sf 1}0 {\sf 1}0 \\ {\sf 0}0 {\sf 1}1 {\sf 1}0 {\sf 0}0 {\sf 1}0 \\ {\sf 0}0 {\sf 1}0 {\sf 0}0 {\sf 1}1 \\ {\sf 0}0 {\sf 0}0 {\sf 1}1 \\ {\sf 0}0 {\sf 1}1 {\sf 0}0 {\sf 1}1 \\ {\sf 0}0 {\sf 1}1 {\sf 0}0 {\sf 1}1 \\ {\sf 0}0 {\sf 0}0 {\sf 1}0 {\sf 0}0 {\sf 1}1 \\ {\sf 0}0 {\sf 0}0 {\sf 0}0 {\sf 0}0 {\sf 0}0 {\sf 0}0 {\sf 1}1 \\ {\sf 0}0 {\sf 0}1 {\sf 0}1 {\sf 1}2 \\ {\sf 0}0 {\sf 0}1 {\sf 0}1 {\sf 1}2 \\ {\sf 0}0 {\sf 0}1 {\sf 0}1 {\sf 0}1 {\sf 0}1 \\ {\sf 0}1 {\sf 0}1 {\sf 0}1 \\ {\sf 0}0 {\sf 0}1 {\sf 0}1 {\sf 0}1 \\ {\sf 0}1 {\sf 0}1 {\sf 0}1 {\sf 0}1 \\ {\sf 0}1 {\sf 0}1 {\sf 0}1 {\sf 0}1 \\ {\sf 0}1 {\sf 0}1 {\sf 0}1 {\sf 0}1 \\ {\sf 0}1 {\sf 0}1 {\sf 0}1 {\sf 0}1 \\ {\sf 0}1 {\sf 0}1 {\sf 0}1 {\sf 0}1 \\ {\sf 0}1 {\sf 0}1 {\sf 0}1 {\sf 0}1 \\ {\sf 0}1 {\sf 0}1 {\sf 0}1 \\ {\sf 0}1 {\sf 0}1 {\sf 0$	Std. Mean Difference
Study of Subgroups, Chara WC-214 Grand WC-214 Hee Sk2016 Uww 2015 Jung 72017 Jung 72017	md.j. Mean SD 1 62 0.3 1.30 0.31 1.31 0.31 1.31 0.11 1.31 0.11 1.31 0.11 1.31 0.12 1.31 0.16 0.71 0.26 1.13 0.11 1.14 0.29 1.15 0.21 1.16 0.271 1.16 0.21 1.16 0.21 1.17 0.22 0.166 0.11 1.13 0.18 0.29 0.16 0.11 0.22 1.16 0.21 1.17 0.22 0.16 0.17 1.12 0.21 1.14 0.12 1.12 0.21 1.13 0.18 1.14 0.19 1.22 0.15 1.41 0.19 1.42 0.15 <td>CC General Mean 64 1.26 30 2.44 30 2.44 1.26 30 2.44 9 0.9 9.9 1.01 1.01 1.01 1.01 1.02 1.02 1.02 1.02 1.02 1.02 1.02 1.02 1.02 1.02</td> <td>SD Tr 0.21 0.04 0.13 0.2 0.13 0.2 0.11 0.28 0.13 0.28 0.141 0.167 0.167 0.167 0.169 0.39 0.162 0.23 0.21 0.21 0.122 0.21 0.122 0.21 0.13 0.2 0.21 0.13 0.22 0.21 0.144 0.13 0.21 0.21</td> <td>43 11 9 10 29 12 7 23 9 14 12 9 12 7 23 9 14 12 9 12 7 25 2 13 69 223 23 14 8 9 9</td> <td>teintt 4.0% 2.1% 2.5% 3.1% 4.0% 3.6% 3.3% 4.0% 3.3% 3.3% 4.0% 3.3%</td> <td>$\begin{array}{c} {\sf M}, {\sf Bandem}, {\sf gS}(5, L) \\ {\sf 1}, {\sf 3} = \{0, 91, 1, 76\} \\ {\sf 1}, {\sf 3} = \{0, 91, 1, 76\} \\ {\sf 1}, {\sf 3} = \{0, 91, 1, 76\} \\ {\sf 1}, {\sf 3}, {\sf 0} = \{0, 1, 1, 76\} \\ {\sf 1}, {\sf 3}, {\sf 0} = \{0, 1, 1, 1, 95\} \\ {\sf 1}, {\sf 3}, {\sf 1}, {\sf$</td> <td>Std. Mean Difference</td>	CC General Mean 64 1.26 30 2.44 30 2.44 1.26 30 2.44 9 0.9 9.9 1.01 1.01 1.01 1.01 1.02 1.02 1.02 1.02 1.02 1.02 1.02 1.02 1.02 1.02	SD Tr 0.21 0.04 0.13 0.2 0.13 0.2 0.11 0.28 0.13 0.28 0.141 0.167 0.167 0.167 0.169 0.39 0.162 0.23 0.21 0.21 0.122 0.21 0.122 0.21 0.13 0.2 0.21 0.13 0.22 0.21 0.144 0.13 0.21 0.21	43 11 9 10 29 12 7 23 9 14 12 9 12 7 23 9 14 12 9 12 7 25 2 13 69 223 23 14 8 9 9	teintt 4.0% 2.1% 2.5% 3.1% 4.0% 3.6% 3.3% 4.0% 3.3% 3.3% 4.0% 3.3%	$ \begin{array}{c} {\sf M}, {\sf Bandem}, {\sf gS}(5, L) \\ {\sf 1}, {\sf 3} = \{0, 91, 1, 76\} \\ {\sf 1}, {\sf 3} = \{0, 91, 1, 76\} \\ {\sf 1}, {\sf 3} = \{0, 91, 1, 76\} \\ {\sf 1}, {\sf 3}, {\sf 0} = \{0, 1, 1, 76\} \\ {\sf 1}, {\sf 3}, {\sf 0} = \{0, 1, 1, 1, 95\} \\ {\sf 1}, {\sf 3}, {\sf 1}, {\sf$	Std. Mean Difference
Stark or Subarcoup Charg W2014 (uw V2014) (uw V2014) (u	md.j. Mean SD 1.62 0.3 1.33 0.31 1.43 0.19 1.14 0.19 1.1 0.11 1.14 0.22 1.15 0.11 1.14 0.26 1.12 0.23 0.99 0.13 0.71 0.26 1.12 0.27 1.12 0.23 1.12 0.21 1.12 0.22 1.12 0.22 1.12 0.22 1.12 0.22 1.12 0.22 1.12 0.22 1.12 0.22 1.12 0.22 1.12 0.21 1.12 0.21 1.12 0.22 1.12 0.21 1.12 0.21 1.12 0.21 1.12 0.21 1.12 0.21 1.12 0.15	CC Total Mean. 64 1.26 30 2.44 10 1.16 9 0.9 18 0.9 18 0.9 18 0.9 18 0.9 18 0.9 19 0.9 19 0.9 19 0.9 19 0.9 10 0.9 10 0.9 10 0.9 10 0.9 11 0.0 10 0.9 11 0.0 10 0.9 11 0.0 11 0.0 10	SD Tr 0.21 0.04 0.13 0.2 0.13 0.2 0.13 0.2 0.131 0.28 0.167 0.167 0.167 0.167 0.162 0.199 0.163 0.23 0.566 0.123 0.21 0.21 0.13 0.2 0.24 0.13 0.27 0.2 0.13 0.27 0.247 0.247	$\begin{array}{c} 43\\ 18\\ 19\\ 10\\ 29\\ 12\\ 7\\ 29\\ 14\\ 18\\ 29\\ 14\\ 25\\ 2\\ 13\\ 69\\ 23\\ 23\\ 14\\ 28\\ 9\\ 24\\ \end{array}$	teinth 4,0% 2,1% 2,2% 3,1% 3,2% 4,0% 3,6% 3,3% 3,6% 3,3% 4,0% 3,3% 3,3% 4,1% 3,3% 4,1% 3,3% 4,1% 3,3% 3,3% 4,1% 3,3% 3,3% 4,1% 3,3% 3,3% 4,0% 3,3% 3,3% 4,0% 3,3% 3,3% 4,0% 3,3% 3,3% 4,0% 3,3% 4,0% 3,3% 4,0% 3,3% 4,0% 3,3% 4,0% 3,3% 4,0% 3,3% 4,0% 3,3% 4,0% 3,3% 4,0% 3,3% 4,0% 3,3% 4,0% 3,3% 4,0% 3,3% 4,0% 3,3% 3,3% 4,0% 3,3% 3,3% 4,0% 3,3% 3,3% 4,0% 3,3% 3,3% 3,3% 3,3% 3,3% 3,3% 3,3% 3	$ \begin{array}{c} \underline{N}, \underline{Banden}, \underline{95}; \underline{C}, \\ 1,34 \ [0,91,1.76] \\ -5.61 \ [+ 6.92, -4.30] \\ 0.36 \ [0,07,1.91] \\ 1.6 \ [0,04,1.72] \\ 1.6 \ [0,04,1.72] \\ 1.6 \ [0,04,1.72] \\ 1.6 \ [0,04,1.72] \\ 1.6 \ [0,04,1.73] \\ 1.6 \ $	Std. Mean Difference
Stash or Subsection Characterized Control Characterized Control Characterized Control News 2016 Hes School Control Hes School Control Hes School Control Hes School Control Hes School Control Native Action Main Accord Native Action School Control School Control School Control School Control School Control School Control Hes School Control School Control Hes School Control	md41 Mean SD 1.02 0.31 1.13 0.11 1.13 0.11 1.14 0.28 1.14 0.28 1.14 0.23 0.70 0.29 0.71 0.26 0.72 0.27 1.14 0.28 1.134 0.28 1.14 0.28 1.12 0.22 1.12 0.22 1.12 0.22 1.12 0.22 1.12 0.22 1.13 0.866 1.28 0.17 1.29 0.17 0.28 0.15 1.14 0.18 1.29 0.16 1.20 0.16 1.21 0.16 1.22 0.16 1.21 0.16 1.21 0.16 1.21 0.16	CC Total Mean 0.84 1.26 30 2.44 1.0 1.16 30 2.44 1.0 1.16 10 21 1.0 2.44 1.16 10 1.0 1.22 1.02 1.02 1.01 1.01 21 1.06 23 2.0 3.0 0.68 1.03 6.68 0.855 1.0 0.695 51 0.62 37 1.1 1.1 1.03 3.1 1.02 37 1.1 1.03 2.0 5.0 0.675 51 0.62 37 1.1 1.03 3.0 1.68 1.33 1.11 1.03 1.30 1.32 1.02 37 1.02 37 1.02 31 1.02 31 1.02 31 1.02 31 1.02 31 1.02 31 1.02 31 1.02 31 1.02 31 1.02 31<	SD Tr 0.21 0.44 0.16 0.13 0.2 0.16 0.13 0.2 0.11 0.28 0.13 0.21 0.13 0.13 0.13 0.13 0.13 0.17 0.162 0.19 0.162 0.19 0.122 0.20 0.21 0.241 0.236 0.241 0.236	43 18 11 9 10 29 12 7 23 9 14 26 19 23 9 14 26 9 24 24 24 5586 10 10 23 23 23 24 24 25 26 10 23 23 23 23 23 24 25 25 25 25 25 25 25 25 25 25	benth 4.0% 2.9% 2.5% 4.0% 3.6% 4.0% 3.6% 4.0% 3.3% 4.0% 3.8% 3.6% 3.8% 3.8% 3.8% 3.8% 3.8% 3.8% 3.8% 3.8	$\begin{array}{c} {\sf M}, {\sf Bandem}, {\sf gS}_{5:C}, {\sf I}\\ {\sf 1}, {\sf 3} = \{0, 0, 1, 1, 76\}\\ {\sf 1}, {\sf 3} = \{0, 0, 1, 1, 76\}\\ {\sf 1}, {\sf 3}, {\sf 0}, {\sf 1}, {\sf 1}, {\sf 1}, {\sf 1}\\ {\sf 1}, {\sf 6}, {\sf 0}, {\sf 1}, {\sf 1}, {\sf 1}, {\sf 1}\\ {\sf 1}, {\sf 6}, {\sf 0}, {\sf 1}, {\sf 1}, {\sf 1}\\ {\sf 1}, {\sf 6}, {\sf 1}, {\sf 1}, {\sf 1}, {\sf 1}\\ {\sf 1}, {\sf 6}, {\sf 1}, {\sf 1}\\ {\sf 0}, {\sf 1}, {\sf 0}, {\sf 1}, {$	Std. Mean Difference
Status of Status and Status of Statu	Mean ref J 162 33 163 0.31 1.34 0.19 1.1 0.11 1.14 0.28 1.15 0.16 1.14 0.28 1.14 0.28 0.081 0.22 1.13 0.28 1.13 0.28 1.13 0.28 1.13 0.28 1.12 0.23 0.066 0.11 1.12 0.21 0.13 0.18 1.2 0.21 1.2 0.21 0.266 0.11 1.2 0.21 1.13 0.18 1.2 0.11 1.2 0.11 1.2 0.11 1.2 0.11 1.2 0.12 1.3 0.18 1.4 0.19 1.2 0.15 1.2 0.15 1.2 <td< td=""><td>ACC Total Mean. 64 1.26 30 2.44 10 1.46 1.06 31 10 2.44 10 1.16 9 0.9 11 10 1.16 10 1.16 10 11<!--</td--><td>SD Tr 0.21 0.44 0.16 0.13 0.2 0.16 0.13 0.2 0.11 0.28 0.13 0.21 0.13 0.13 0.13 0.13 0.13 0.17 0.162 0.19 0.162 0.19 0.122 0.20 0.21 0.241 0.236 0.241 0.236</td><td>43 18 11 9 10 29 12 7 23 9 14 26 19 23 9 14 26 9 24 24 24 5586 10 10 23 23 23 24 24 25 26 10 23 23 23 23 23 24 25 25 25 25 25 25 25 25 25 25</td><td>benth 4.0% 2.9% 2.5% 4.0% 3.6% 4.0% 3.6% 4.0% 3.3% 4.0% 3.8% 3.6% 3.8% 3.8% 3.8% 3.8% 3.8% 3.8% 3.8% 3.8</td><td>$\begin{array}{c} {\sf M}, {\sf Bandem}, {\sf gS}_{5:C}, {\sf I}\\ 1,34 \ [0,01,1,76]\\ -5.61 \ [+0,02,4.30]\\ 1,40 \ (-0,01,176)\\ -5.61 \ [+0,02,-320]\\ 1,40 \ (-0,01,176)\\ -0.64 \ (-0,01,176)\\ -0.6$</td><td>Std. Mean Difference N. Randem, 95% CI </td></td></td<>	ACC Total Mean. 64 1.26 30 2.44 10 1.46 1.06 31 10 2.44 10 1.16 9 0.9 11 10 1.16 10 1.16 10 11 </td <td>SD Tr 0.21 0.44 0.16 0.13 0.2 0.16 0.13 0.2 0.11 0.28 0.13 0.21 0.13 0.13 0.13 0.13 0.13 0.17 0.162 0.19 0.162 0.19 0.122 0.20 0.21 0.241 0.236 0.241 0.236</td> <td>43 18 11 9 10 29 12 7 23 9 14 26 19 23 9 14 26 9 24 24 24 5586 10 10 23 23 23 24 24 25 26 10 23 23 23 23 23 24 25 25 25 25 25 25 25 25 25 25</td> <td>benth 4.0% 2.9% 2.5% 4.0% 3.6% 4.0% 3.6% 4.0% 3.3% 4.0% 3.8% 3.6% 3.8% 3.8% 3.8% 3.8% 3.8% 3.8% 3.8% 3.8</td> <td>$\begin{array}{c} {\sf M}, {\sf Bandem}, {\sf gS}_{5:C}, {\sf I}\\ 1,34 \ [0,01,1,76]\\ -5.61 \ [+0,02,4.30]\\ 1,40 \ (-0,01,176)\\ -5.61 \ [+0,02,-320]\\ 1,40 \ (-0,01,176)\\ -0.64 \ (-0,01,176)\\ -0.6$</td> <td>Std. Mean Difference N. Randem, 95% CI </td>	SD Tr 0.21 0.44 0.16 0.13 0.2 0.16 0.13 0.2 0.11 0.28 0.13 0.21 0.13 0.13 0.13 0.13 0.13 0.17 0.162 0.19 0.162 0.19 0.122 0.20 0.21 0.241 0.236 0.241 0.236	43 18 11 9 10 29 12 7 23 9 14 26 19 23 9 14 26 9 24 24 24 5586 10 10 23 23 23 24 24 25 26 10 23 23 23 23 23 24 25 25 25 25 25 25 25 25 25 25	benth 4.0% 2.9% 2.5% 4.0% 3.6% 4.0% 3.6% 4.0% 3.3% 4.0% 3.8% 3.6% 3.8% 3.8% 3.8% 3.8% 3.8% 3.8% 3.8% 3.8	$ \begin{array}{c} {\sf M}, {\sf Bandem}, {\sf gS}_{5:C}, {\sf I}\\ 1,34 \ [0,01,1,76]\\ -5.61 \ [+0,02,4.30]\\ 1,40 \ (-0,01,176)\\ -5.61 \ [+0,02,-320]\\ 1,40 \ (-0,01,176)\\ -0.64 \ (-0,01,176)\\ -0.6$	Std. Mean Difference N. Randem, 95% CI
Stabl or Subsection Chang WC2014 Chang WC2014 Out 2015 Hee SH2010 Hee SH2010	Mean ref J 162 33 163 0.31 1.34 0.19 1.1 0.11 1.14 0.28 1.15 0.16 1.14 0.28 1.14 0.28 0.081 0.22 1.13 0.28 1.13 0.28 1.13 0.28 1.13 0.28 1.12 0.23 0.066 0.11 1.12 0.21 0.13 0.18 1.2 0.21 1.2 0.21 0.266 0.11 1.2 0.21 1.13 0.18 1.2 0.11 1.2 0.11 1.2 0.11 1.2 0.11 1.2 0.12 1.3 0.18 1.4 0.19 1.2 0.15 1.2 0.15 1.2 <td< td=""><td>ACC Total Mean. 64 1.26 30 2.44 10 1.46 1.06 31 10 2.44 10 1.16 9 0.9 11 10 1.16 10 1.16 10 11<!--</td--><td>SD Tr 0.21 0.44 0.16 0.13 0.2 0.16 0.13 0.2 0.11 0.28 0.13 0.21 0.13 0.13 0.13 0.13 0.13 0.17 0.162 0.19 0.162 0.19 0.122 0.20 0.21 0.241 0.236 0.241 0.236</td><td>43 18 11 9 10 29 12 7 23 9 14 26 19 23 9 14 26 9 24 24 24 5586 10 10 23 23 23 24 24 25 26 10 23 23 23 23 23 24 25 25 25 25 25 25 25 25 25 25</td><td>benth 4.0% 2.9% 2.5% 4.0% 3.6% 4.0% 3.6% 4.0% 3.3% 4.0% 3.8% 3.6% 3.8% 3.8% 3.8% 3.8% 3.8% 3.8% 3.8% 3.8</td><td>$\begin{array}{c} {\sf M}, {\sf Bandem}, {\sf gS}_{5:C}, {\sf I}\\ 1,34 \ [0,01,1,76]\\ -5.61 \ [+0,02,4.30]\\ 1,40 \ (-0,01,176)\\ -5.61 \ [+0,02,-320]\\ 1,40 \ (-0,01,176)\\ -0.64 \ (-0,01,176)\\ -0.6$</td><td>Std. Mean Difference W. Bandom, 955 Cl </td></td></td<>	ACC Total Mean. 64 1.26 30 2.44 10 1.46 1.06 31 10 2.44 10 1.16 9 0.9 11 10 1.16 10 1.16 10 11 </td <td>SD Tr 0.21 0.44 0.16 0.13 0.2 0.16 0.13 0.2 0.11 0.28 0.13 0.21 0.13 0.13 0.13 0.13 0.13 0.17 0.162 0.19 0.162 0.19 0.122 0.20 0.21 0.241 0.236 0.241 0.236</td> <td>43 18 11 9 10 29 12 7 23 9 14 26 19 23 9 14 26 9 24 24 24 5586 10 10 23 23 23 24 24 25 26 10 23 23 23 23 23 24 25 25 25 25 25 25 25 25 25 25</td> <td>benth 4.0% 2.9% 2.5% 4.0% 3.6% 4.0% 3.6% 4.0% 3.3% 4.0% 3.8% 3.6% 3.8% 3.8% 3.8% 3.8% 3.8% 3.8% 3.8% 3.8</td> <td>$\begin{array}{c} {\sf M}, {\sf Bandem}, {\sf gS}_{5:C}, {\sf I}\\ 1,34 \ [0,01,1,76]\\ -5.61 \ [+0,02,4.30]\\ 1,40 \ (-0,01,176)\\ -5.61 \ [+0,02,-320]\\ 1,40 \ (-0,01,176)\\ -0.64 \ (-0,01,176)\\ -0.6$</td> <td>Std. Mean Difference W. Bandom, 955 Cl </td>	SD Tr 0.21 0.44 0.16 0.13 0.2 0.16 0.13 0.2 0.11 0.28 0.13 0.21 0.13 0.13 0.13 0.13 0.13 0.17 0.162 0.19 0.162 0.19 0.122 0.20 0.21 0.241 0.236 0.241 0.236	43 18 11 9 10 29 12 7 23 9 14 26 19 23 9 14 26 9 24 24 24 5586 10 10 23 23 23 24 24 25 26 10 23 23 23 23 23 24 25 25 25 25 25 25 25 25 25 25	benth 4.0% 2.9% 2.5% 4.0% 3.6% 4.0% 3.6% 4.0% 3.3% 4.0% 3.8% 3.6% 3.8% 3.8% 3.8% 3.8% 3.8% 3.8% 3.8% 3.8	$ \begin{array}{c} {\sf M}, {\sf Bandem}, {\sf gS}_{5:C}, {\sf I}\\ 1,34 \ [0,01,1,76]\\ -5.61 \ [+0,02,4.30]\\ 1,40 \ (-0,01,176)\\ -5.61 \ [+0,02,-320]\\ 1,40 \ (-0,01,176)\\ -0.64 \ (-0,01,176)\\ -0.6$	Std. Mean Difference W. Bandom, 955 Cl
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Study of Subarder Ghang WC2014 (Shang WC2014) Hos SH2010 Hos SH2010 Hos SH2010 Jang 72017 Jang 7201	$\begin{tabular}{ c c c c } \hline Mean & State & $	ACC Maximum Total Maximum Maximum 64 124 65 126 7 106 7 108 7 108 7 144 7 125 7 144 144 103 7 125 7 124 7 125 7 144 144 133 154 122 144 133 154 122 144 133 144 134 144 134 144 134 144 134 144 134 144 134 144 134 144 134 144 134 144 134 144 134 145 125 144 122 144	SD T. 0.21 0.24 0.24 0.21 0.40 0.33 0.13 0.2 0.14 0.13 0.15 0.16 0.16 0.13 0.17 0.19 0.19 0.36 0.22 0.14 0.30 0.17 0.40 0.23 0.10 0.23 0.24 0.24 0.23 0.24 0.247 0.247 0.247 0.246 0.248 0.248 0.442 0.248	43 43 43 43 42 42 42 42 42 42 42 42 42 42	visitit 4.0% 4.0% 2.1% 3.1% 3.6% 3.3.3.3.3 3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.	M. Bandem, 95%-C. 1.34 (0.01, 1.76) -5.61 (P.0.31, 4.30) -5.61 (P.0.31, 4.30) -5.61 (P.0.31, 4.30) -5.61 (P.0.31, 4.30) 1.44 (0.04, 2.75) 0.41 (P.0.42, 2.75) 0.51 (P.0.31, 4.30) 0.62 (P.0.42, 2.75) 0.51 (P.0.42, 2.75) 0.51 (P.0.42, 2.75) 0.52 (P.0.42, 2.75) 0.54 (P.0.42, 0.53) 0.54 (P.0.42, 0.53) 0.54 (P.0.42, 0.53) 0.55 (P.0.42, 0.54) 1.11 (P.47, 1.75) 0.55 (P.0.42, 0.54) 1.20 (P.77, 1.63) 0.47 (P.0.42, 0.56) 0.47 (P.0.42, 0.56) 1.20 (P.77, 1.63) 0.55 (P.0.42, 0.56) </td <td>Std. Mean Difference W. Random, 955 CI</td>	Std. Mean Difference W. Random, 955 CI
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Subt at Subtraction Grant Wic2rist Grant Wic2rist Heis Sk2016 Jung 72/17 Heis Sk2010 Heis Sk2010 Jung 72/17 Heis Sk2010 Jung 72/17 Heis Sk2016 Jung 72/17 Heis Sk2016 Jung 72/17 Skan Grant Sk2016 Sk2017 Sk200 Sk200 Sk200 Sk200 Sk200 Sk200 Sk	$\begin{tabular}{ c c c c } \hline Mean & State & $	ACC Instance Instal Maximum Instal Install Install In	SUD T: 0.21 0.21 0.24 0.24 0.24 0.26 0.16 0.16 0.16 0.17 0.131 0.17 0.167 0.167 0.167 0.167 0.167 0.167 0.250 0.23 0.23 0.23 0.23 0.247 0.250 0.15 0.27 0.247 0.247 0.247 0.247 0.250 0.15 0.250 0.15 0.250 0.15 0.257 0.250 0.15 0.257 0.257 0.257 0.257 0.247 0.257	43 43 43 18 11 9 10 29 12 23 9 14 27 23 9 14 27 23 9 14 27 23 9 14 27 23 9 14 27 23 23 23 23 24 24 10 10 25 24 24 10 10 25 24 24 10 10 25 27 27 20 20 20 20 20 20 20 20 20 20	Ventative 4.01% 4.01% 2.15% 3.10% 3.65% 3.3.3.8% 3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.3.	M. Bandem, 95%.Cl 1.34 (0.01, 1.76) 1.34 (0.01, 1.76) -5.07 (1.00, 1.01, 1.76) 1.64 (0.04, 1.76) 1.64 (0.04, 2.75) 0.01 (1.01, 0.13, 1.76) 0.05 (0.04, 2.75) 0.05 (0.04, 2.75) 0.05 (0.04, 2.75) 0.05 (0.04, 2.75) 0.05 (0.04, 2.75) 0.05 (0.04, 2.75) 0.05 (0.04, 2.75) 0.05 (0.04, 2.75) 0.05 (0.04, 2.75) 0.05 (0.04, 2.75) 0.05 (0.04, 2.75) 0.05 (0.04, 2.75) 0.05 (0.04, 2.75) 0.05 (0.04, 2.75) 0.05 (0.14, 0.04, 0.51) 0.05 (0.14, 0.04, 0.51) 0.05 (0.14, 0.04, 0.05) 0.05 (0.14, 0.04, 0.05) 1.01 (0.77, 1.63) 0.05 (0.14, 0.16, 0.56) 0.05 (0.12, 0.17, 0.15) 0.05 (0.12, 0.17, 0.15) 0.05 (0.12, 0.17, 0.15) 0.05 (0.12, 0.17, 0.15) 0.05 (0.12, 0.17, 0.15) 0.05 (0.12, 0.17, 0.15) 0.05 (0.12, 0.17, 0.15) 0.05 (0.02, 0.17) 0.05 (0.02, 0.17)	Std. Mean Difference W. Random, 955 CI
Stady of Subarcose. Charag W2:2014 Grands 2016 Gov 2015 Heis SH2010 Heis SH201	Mean red 4 Maan 00. 1 62 0.3 1 62 0.3 1 14 0.18 1 14 0.18 1 14 0.18 1 14 0.18 1 14 0.18 0 10 0.52 1 11 0.23 0 10 0.22 1 11 0.23 1 12 0.21 1 12 0.21 1 12 0.21 1 10 1.2 0 11 1.13 0 12 0.11 1 12 0.11 1 12 0.11 1 10 1.22 0 11 0.17 1 12 0.16 1 14 0.19 1 24 0.15 1 24 0.16 1 24 0.16 1 24 0.16 1 24 0.16 1 24 0.16 1 24 0.16 1 24	International Control of the second	SD T. T. 0.21 0.24 0.24 0.24 0.13 0.21 0.21 0.13 0.21 0.13 0.21 0.24 0.13 0.21 0.21 0.21 0.13 0.13 0.13 0.13 0.14 0.162 0.150 0.162 0.162 0.236 0.22 0.2 0.245 0.236 0.236 0.236 0.245 0.245 0.245 0.245 0.245 0.245 0.245 0.245 0.245 0.245 0.245 0.245 0.245 0.245 0.245 0.246 0.245 0.246 0.245 0.246 0.245 0.246	43 43 43 18 11 9 10 29 12 23 9 14 27 23 9 14 27 23 9 14 27 23 9 14 27 23 9 14 27 23 23 23 23 24 24 10 10 25 24 24 10 10 25 24 24 10 10 25 27 27 20 20 20 20 20 20 20 20 20 20	binth \$4.0% 2.1% 4.0% 2.5% 4.0% 3.2% 3.3% 4.0% 3.3% 4.0% 3.3% 4.0% 3.3% 4.0% 3.3% 6% 1.6% 5.6% 5.6% 5.6% 5.6% 5.6% 5.6% 5.6% 5.6% 5.6% 5.6% 5.6% 5.6% 5.6%	M. Bandem, 95%.Cl 1.34 (0.01, 1.76) -5.61 (F.0.37, 4.30) -5.61 (F.0.38, 4.30) -5.61 (F.0.38, 4.31) -5.61 (F.0.38, 4.32) -5.61 (F.0.38, 0.32) -5.61 (F.0.38, 0.32) <td>Std. Mean Difference W. Random, 955 CI</td>	Std. Mean Difference W. Random, 955 CI

FIGURE 3 | (A) Forest plot of ADCmean between wdHCC and mdHCC. The SMD indicated that the ADCmean of mdHCC was significantly lower than that of wdHCC. (B) Forest plot of the ADCmean between wdHCC and pdHCC. The SMD indicated that the ADCmean of pdHCC was significantly lower than that of wdHCC. (C) Forest plot of the ADCmean between mdHCC and pdHCC; the SMD indicated that the ADCmean of pdHCC was significantly lower than that of mdHCC. (D) Forest plot of the ADCmean between MVI- and MVI+. The SMD indicated that the ADCmean of MVI+ HCC was significantly lower than that of MVI- HCC, well differentiated hepatocellular carcinoma; md-HCC, moderately differentiated hepatocellular carcinoma; pd-HCC, poorly differentiated hepatocellular carcinoma; SMD, standardized mean difference.

	1	wd-HCC			md-H	ICC		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl
Kim JG2019	1.01	0.35	9	0.82	0.24	122	16.7%	0.76 [0.08, 1.44]	
Lee S2018		0.198		0.837		75	23.9%		
Li X2016	1.04	0.36	20	0.98	0.24	198	36.7%	0.24 [-0.22, 0.70]	
Moriya T2017		0.388		0.411	0.278	35	17.5%	0.55 [-0.11, 1.22]	+
Nakanishi M2012	1.15	0.1	3	0.98	0.18	29	5.3%	0.94 [-0.27, 2.16]	
Total (95% Cl)			58			459	100.0%	0.39 [0.12, 0.67]	•
Heterogeneity: Chi ² =	3.32, df	= 4 (P =	0.51);	$l^2 = 0\%$				-	
Test for overall effect:	Z = 2.77	' (P = 0.0	006)						Favours [experimental] Favours [control]
		wd-HCC			pd -HC(Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean			Mean			Weight		IV, Fixed, 95% Cl
Kim JG2019	1.01	0.35	9	0.76	0.22	12	19.0%	0.85 [-0.06, 1.76]	
Lee S2018		0.198		0.624	0.24	7	16.4%	1.09 [0.11, 2.07]	
Li X2016	1.04	0.36	20	0.78	0.2	23	39.5%	0.89 [0.26, 1.53]	
Moriya T2017		0.388			0.102	9	17.8%	1.11 [0.17, 2.05]	
Nakanishi M2012	1.15	0.1	3	0.69	0.19	18	7.3%	2.42 [0.95, 3.89]	
Total (95% CI)			58			69	100.0%	1.07 [0.67, 1.46]	◆
Heterogeneity: Chi ² =								-	-4 -2 0 2 4
Test for overall effect:	Z = 5.28	3 (P < 0.0	00001)						Favours [experimental] Favours [control]
		md-H	100					Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean			Mean	pd -HC(Weight		IV, Random, 95% Cl
Kim JG2019	0.82	0.24	122	0.76	0.22	12	21.4%	0.25 [-0.34, 0.84]	
Lee S2018		0.197		0.624	0.22	7	15.9%	1.05 [0.26, 1.84]	
Li X2016	0.98	0.24	198	0.78	0.24	23	26.8%	0.84 [0.40, 1.28]	
Moriya T2017		0.278		0.235		20	17.0%	0.68 [-0.07, 1.43]	
Nakanishi M2012	0.98	0.18	29	0.69	0.19	18	19.0%	1.55 [0.88, 2.22]	
Total (95% CI)			459			69	100.0%	0.86 [0.44, 1.27]	•
Heterogeneity: Tau ² =	0.11.0	hi≅ – 8.5		4 (P - 0	07):12-		100.070		
Test for overall effect:				4(1 - 0		55.0			-4 -2 0 2 4 Favours [experimental] Favours [control]
									Favours (experimental) Favours (control)
1		MVI(-)			/Ⅳ(+)			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean		Total	Mean		Total	Weight		IV, Random, 95% Cl
Chuang YH2019	1.03	0.23	79	0.83	0.24	18	20.5%	0.86 [0.33, 1.38]	
Kim JG2019	0.85	0.23	79	0.83	0.24	69	20.5%	0.20 [-0.13, 0.53]	+ -
Lee S2018		0.24		0.687		37	23.7%	1.14 [0.72, 1.56]	
Zhao J2017	1.06	0.172	107	0.687	0.199	211	23.7%	0.79 [0.55, 1.03]	
	1.00	0.17		0.52	0.10				
Total (95% CI)			337				100.0%	0.73 [0.34, 1.12]	
I later was a site Taw?	0.12; C			= 3 (P =	0.003);	² = 799	%	-	
Heterogeneity: Tau ² = Test for overall effect:									

wdHCC. (B) Forest plot of the ADCmin between wdHCC and pdHCC. The SMD indicated that the ADCmin of pdHCC was significantly lower than that of wdHCC. (C) Forest plot of the ADCmin between mdHCC and pdHCC. The SMD indicated that the ADCmin of pdHCC was significantly lower than that of wdHCC. (C) Forest plot of the ADCmin between mdHCC and pdHCC. The SMD indicated that the ADCmin of pdHCC was significantly lower than that of mdHCC. (D) Forest plot of the ADCmin between mdHCC and pdHCC. The SMD indicated that the ADCmin of pdHCC was significantly lower than that of mdHCC. (D) Forest plot of the ADCmin between MVI- HCC and MVI+ HCC. The SMD indicated that the ADCmin of MVI+ HCC was significantly lower than that of MVI- HCC, wd-HCC, well differentiated hepatocellular carcinoma; md-HCC, moderately differentiated hepatocellular carcinoma; pd-HCC, poorly differentiated hepatocellular carcinoma; MVI, microvascular invasion; SMD, standardized mean difference.

the other studies were stable and reliable, except for the ADCmean value to identify wdHCC vs. mdHCC, and the D value to identify wdHCC vs. pdHCC and mdHCC vs. pdHCC. After removing the study by Jiang et al. (26), the result of the ADCmean in discriminating wdHCC vs. mdHCC was stable and reliable (SMD = 0.61, P < 0.00001, **Supplementary Figure S8**). After removing the studies by Shan et al. (25) and Granata et al. (22), the results of the D values in discriminating the D values in

discriminating wdHCC vs. pdHCC and were stable and reliable (SMD = 2.48, SMD = 1.01, P < 0.00001; **Supplementary Figures S9, S10**). The heterogeneity was lower than before, which suggested that these studies were likely the source of heterogeneity.

Diagnostic Performance

The pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and

		vd-HCC			md-H			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean			Mean			Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Granata V2016	0.86	0.09	14	0.81	0.49	30		0.12 [-0.52, 0.75]	
Shan QG2017	1.01	0.36	18	0.91	1.44	66		0.08 [-0.44, 0.60]	
Wei Y 2019	1.2	0.17	15	0.96	0.16	41	10.3%	1.45 [0.80, 2.11]	
Wei Y20 19	1.33	0.17	15	1.13	0.13	41	10.4%	1.39 [0.74, 2.04]	
Nei Y2019	1.47	0.04	15	1.23	0.09	41	9.4%	2.95 [2.14, 3.77]	
Woo S2014	1.3	0.28	4	1.15	0.13	20	7.8%	0.91 [-0.20, 2.02]	
/Vu B2020	1.18	0.33	19	0.92	0.26	30	10.6%	0.89 [0.28, 1.49]	
Zhou Y2021	1.06	0.17	15	0.88	0.16	46	10.5%	1.09 [0.48, 1.71]	
Zhu SC 2018		0.214	14		0.151	24	9.8%	1.53 [0.78, 2.28]	
Zhu SC2018		0.226	14		0.148	24	9.8%	1.54 [0.78, 2.29]	
Total (95% CI)			143			363	100.0%	1.17 [0.67, 1.68]	◆
Heterogeneity: Tau ² :	= 0.52: C	hi ² = 48	.49. df =	= 9 (P <	0.00001	1): $I^2 = 0$	31%		
Test for overall effect						.,,			-4 -2 0 2 4
			00001,						Favours [experimental] Favours [control]
		vd -HCC			pd -HCC			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Granata V2016	0.86	0.09	14	1.51	0.11	18	8.7%	-6.22 [-7.99, -4.45]	
Shan QG2017	1.01	0.36	18	0.82	0.57	25	10.7%	0.38 [-0.23, 0.99]	+
Vei Y 2019	1.2	0.17	15	0.83	0.11	23	10.3%	2.65 [1.75, 3.56]	-
Vei Y20 19	1.33	0.17	15	0.96	0.1	23	10.3%	2.75 [1.83, 3.67]	
Vei Y2019	1.47	0.04	15	1.07	0.06	23	8.5%	7.37 [5.50, 9.24]	
Noo S2014	1.3	0.28	4	1.02	0.13	14	9.7%	1.58 [0.33, 2.84]	
Nu B2020	1.18	0.33	19	0.79	0.13	28	10.6%	1.48 [0.81, 2.14]	+
Zhou Y2021	1.06	0.33	15	0.76	0.18	20	10.2%		
								1.67 [0.69, 2.64]	
Zhu SC 2018	1.186			0.775		24	10.4%	2.04 [1.22, 2.86]	
Zhu SC2018	1.193	0.226	14	0.771	0.187	24	10.4%	2.05 [1.23, 2.86]	
	1.193	0.226		0.771	0.187				-
	1.193	0.226	14 143	0.771	0.187		10.4%	2.05 [1.23, 2.86] 1.59 [0.44, 2.74]	▲
Zhu SC2018 Total (95% CI) Heterogeneity: Tau² =			143			211	100.0%		→ + + + + + + +
Total (95% CI)	= 3.13; Cl	hi² = 140	143 0.49, df			211	100.0%		-10 -5 0 5 10
Total (95% CI) Heterogeneity: Tau² =	= 3.13; Cl	hi² = 140	143 0.49, df			211	100.0%		-10 -5 0 5 10 Favours [experimental] Favours [control]
f otal (95% CI) Heterogeneity: Tau² =	= 3.13; Cl	hi² = 14((P = 0.(143 0.49, df 007)		< 0.0000	211)1); ²=	100.0 % 94%	1.59 [0.44, 2.74]	Favours [experimental] Favours [control]
Fotal (95% CI) Heterogeneity: Tau² = Fest for overall effect:	= 3.13; Cl : Z = 2.71	hi ² = 14((P = 0.(md -H	143 0.49, df 007) ICC	'= 9 (P <	< 0.0000	211 01); I ² =	100.0 % 94%	1.59 [0.44, 2.74] - Std. Mean Difference	Favours [experimental] Favours [control] Std. Mean Difference
Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: Study or Subgroup	= 3.13; Cl : Z = 2.71 <u>Mean</u>	hi ² = 14((P = 0.(md-H SD	143 0.49, df 007) ICC Total	⁷ =9(P ∘ <u>Mean</u>	< 0.0000 pd-HC(SD	211)1); I² = C Total	100.0% 94% Weight	1.59 [0.44, 2.74] - Std. Mean Difference IV, Random, 95% Cl	Favours [experimental] Favours [control]
Fotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: <u>Study or Subgroup</u> Granata V2016	= 3.13; Ci : Z = 2.71 <u>Mean</u> 0.81	hi ^z = 14((P = 0.(md-H <u>SD</u> 0.49	143 0.49, df 007) ICC <u>Total</u> 30	[•] = 9 (P < <u>Mean</u> 1.51	 0.0000 pd-HC0 SD 0.11 	211)1); ² = C <u>Total</u> 18	100.0% 94% <u>Weight</u> 9.7%	1.59 [0.44, 2.74] Std. Mean Difference <u>IV, Random, 95% Cl</u> -1.74 [-2.43, -1.06]	Favours [experimental] Favours [control] Std. Mean Difference
Fotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: <u>Study or Subgroup</u> Granata V2016 Shan QG2017	= 3.13; Cl : Z = 2.71 <u>Mean</u> 0.81 0.91	hi ² = 14((P = 0.(md-H SD 0.49 1.44	143 0.49, df 007) ICC <u>Total</u> 30 66	⁷ = 9 (P • <u>Mean</u> 1.51 0.82	 0.0000 pd-HC(SD 0.11 0.57 	211 11); I ² = C <u>Total</u> 18 25	100.0% 94% Weight 9.7% 10.5%	1.59 [0.44, 2.74] Std. Mean Difference <u>IV, Random, 95% Cl</u> -1.74 [-2.43, -1.06] 0.07 [-0.39, 0.53]	Favours [experimental] Favours [control] Std. Mean Difference
Fotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: <u>Study or Subgroup</u> Granata V2016 Shan QG2017	= 3.13; Ci : Z = 2.71 <u>Mean</u> 0.81	hi ^z = 14((P = 0.(md-H <u>SD</u> 0.49	143 0.49, df 007) ICC <u>Total</u> 30	[•] = 9 (P < <u>Mean</u> 1.51	 0.0000 pd-HC0 SD 0.11 	211)1); ² = C <u>Total</u> 18	100.0% 94% <u>Weight</u> 9.7%	1.59 [0.44, 2.74] Std. Mean Difference <u>IV, Random, 95% Cl</u> -1.74 [-2.43, -1.06]	Favours [experimental] Favours [control] Std. Mean Difference
Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y 2019	= 3.13; Cl : Z = 2.71 <u>Mean</u> 0.81 0.91	hi ² = 14((P = 0.(md-H SD 0.49 1.44	143 0.49, df 007) ICC <u>Total</u> 30 66	⁷ = 9 (P • <u>Mean</u> 1.51 0.82	 0.0000 pd-HC(SD 0.11 0.57 	211 11); I ² = C <u>Total</u> 18 25	100.0% 94% Weight 9.7% 10.5%	1.59 [0.44, 2.74] Std. Mean Difference <u>IV, Random, 95% Cl</u> -1.74 [-2.43, -1.06] 0.07 [-0.39, 0.53]	Favours [experimental] Favours [control] Std. Mean Difference
Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: Study or Subgroup Stranata V2016 Shan QG2017 Wei Y 2019 Wei Y2019	= 3.13; Cl : Z = 2.71 <u>Mean</u> 0.81 0.91 0.96	hi ² = 14((P = 0.0 md-F <u>SD</u> 0.49 1.44 0.16	143 0.49, df 007) ICC <u>Total</u> 30 66 41	⁷ = 9 (P < <u>Mean</u> 1.51 0.82 0.83	 0.0000 pd-HC0 SD 0.11 0.57 0.11 	211 11); ² = C <u>Total</u> 18 25 23	100.0% 94% Weight 9.7% 10.5% 10.3%	1.59 [0.44, 2.74] Std. Mean Difference <u>IV. Random, 95% Cl</u> -1.74 [-2.43, -1.06] 0.07 [-0.39, 0.53] 0.89 [0.36, 1.43]	Favours [experimental] Favours [control] Std. Mean Difference
Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Mei Y2019 Nei Y2019 Nei Y2019	= 3.13; Cl : Z = 2.71 <u>Mean</u> 0.81 0.91 0.96 1.13	hi ² = 14((P = 0.0 md-F <u>SD</u> 0.49 1.44 0.16 0.13	143 0.49, df 007) ICC <u>Total</u> 30 66 41 41	⁷ = 9 (P < <u>Mean</u> 1.51 0.82 0.83 0.96	 0.0000 pd-HC0 SD 0.11 0.57 0.11 0.1 	211 11); I ² = Total 18 25 23 23	100.0% 94% Weight 9.7% 10.5% 10.3% 10.1%	1.59 [0.44, 2.74] Std. Mean Difference <u>V, Random, 95% Cl</u> -1.74 [-2.43, -1.06] 0.07 [-0.39, 0.53] 0.89 [0.36, 1.43] 1.40 [0.83, 1.97] 1.96 [1.34, 2.58]	Favours [experimental] Favours [control] Std. Mean Difference
Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Wei Y2019 Woi S2014	= 3.13; CI : Z = 2.71 0.81 0.91 0.96 1.13 1.23 1.15	hi ² = 14((P = 0.0 md-F <u>SD</u> 0.49 1.44 0.16 0.13 0.09	143 0.49, df 007) ICC Total 30 66 41 41 41	[•] = 9 (P • <u>Mean</u> 1.51 0.82 0.83 0.96 1.07	 0.0000 pd-HC0 SD 0.11 0.57 0.11 0.1 0.16 	211 11); I ² = Total 18 25 23 23 23 23	100.0% 94% 9.7% 10.5% 10.3% 10.1% 9.9% 9.5%	1.59 [0.44, 2.74] Std. Mean Difference <u>IV, Random, 95% CI</u> -1.74 [-2.43, -1.06] 0.07 [-0.39, 0.53] 0.89 [0.36, 1.43] 1.40 [0.83, 1.97] 1.96 [1.34, 2.58] 0.98 [0.25, 1.70]	Favours [experimental] Favours [control] Std. Mean Difference
Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Wei Y2019 Woi S2014 Wu B2020	= 3.13; CI : Z = 2.71 0.81 0.91 0.96 1.13 1.23 1.15 0.92	mi ² = 14((P = 0.0 0.49 1.44 0.16 0.13 0.09 0.13 0.26	143 0.49, df 007) ICC Total 30 66 41 41 41 20	⁷ = 9 (P < <u>Mean</u> 1.51 0.82 0.83 0.96 1.07 1.02 0.79	 0.0000 pd-HC0 SD 0.11 0.57 0.11 0.11 0.06 0.13 0.2 	211 11); ² = Total 18 25 23 23 23 23 14 28	100.0% 94% 9.7% 10.5% 10.3% 10.1% 9.9% 9.5% 10.3%	1.59 [0.44, 2.74] Std. Mean Difference <u>IV, Random, 95% Cl</u> -1.74 [-2.43, -1.06] 0.07 [-0.39, 0.53] 0.89 [0.36, 1.43] 1.40 [0.83, 1.97] 1.96 [1.34, 2.58] 0.98 [0.25, 1.70] 0.55 [0.03, 1.08]	Favours [experimental] Favours [control] Std. Mean Difference
Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Nei Y2019 Nei Y2019 Nei Y2019 Nei S2014 Nu B2020 Zhou Y2021	= 3.13; C : Z = 2.71 0.81 0.91 0.96 1.13 1.15 0.92 0.88	mi ² = 14((P = 0.0 0.49 1.44 0.16 0.13 0.09 0.13 0.26 0.16	143 0.49, df 007) ICC Total 30 66 41 41 41 20 30 46	Mean 1.51 0.82 0.83 0.96 1.07 1.02 0.79 0.76	 0.00000 pd-HC0 SD 0.11 0.11 0.11 0.11 0.13 0.2 0.18 	211)1); ² = Total 18 25 23 23 23 14 28 9	100.0% 94% 97% 9.7% 10.5% 10.3% 9.9% 9.5%	1.59 [0.44, 2.74] Std. Mean Difference <u>IV. Random, 95% Cl</u> -1.74 [-2.43, -1.06] 0.07 [-0.39, 0.53] 0.89 [0.36, 1.43] 1.40 [0.83, 1.97] 1.96 [1.34, 2.58] 0.98 [0.25, 1.70] 0.55 [0.03, 1.08] 0.72 [-0.00, 1.45]	Favours [experimental] Favours [control] Std. Mean Difference
Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: Stana Q2016 Shan QG2017 Nei Y 2019 Nei Y 2019 Nei Y2019 Noo S2014 Mu B2020 Zhou Y2021 Zhou SC 2018	= 3.13; C : Z = 2.71 0.81 0.91 0.96 1.13 1.15 0.92 0.88 0.91	mi ² = 14((P = 0.0 0.49 0.44 0.16 0.13 0.09 0.13 0.26 0.16 0.151	143 0.49, df 007) ICC Total 30 66 41 41 41 20 30 46 24	Mean 1.51 0.82 0.83 0.96 1.07 1.02 0.79 0.76 0.775	 0.00000 pd-HC0 SD 0.11 0.11 0.11 0.11 0.13 0.2 0.18 0.187 	211 11); ² = Total 18 25 23 23 23 14 28 9 24	100.0% 94% 97% 9.7% 10.5% 10.3% 9.9% 9.5% 10.3% 9.5% 10.3%	1.59 [0.44, 2.74] Std. Mean Difference <u>IV, Random, 95% Cl</u> -1.74 [-2.43, -1.06] 0.07 [-0.39, 0.53] 0.89 [0.36, 1.43] 1.40 [0.83, 1.97] 1.96 [1.34, 2.58] 0.98 [0.25, 1.70] 0.55 [0.03, 1.08] 0.72 [-0.00, 1.45] 0.78 [0.19, 1.37]	Favours [experimental] Favours [control] Std. Mean Difference
Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: Stana Q2016 Shan QG2017 Nei Y 2019 Nei Y 2019 Nei Y2019 Noo S2014 Mu B2020 Zhou Y2021 Zhou SC 2018	= 3.13; C : Z = 2.71 0.81 0.91 0.96 1.13 1.15 0.92 0.88 0.91	mi ² = 14((P = 0.0 0.49 1.44 0.16 0.13 0.09 0.13 0.26 0.16	143 0.49, df 007) ICC Total 30 66 41 41 41 20 30 46 24	Mean 1.51 0.82 0.83 0.96 1.07 1.02 0.79 0.76	 0.00000 pd-HC0 SD 0.11 0.11 0.11 0.11 0.13 0.2 0.18 0.187 	211)1); ² = Total 18 25 23 23 23 14 28 9	100.0% 94% 97% 9.7% 10.5% 10.3% 9.9% 9.5%	1.59 [0.44, 2.74] Std. Mean Difference <u>IV. Random, 95% Cl</u> -1.74 [-2.43, -1.06] 0.07 [-0.39, 0.53] 0.89 [0.36, 1.43] 1.40 [0.83, 1.97] 1.96 [1.34, 2.58] 0.98 [0.25, 1.70] 0.55 [0.03, 1.08] 0.72 [-0.00, 1.45]	Favours [experimental] Favours [control] Std. Mean Difference
Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 Zhu SC 2018 Zhu SC 2018	= 3.13; C : Z = 2.71 0.81 0.91 0.96 1.13 1.15 0.92 0.88 0.91	mi ² = 14((P = 0.0 0.49 0.44 0.16 0.13 0.09 0.13 0.26 0.16 0.151	143 0.49, df 007) HCC Total 30 66 41 41 41 20 30 46 24 24 24	Mean 1.51 0.82 0.83 0.96 1.07 1.02 0.79 0.76 0.775	 0.00000 pd-HC0 SD 0.11 0.11 0.11 0.11 0.13 0.2 0.18 0.187 	211)1); ² = Total 18 25 23 23 23 14 28 9 24 24	100.0% 94% 9.7% 10.5% 10.3% 9.5% 10.3% 9.5% 10.3% 9.5% 10.1%	1.59 [0.44, 2.74] Std. Mean Difference <u>V. Random, 95% CI</u> -1.74 [-2.43, -1.06] 0.07 [-0.39, 0.53] 0.89 [0.36, 1.43] 1.40 [0.83, 1.97] 1.96 [1.34, 2.58] 0.98 [0.25, 1.70] 0.55 [0.03, 1.08] 0.72 [-0.00, 1.45] 0.78 [0.19, 1.37] 0.81 [0.22, 1.40]	Favours [experimental] Favours [control] Std. Mean Difference
Fotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Stanata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Wei Y2019 Woo S2014 Mu B2020 Zhou Y2021 Zhu SC 2018 Total (95% CI)	= 3.13; C : Z = 2.71 0.81 0.91 0.91 1.13 1.23 1.15 0.92 0.88 0.91 0.91	hi ² = 14((P = 0.(md-F SD 0.49 1.44 0.16 0.13 0.09 0.13 0.26 0.16 0.151 0.148	143 0.49, df 007) ICC Total 30 66 41 41 41 20 30 46 24 24 24 363	Mean 1.51 0.82 0.83 0.96 1.07 1.02 0.79 0.76 0.775 0.771	 0.00000 pd-HC0 SD 0.11 0.57 0.11 0.16 0.13 0.2 0.18 0.187 0.187 	211 11); ² = Total 18 25 23 23 23 23 14 28 9 24 24 211	100.0% 94% 9.7% 10.5% 10.3% 9.5% 10.3% 9.5% 10.3% 9.5% 10.1% 10.1% 10.1% 100.0%	1.59 [0.44, 2.74] Std. Mean Difference <u>IV, Random, 95% Cl</u> -1.74 [-2.43, -1.06] 0.07 [-0.39, 0.53] 0.89 [0.36, 1.43] 1.40 [0.83, 1.97] 1.96 [1.34, 2.58] 0.98 [0.25, 1.70] 0.55 [0.03, 1.08] 0.72 [-0.00, 1.45] 0.78 [0.19, 1.37]	Favours [experimental] Favours [control] Std. Mean Difference
Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Wei Y2019 Wei Y2019 Woi S2014 Wu B2020 Zhou S2014 Zhu SC 2018 Zhu SC 2018 Fotal (95% CI) Heterogeneity: Tau ² =	= 3.13; C : Z = 2.71 0.81 0.91 0.96 1.13 1.23 1.15 0.92 0.88 0.91 0.91 = 0.70; C	$hi^2 = 14($ (P = 0.0 md-F SD 0.49 1.44 0.16 0.16 0.13 0.26 0.16 0.151 0.148 $hi^2 = 78.$	143 0.49, df 007) HCC Total 30 66 41 41 41 20 30 46 24 24 24 363 56, df=	Mean 1.51 0.82 0.83 0.96 1.07 1.02 0.79 0.76 0.775 0.771	 0.00000 pd-HC0 SD 0.11 0.57 0.11 0.16 0.13 0.2 0.18 0.187 0.187 	211 11); ² = Total 18 25 23 23 23 23 14 28 9 24 24 211	100.0% 94% 9.7% 10.5% 10.3% 9.5% 10.3% 9.5% 10.3% 9.5% 10.1% 10.1% 10.1% 100.0%	1.59 [0.44, 2.74] Std. Mean Difference <u>V. Random, 95% CI</u> -1.74 [-2.43, -1.06] 0.07 [-0.39, 0.53] 0.89 [0.36, 1.43] 1.40 [0.83, 1.97] 1.96 [1.34, 2.58] 0.98 [0.25, 1.70] 0.55 [0.03, 1.08] 0.72 [-0.00, 1.45] 0.78 [0.19, 1.37] 0.81 [0.22, 1.40]	Favours [experimental] Favours [control] Std. Mean Difference
Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Wei Y2019 Wei Y2019 Woi S2014 Wu B2020 Zhou S2014 Zhu SC 2018 Zhu SC 2018 Fotal (95% CI) Heterogeneity: Tau ² =	= 3.13; C : Z = 2.71 0.81 0.91 0.96 1.13 1.23 1.15 0.92 0.88 0.91 0.91 = 0.70; C	$hi^2 = 14($ (P = 0.0 md-F SD 0.49 1.44 0.16 0.16 0.13 0.26 0.16 0.151 0.148 $hi^2 = 78.$	143 0.49, df 007) HCC Total 30 66 41 41 41 20 30 46 24 24 24 363 56, df=	[•] = 9 (P • <u>Mean</u> 1.51 0.82 0.83 0.96 1.07 1.02 0.79 0.76 0.775 0.771	 0.00000 pd-HC0 SD 0.11 0.57 0.11 0.16 0.13 0.2 0.18 0.187 0.187 	211 11); ² = Total 18 25 23 23 23 23 14 28 9 24 24 211	100.0% 94% 9.7% 10.5% 10.3% 9.5% 10.3% 9.5% 10.3% 9.5% 10.1% 10.1% 10.1% 100.0%	1.59 [0.44, 2.74] Std. Mean Difference <u>V. Random, 95% CI</u> -1.74 [-2.43, -1.06] 0.07 [-0.39, 0.53] 0.89 [0.36, 1.43] 1.40 [0.83, 1.97] 1.96 [1.34, 2.58] 0.98 [0.25, 1.70] 0.55 [0.03, 1.08] 0.72 [-0.00, 1.45] 0.78 [0.19, 1.37] 0.81 [0.22, 1.40]	Favours [experimental] Favours [control]
Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Wei Y2019 Wei Y2019 Woi S2014 Wu B2020 Zhou S2014 Zhu SC 2018 Zhu SC 2018 Fotal (95% CI) Heterogeneity: Tau ² =	= 3.13; C : Z = 2.71 0.81 0.91 0.96 1.13 1.23 1.15 0.92 0.88 0.91 0.91 = 0.70; C	$hi^2 = 14($ (P = 0.0 md-F SD 0.49 1.44 0.16 0.16 0.13 0.26 0.16 0.151 0.148 $hi^2 = 78.$	143 0.49, df 007) HCC Total 30 66 41 41 41 20 30 46 24 24 24 363 56, df=	[•] = 9 (P • <u>Mean</u> 1.51 0.82 0.83 0.96 1.07 1.02 0.79 0.76 0.775 0.771	 0.00000 pd-HC0 SD 0.11 0.57 0.11 0.16 0.13 0.2 0.18 0.187 0.187 	211 11); ² = Total 18 25 23 23 23 23 14 28 9 24 24 211	100.0% 94% 9.7% 10.5% 10.3% 9.5% 10.3% 9.5% 10.3% 9.5% 10.1% 10.1% 10.1% 100.0%	1.59 [0.44, 2.74] Std. Mean Difference <u>V. Random, 95% CI</u> -1.74 [-2.43, -1.06] 0.07 [-0.39, 0.53] 0.89 [0.36, 1.43] 1.40 [0.83, 1.97] 1.96 [1.34, 2.58] 0.98 [0.25, 1.70] 0.55 [0.03, 1.08] 0.72 [-0.00, 1.45] 0.78 [0.19, 1.37] 0.81 [0.22, 1.40]	Favours [experimental] Favours [control]
Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Wei Y2019 Wei Y2019 Woi S2014 Wu B2020 Zhou S2014 Zhu SC 2018 Zhu SC 2018 Fotal (95% CI) Heterogeneity: Tau ² =	= 3.13; C : Z = 2.71 0.81 0.96 1.13 1.23 1.15 0.92 0.88 0.91 0.91 = 0.70; C : Z = 2.30	$hi^2 = 14($ (P = 0.0 md-F SD 0.49 1.44 0.16 0.16 0.13 0.26 0.16 0.151 0.148 $hi^2 = 78.$	143 0.49, df 007) HCC Total 30 66 41 41 41 20 30 46 24 24 24 363 56, df=	Mean 1.51 0.82 0.83 0.96 1.07 1.02 0.79 0.76 0.771 9 (P <	 0.00000 pd-HC0 SD 0.11 0.57 0.11 0.16 0.13 0.2 0.18 0.187 0.187 	211 11); ² = Total 18 25 23 23 23 23 14 28 9 24 24 211	100.0% 94% 9.7% 10.5% 10.1% 9.5% 10.1% 9.5% 10.3% 9.5% 10.1% 10.1% 10.1%	1.59 [0.44, 2.74] Std. Mean Difference <u>V. Random, 95% CI</u> -1.74 [-2.43, -1.06] 0.07 [-0.39, 0.53] 0.89 [0.36, 1.43] 1.40 [0.83, 1.97] 1.96 [1.34, 2.58] 0.98 [0.25, 1.70] 0.55 [0.03, 1.08] 0.72 [-0.00, 1.45] 0.78 [0.19, 1.37] 0.81 [0.22, 1.40]	Favours [experimental] Favours [control]
Fotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Wei Y2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 Zhu SC 2018 Zhu SC 2018 Fotal (95% CI) Heterogeneity: Tau ² = Test for overall effect:	= 3.13; C : Z = 2.71 0.81 0.91 0.91 1.13 1.23 1.15 0.92 0.88 0.91 0.91 = 0.70; C : Z = 2.30	$hi^2 = 14($ (P = 0.0) 0.49 1.44 0.16 0.13 0.26 0.151 0.148 $hi^2 = 78.$ (P = 0.0) MVI(-)	143 0.49, df 1007) 10CC <u>Total</u> 30 66 41 41 41 41 20 30 46 24 24 363 556, df= 02)	= 9 (P ≪ 1.51 0.82 0.83 0.96 1.07 1.02 0.79 0.76 0.775 0.771 = 9 (P ≪	 0.00000 pd-HC0 SD 0.11 0.17 0.11 0.16 0.13 0.2 0.18 0.187 0.00001 	211)1); F = C Total 18 25 23 23 23 14 28 9 24 24 211); F = 8	100.0% 94% 9.7% 10.5% 10.3% 9.5% 10.1% 10.1% 10.1% 10.1% 10.1% 39%	1.59 [0.44, 2.74] Std. Mean Difference <u>IV. Random, 95% CI</u> -1.74 [-2.43, -1.06] 0.07 [-0.39, 0.53] 0.89 [0.36, 1.43] 1.40 [0.83, 1.97] 1.96 [1.34, 2.58] 0.98 [0.25, 1.70] 0.55 [0.03, 1.08] 0.72 [-0.00, 1.45] 0.78 [0.19, 1.37] 0.81 [0.22, 1.40] 0.65 [0.09, 1.20]	Favours [experimental] Favours [control]
Fotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Wei Y2019 Wei Y2019 Woo S2014 Wu B2020 Zhou SC2018 Zhu SC2018 Fotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup	= 3.13; C : Z = 2.71 0.81 0.91 0.91 1.13 1.23 1.15 0.92 0.88 0.91 0.91 = 0.70; C : Z = 2.30	$hi^2 = 14($ (P = 0.0) (P = 0.0) 0.49 1.44 0.16 0.13 0.26 0.16 0.151 0.148 $hi^2 = 78.0$ (P = 0.0) VV(-) SD	143 0.49, df 1007) ICC Total 30 66 41 41 41 41 20 30 46 24 24 24 24 56, df= 02)	= 9 (P < <u>Mean</u> 1.51 0.82 0.83 0.96 1.07 1.02 0.79 0.76 0.775 0.771 = 9 (P < <u>Mean</u>	 O.00000 pd-HC0 SD 0.11 0.57 0.11 0.16 0.13 0.2 0.18 0.187 0.187 0.187 0.00001 VI(+) SD T 	211)1); ² = C Total 18 25 23 23 23 14 28 9 24 24 24 24 24 211); ² = €	100.0% 94% 9.7% 10.5% 10.3% 9.5% 10.3% 9.5% 10.1% 10.1% 10.1% 100.0% 19%	1.59 [0.44, 2.74] Std. Mean Difference <u>IV, Random, 95% CI</u> -1.74 [-2.43, -1.06] 0.07 [-0.39, 0.53] 0.89 [0.36, 1.43] 1.40 [0.83, 1.97] 1.96 [1.34, 2.58] 0.98 [0.25, 1.70] 0.55 [0.03, 1.08] 0.72 [-0.00, 1.45] 0.78 [0.19, 1.37] 0.81 [0.22, 1.40] 0.65 [0.09, 1.20] td. Mean Difference IV, Fixed, 95% CI	Favours [experimental] Favours [control] Std. Mean Difference IV. Random, 95% CI
Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: Granata V2016 Shan QG2017 Nei Y 2019 Nei Y2019 Nei Y2019 Noo S2014 Nu S2020 Zhou Y2021 Zhu SC 2018 Total (95% CI) Heterogeneity: Tau ² = Fest for overall effect: Study or Subgroup Chen J2021	= 3.13; C : Z = 2.71 0.81 0.91 0.96 1.13 1.23 1.15 0.92 0.88 0.91 0.91 = 0.70; C : Z = 2.30 I Mean 1.03	$hi^2 = 14($ (P = 0.0 0.49 1.44 0.16 0.13 0.26 0.16 0.151 0.148 $hi^2 = 78.$ (P = 0.0 VIVI(-) SD 0.13	143 0.49, dt 007) 4CC Total 30 66 66 64 41 41 41 41 41 20 30 30 46 24 24 363 55, df= 502) Total 33	⁷ = 9 (P ≤ 1.51 0.82 0.83 0.96 1.07 1.02 0.79 0.76 0.775 0.771 = 9 (P ≤ M Mean 0.84	 O.00000 pd-HC0 0.11 0.57 0.11 0.16 0.13 0.2 0.18 0.187 0.187 0.187 0.00001 VI(+) SD I 0.11 	211)1); ² = Total 18 23 23 23 23 23 23 14 28 9 24 24 24 211); ² = € (otal 1)	100.0% 94% 97% 10.5% 10.3% 10.1% 9.9% 9.5% 10.3% 10.1% 10.1% 10.1% 10.1% 100.0% 39% S Meight 19.7%	1.59 [0.44, 2.74] Std. Mean Difference <u>IV. Random, 95% CI</u> -1.74 [-2.43, -1.06] 0.07 [-0.39, 0.53] 0.89 [0.36, 1.43] 1.40 [0.83, 1.97] 1.96 [1.34, 2.58] 0.98 [0.25, 1.70] 0.55 [0.03, 1.08] 0.72 [-0.00, 1.45] 0.78 [0.19, 1.37] 0.81 [0.22, 1.40] 0.65 [0.09, 1.20] td. Mean Difference <u>IV. Fixed, 95% CI</u> 1.55 [0.98, 2.12]	Favours [experimental] Favours [control] Std. Mean Difference IV, Random, 95% CI
Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Nei Y2019 Nei Y2019 Nei Y2019 Noo S2014 Nu B2020 Zhou Y2021 Zhou Y2021 Zhou SC 2018 Fotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Chen J2021 Li H2018	= 3.13; C : Z = 2.71 0.81 0.96 1.13 1.23 1.15 0.92 0.88 0.91 0.91 : Z = 2.30 Mean 1.03 0.98	$hi^2 = 14($ (P = 0.0) (P = 0.0) 0.49 0.13 0.26 0.16 0.151 0.148 $hi^2 = 78.0$ (P = 0.0) MVI(-) SD 0.13 0.28	143 0.49, dt 007) 4CC Total 30 66 41 41 41 41 20 30 30 46 24 24 24 363 56, df= 22) Total 33 20	² = 9 (P ≤ 1.51 0.82 0.83 0.96 1.07 1.02 0.79 0.76 0.775 0.771 = 9 (P ≤ M Mean 0.84 0.79	 0.00000 pd-HC0 SD 0.11 0.57 0.11 0.13 0.2 0.187 0.187 0.000011 VI(+) SD T 0.11 0.13 	211)1); ² = Total 18 25 23 23 23 23 23 23 14 28 9 24 24 24 211); ² = € (³) (100.0% 94% 94% 9.7% 10.5% 10.3% 9.5% 10.3% 9.5% 10.1% 10.1% 10.1% 10.1% 100.0% 95% S <u>Weight</u> 19.7% 15.3%	1.59 [0.44, 2.74] Std. Mean Difference <u>IV, Random, 95% CI</u> -1.74 [-2.43, -1.06] 0.07 [-0.39, 0.53] 0.89 [0.36, 1.43] 1.40 [0.83, 1.97] 1.96 [1.34, 2.58] 0.98 [0.25, 1.70] 0.55 [0.03, 1.08] 0.72 [-0.00, 1.45] 0.78 [0.19, 1.37] 0.81 [0.22, 1.40] 0.65 [0.09, 1.20] td. Mean Difference <u>IV, Fixed, 95% CI</u> 1.55 [0.98, 2.12] 0.86 [0.22, 1.50]	Favours [experimental] Favours [control] Std. Mean Difference IV. Random, 95% CI
Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Wei Y2019 Wo S2014 Wu B2020 Zhou Y2021 Zhou Y2021 Zhou SC 2018 Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: Study or Subgroup Chen J2021 Li H2018 Wei Y2019	= 3.13; CI : Z = 2.71 0.81 0.96 1.13 1.23 1.15 0.92 0.88 0.91 0.91 = 0.70; CI : Z = 2.30 I Mean 1.03 0.98 1.07	$hi^2 = 14($ (P = 0.0) (P = 0.0) 0.49 1.44 0.16 0.13 0.26 0.151 0.151 0.148 $hi^2 = 78.$ (P = 0.0) I(P =	143 0.49, df 007) 4CC Total 30 66 41 41 41 41 41 41 41 46 24 24 363 56, df 22) 702) 702 80 80	² = 9 (P < <u>Mean</u> 1.51 0.82 0.83 0.96 1.07 1.02 0.79 0.76 0.775 0.771 = 9 (P < <u>Mean</u> 0.84 0.79 0.77	 * 0.00000 pd-HC(SD 0.11 0.17 0.13 0.187 0.000001 SD T 0.13 0.13 0.16 	211)1); ² = Total 18 25 23 23 23 23 23 23 23 23 23 23	100.0% 94% 94% 9.7% 10.3% 10.3% 9.5% 10.1% 9.5% 10.1% 10.1% 10.1% 10.1% 10.1% 10.1% 10.3% 47.2%	1.59 [0.44, 2.74] Std. Mean Difference <u>IV. Random, 95% Cl</u> -1.74 [-2.43, -1.06] 0.07 [-0.39, 0.53] 0.89 [0.36, 1.43] 1.40 [0.83, 1.97] 1.96 [1.34, 2.58] 0.98 [0.25, 1.70] 0.55 [0.03, 1.08] 0.72 [-0.00, 1.45] 0.78 [0.19, 1.37] 0.81 [0.22, 1.40] 0.65 [0.09, 1.20] td. Mean Difference <u>IV. Fixed, 95% Cl</u> 1.55 [0.98, 2.12] 0.86 [0.22, 1.50] 1.06 [0.69, 1.43]	Favours [experimental] Favours [control] Std. Mean Difference IV. Random, 95% CI
Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: Study or Subgroup Sranata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Wei Y2019 Wos S2014 Wu B2020 Zhou Y2021 Zhou Y2021 Zhou SC2018 Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: Study or Subgroup Chen J2021 Li H2018 Wei Y2019	= 3.13; CI : Z = 2.71 0.81 0.96 1.13 1.23 1.15 0.92 0.88 0.91 0.91 = 0.70; CI : Z = 2.30 I Mean 1.03 0.98 1.07	$hi^2 = 14($ (P = 0.0) (P = 0.0) 0.49 0.13 0.26 0.16 0.151 0.148 $hi^2 = 78.0$ (P = 0.0) MVI(-) SD 0.13 0.28	143 0.49, dt 007) 4CC Total 30 66 41 41 41 41 20 30 30 46 24 24 24 363 56, df= 22) Total 33 20	² = 9 (P ≤ 1.51 0.82 0.83 0.96 1.07 1.02 0.79 0.76 0.775 0.771 = 9 (P ≤ M Mean 0.84 0.79	 * 0.00000 pd-HC(SD 0.11 0.17 0.13 0.187 0.000001 SD T 0.13 0.13 0.16 	211)1); ² = Total 18 25 23 23 23 23 23 23 23 23 23 23	100.0% 94% 94% 9.7% 10.5% 10.3% 9.5% 10.3% 9.5% 10.1% 10.1% 10.1% 10.1% 100.0% 95% S <u>Weight</u> 19.7% 15.3%	1.59 [0.44, 2.74] Std. Mean Difference <u>IV, Random, 95% CI</u> -1.74 [-2.43, -1.06] 0.07 [-0.39, 0.53] 0.89 [0.36, 1.43] 1.40 [0.83, 1.97] 1.96 [1.34, 2.58] 0.98 [0.25, 1.70] 0.55 [0.03, 1.08] 0.72 [-0.00, 1.45] 0.78 [0.19, 1.37] 0.81 [0.22, 1.40] 0.65 [0.09, 1.20] td. Mean Difference <u>IV, Fixed, 95% CI</u> 1.55 [0.98, 2.12] 0.86 [0.22, 1.50]	Favours [experimental] Favours [control] Std. Mean Difference IV. Random, 95% CI
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Granata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 Zhu SC 2018 Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Chen J2021 Li H2018 Wei Y2019 Zhao W2018	= 3.13; CI : Z = 2.71 0.81 0.96 1.13 1.23 1.15 0.92 0.88 0.91 0.91 = 0.70; CI : Z = 2.30 I Mean 1.03 0.98 1.07	$hi^2 = 14($ (P = 0.0) (P = 0.0) 0.49 1.44 0.16 0.13 0.26 0.151 0.151 0.148 $hi^2 = 78.$ (P = 0.0) I(P =	143 0.49, df 1007) 1007 1007 1007 1007 1007 1007 100	² = 9 (P < <u>Mean</u> 1.51 0.82 0.83 0.96 1.07 1.02 0.79 0.76 0.775 0.771 = 9 (P < <u>Mean</u> 0.84 0.79 0.77	 * 0.00000 pd-HC(SD 0.11 0.17 0.13 0.187 0.000001 SD T 0.13 0.13 0.16 	211)1); ² = Total 18 25 23 23 23 14 28 9 24 24 211 (); ² = 8	100.0% 94% 97% 10.5% 10.3% 9.5% 10.1% 10.1% 10.1% 10.1% 10.1% 10.1% 10.1% 10.7% 10.3% 10.7% 15.3% 47.2%	1.59 [0.44, 2.74] Std. Mean Difference <u>IV. Random, 95% CI</u> -1.74 [-2.43, -1.06] 0.07 [-0.39, 0.53] 0.89 [0.36, 1.43] 1.40 [0.83, 1.97] 1.96 [1.34, 2.58] 0.98 [0.25, 1.70] 0.55 [0.03, 1.08] 0.72 [-0.00, 1.45] 0.78 [0.19, 1.37] 0.81 [0.22, 1.40] 0.65 [0.09, 1.20] 1.65 [0.09, 1.20] 1.55 [0.98, 2.12] 0.86 [0.22, 1.50] 1.06 [0.69, 1.43] 0.82 [0.22, 1.42]	Favours [experimental] Favours [control] Std. Mean Difference IV. Random, 95% CI
Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: Granata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Wei Y2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 Zhou SC 2018 Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: Grudy or Subgroup Chen J2021 Li H2018 Wei Y2019 Zhao W2018 Fotal (95% CI)	= 3.13; CI ; Z = 2.71 0.81 0.91 0.96 1.13 1.23 1.15 0.92 0.88 0.91 0.91 = 0.70; CI ; Z = 2.30 Mean 1.03 0.98 1.07 1.21	$hi^2 = 14($ (P = 0.0 0.49 1.44 0.16 0.13 0.26 0.16 0.151 0.148 $hi^2 = 78.$ (P = 0.0 VIVI(-) SD 0.13 0.28 0.34 0.29	143 0.49, df 1007) 1007 1007 1007 1007 100 100 100 100 100	= 9 (P < <u>Mean</u> 1.51 0.82 0.83 0.96 1.07 1.02 0.79 0.76 0.775 0.771 = 9 (P < <u>Mean</u> 0.84 0.79 0.77 0.99	 0.00000 pd-HC0 SD 0.11 0.57 0.11 0.16 0.2 0.187 0.187 	211)1); ² = Total 18 25 23 23 23 14 28 9 24 24 211 (); ² = 8	100.0% 94% 94% 9.7% 10.3% 10.3% 9.5% 10.1% 9.5% 10.1% 10.1% 10.1% 10.1% 10.1% 10.1% 10.3% 47.2%	1.59 [0.44, 2.74] Std. Mean Difference <u>IV. Random, 95% Cl</u> -1.74 [-2.43, -1.06] 0.07 [-0.39, 0.53] 0.89 [0.36, 1.43] 1.40 [0.83, 1.97] 1.96 [1.34, 2.58] 0.98 [0.25, 1.70] 0.55 [0.03, 1.08] 0.72 [-0.00, 1.45] 0.78 [0.19, 1.37] 0.81 [0.22, 1.40] 0.65 [0.09, 1.20] td. Mean Difference <u>IV. Fixed, 95% Cl</u> 1.55 [0.98, 2.12] 0.86 [0.22, 1.50] 1.06 [0.69, 1.43]	Favours [experimental] Favours [control] Std. Mean Difference IV. Random, 95% CI
Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Wei Y2019 Wo S2014 Wu B2020 Zhou Y2021 Zhou Y2021 Zhou SC 2018 Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: Study or Subgroup Chen J2021 Li H2018 Wei Y2019	= 3.13; CI ; Z = 2.71 0.81 0.91 0.96 1.13 1.23 1.15 0.92 0.88 0.91 0.91 = 0.70; CI ; Z = 2.30 Mean 1.03 0.98 1.07 1.21	$hi^2 = 14($ (P = 0.0 0.49 1.44 0.16 0.13 0.26 0.16 0.151 0.148 $hi^2 = 78.$ (P = 0.0 VIVI(-) SD 0.13 0.28 0.34 0.29	143 0.49, df 1007) 1007 1007 1007 1007 100 100 100 100 100	= 9 (P < <u>Mean</u> 1.51 0.82 0.83 0.96 1.07 1.02 0.79 0.76 0.775 0.771 = 9 (P < <u>Mean</u> 0.84 0.79 0.77 0.99	 0.00000 pd-HC0 SD 0.11 0.57 0.11 0.16 0.2 0.187 0.187 	211)1); ² = Total 18 25 23 23 23 14 28 9 24 24 211 (); ² = 8	100.0% 94% 97% 10.5% 10.3% 9.5% 10.1% 10.1% 10.1% 10.1% 10.1% 10.1% 10.1% 10.7% 10.3% 10.7% 15.3% 47.2%	1.59 [0.44, 2.74] Std. Mean Difference <u>IV. Random, 95% CI</u> -1.74 [-2.43, -1.06] 0.07 [-0.39, 0.53] 0.89 [0.36, 1.43] 1.40 [0.83, 1.97] 1.96 [1.34, 2.58] 0.98 [0.25, 1.70] 0.55 [0.03, 1.08] 0.72 [-0.00, 1.45] 0.78 [0.19, 1.37] 0.81 [0.22, 1.40] 0.65 [0.09, 1.20] 1.65 [0.09, 1.20] 1.55 [0.98, 2.12] 0.86 [0.22, 1.50] 1.06 [0.69, 1.43] 0.82 [0.22, 1.42]	Favours [experimental] Favours [control] Std. Mean Difference IV. Random, 95% CI

FIGURE 5 | (A) Forest plot of the D values between wdHCC and mdHCC. The SMD indicated that the D values of mdHCC were significantly lower than those of wdHCC. (B) Forest plot of the D values between wdHCC and pdHCC. The SMD indicated that the D values of pdHCC were significantly lower than those of wdHCC. (C) Forest plot of the D values between mdHCC and pdHCC. The SMD indicated that the D values of pdHCC were significantly lower than those of mdHCC. (D) Forest plot of the D values between MVI- HCC and MVI+ HCC. The SMD indicated that the D values of pdHCC were significantly lower than those of mdHCC. (D) Forest plot of the D values between MVI- HCC and MVI+ HCC. The SMD indicated that the D values of MVI+ HCC were significantly lower than those of MVI- HCC, well differentiated hepatocellular carcinoma; pd-HCC, poorly differentiated hepatocellular carcinoma; MVI, microvascular invasion; SMD, standardized mean difference.

		vd-HCC			md-H(Std. Mean Difference	Std. Mean Difference
tudy or Subgroup	Mean		Total	Mean			Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl
Franata V2016		83.62	14		70.15	30	11.6%	0.13 [-0.50, 0.77]	
lhan QG2017		21.96	18		64.14	66	17.2%	-0.09 [-0.62, 0.43]	
Vei Y 2019		10.98	15		10.23	41	13.1%	0.40 [-0.20, 1.00]	—
Vei Y20 19	18.21	9.21	15	18.54	9.62	41	13.4%	-0.03 [-0.63, 0.56]	
Vei Y2019		12.74	15	18.62		41	13.3%	0.21 [-0.38, 0.80]	
Voo S2014	34.7	21	4	38.8	15	20	4.0%	-0.25 [-1.32, 0.83]	
Vu B2020	134.32		19	120.72		30	14.0%	0.28 [-0.29, 0.86]	
hou Y2021	32.87	14.7	15	41.68	17.9	46	13.4%	-0.51 [-1.10, 0.08]	
otal (95% CI)			115			315	100.0%	0.04 [-0.18, 0.25]	• • •
leterogeneity: Chi ² =	•			²= 0%				-	-4 -2 0 2 4
est for overall effect:	Z = 0.33	(P = 0.7	4)						Favours [experimental] Favours [control]
								Std Maan Difference	Std Mean Difference
tudy or Subgroup	Mean	vd-HCC	Total	Mean	pd -HCC	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Std. Mean Difference IV, Fixed, 95% Cl
Franata V2016		83.62	101a1	13.7	7.39				
		83.62 21.96			221.49	18			
ihan QG2017 Vei Y 2019		21.96	18 15	128.1	12.73	25 23			
ver 1 2019 Vei Y20 19	18.21	9.21	15	14.39	7.73	23			
Vei Y2019		9.21	15	14.39	11.66	23			
Voo S2014	34.7	21	4	30.7	18.4	14			
Vu B2020	134.32			114.24	49.18	28			
hou Y2021	32.87	14.7	15	34.54	18.6	20	8.8%		
otal (95% Cl) leterogeneity: Chi ² = est for overall effect:		•		l² = 37%		163	100.0%	0.23 [-0.01, 0.48]	-4 -2 0 2 4 Favours [experimental] Favours [control]
		md-H	CC		pd -HCC			Std. Mean Difference	Std. Mean Difference
tudy or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
≽ranata V2016	44.49	70.15	30	13.7	7.39	18	12.0%	0.54 [-0.05, 1.14]	
Shan QG2017		64.14	66	128.1	221.49	25			
Vei Y 2019	17.99	10.23	41	16.5	12.73	23			
Vei Y20 19	18.54	9.62	41	14.39	7.73	23	13.3%	0.46 [-0.06, 0.97]	
Vei Y2019	18.62		41	16.19	11.66	23			
/oo S2014	38.8	15	20	30.7	18.4	14			+-
Vu B2020	120.72			114.24	49.18	28			
hou Y2021	41.68	17.9	46	34.54	18.6	9	10.2%	0.39 [-0.33, 1.11]	T=
otal (95% CI)			315				100.0%	0.17 [-0.16, 0.50]	· · · • · · ·
leterogeneity: Tau² =				7 (P = 0.0	006); I ² =	65%		,	-4 -2 0 2 4
est for overall effect:	2=1.021	(P = 0.3	1)						Favours [experimental] Favours [control]
		MVI(-)		м	VI(+)		S	td. Mean Difference	Std. Mean Difference
tudy or Subgroup	Mean	SD	Total	Mean	SD T	otal N	Neight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl
i H2018	68	38	20	64	34	21	19.0%	0.11 [-0.50, 0.72]	
Vei Y2019	17.88	12.68	80	14.38	11.4	55	59.9%	0.29 [-0.06, 0.63]	+=-
V6112013	58.99		33	45.59	21.68	18	21.1%	0.42 [-0.16, 1.00]	+
								0.00 10.04 0.551	
hao W2018			133			94 '	1000	0.28 0.01 0.551	
(hao W2018 (otal (95% Cl) leterogeneity: Chi ² =	0.64 .44	- 2 (P -	133	IZ - 00%		94 '	100.0%	0.28 [0.01, 0.55]	

FIGURE 6 | (A–C) Forest plot of the D* values distinguished wdHCC, mdHCC, and pdHCC. The SMDs indicated that there was no significant difference for grades in HCC. (D) Forest plot of the D* values between MVI- HCC and MVI+ HCC. The SMD indicated that MVI+ HCC had significantly lower D* values than MVI- HCC. wd-HCC, well differentiated hepatocellular carcinoma; md-HCC, moderately differentiated hepatocellular carcinoma; pd-HCC, poorly differentiated hepatocellular carcinoma; MVI, microvascular invasion; SMD, standardized mean difference.

the AUCs of the parameters are listed in **Table 2**. The AUCs of the MK, D value, ADCmean, and ADCmin for preoperative prediction of pdHCC were 0.89 (95% CI: 0.86–0.91), 0.89 (95% CI: 0.86–0.92), 0.86 (95% CI: 0.83–0.89), and 0.81 (95% CI: 0.78–0.84), respectively,

as shown in **Figures 10A–D**. Deek's test suggested no publication bias (P = 0.298, P = 0.473, P = 0.684, P = 0.093). Similarly, the AUCs of the D and ADCmean for preoperative prediction of wdHCC were 0.92 (95% CI: 0.89–0.94) and 0.90 (95% CI: 0.87–

۱.		vd -HCC			md-H	CC		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean			Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Granata V2016	14.48	7.38	14	31.49	17.6	30	12.3%	-1.10 [-1.78, -0.42]	
Shan QG2017		20.35			66.28	66	13.7%	-0.09 [-0.61, 0.43]	
Wei Y 2019	33	12	15	30	13	41	13.1%	0.23 [-0.36, 0.83]	
Wei Y20 19	33	10	15	29	13	41	13.1%	0.32 [-0.27, 0.92]	
Wei Y2019	33	12	15	30	11	41	13.1%	0.26 [-0.33, 0.86]	
Woo S2014	19.9	3.7	4	24.1	12.1	20	8.9%	-0.36 [-1.44, 0.72]	
								and the second descent and the second s	
Wu B2020	37.13	9.13	19	26.35	6.24	30	12.6%	1.42 [0.77, 2.06]	
Zhou Y2021	22	7	15	23	8	46	13.2%	-0.13 [-0.71, 0.46]	-
Total (95% CI)			115				100.0%	0.09 [-0.38, 0.56]	• • • • • • • •
Heterogeneity: Tau ² =	= 0.35; C	hi² = 30.	84, df =	= 7 (P <	0.0001)	$ ^2 = 77$	°%	-	
Test for overall effect:	: Z = 0.37	(P = 0.7	71)						Favours [experimental] Favours [control]
3									
,	V	vd-HCC			pd -HCC			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean		Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Granata V2016	14.48	7.38	14	54.08	2.96	18	8.1%	-7.22 [-9.24, -5.21] *	⊢
Shan QG2017	26	20.35	18	19.35	16.18	25	13.6%	0.36 [-0.25, 0.97]	+
Wei Y 2019	33	12	15	31	13	23	13.5%	0.16 [-0.50, 0.81]	- - -
Wei Y20 19	33	10	15	32	15		13.5%	0.07 [-0.58, 0.72]	- + -
Wei Y2019	33	12	15	33	14		13.5%	0.00 [-0.65, 0.65]	+
Woo S2014	19.9	3.7	4	21	12.2		11.7%	-0.09 [-1.21, 1.02]	
Wu B2020	37.13	9.13	19	23.69	7.79	28	13.4%	1.58 [0.91, 2.25]	
Zhou Y2021	22	5.15	15	18	7.75	20	12.8%	0.55 [-0.29, 1.40]	+
2.104 12021	22								
Total (95% CI)			115			163	100.0%	-0.24 [-1.10, 0.63]	
Total (95% Cl) Heterogeneity: Tau² =	= 1.34; Cl	ni² = 69.	115 86, df =			163	100.0%		4 -2 0 2 4
Total (95% CI)	= 1.34; Cl	ni² = 69.	115 86, df =			163	100.0%		-4 -2 0 2 4 Favours [experimental] Favours [control]
Total (95% Cl) Heterogeneity: Tau² =	= 1.34; Cl	ni² = 69. (P = 0.6	115 86, df = 59)		0.00001	163); I² = 9	100.0 % 10%	-0.24 [-1.10, 0.63]	Favours (experimental) Favours (control)
Total (95% CI) Heterogeneity: Tau² = Test for overall effect:	= 1.34; Cl : Z = 0.54	ni² = 69. (P = 0.9 md-H	115 86,df= 59) ICC	: 7 (P <	0.00001 pd-HC(163); I² = 9	100.0 %	-0.24 [-1.10, 0.63] -	Favours [experimental] Favours [control] Std. Mean Difference
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup	= 1.34; Cl : Z = 0.54 <u>Mean</u>	ni ² = 69. (P = 0.6 md-H SD	115 86, df = 59) ICC Total	:7 (P < Mean	0.00001 pd-HC0 SD	163); I² = 9 C Total	100.0% 10% Weight	-0.24 [-1.10, 0.63] - Std. Mean Difference IV, Random, 95% Cl	Favours (experimental) Favours (control)
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Granata V2016	= 1.34; Cl : Z = 0.54 <u>Mean</u> 31.49	ni ² = 69. (P = 0.5 md-H SD 17.6	115 86, df = 59) ICC <u>Total</u> 30	= 7 (P < <u>Mean</u> 54.08	0.00001 pd-HC0 <u>SD</u> 2.96	163); I ² = 9 <u>Total</u> 18	100.0% 00% <u>Weight</u> 11.4%	-0.24 [-1.10, 0.63] 	Favours [experimental] Favours [control] Std. Mean Difference
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Granata V2016 Shan QG2017	= 1.34; Cl : Z = 0.54 <u>Mean</u> 31.49 31.55	ni ² = 69. (P = 0.5 md-H SD 17.6 66.28	115 86, df = 59) ICC <u>Total</u> 30 66	= 7 (P < <u>Mean</u> 54.08 19.35	0.00001 pd-HC(SD 2.96 16.18	163); I ² = 9 <u>Total</u> 18 25	100.0% 00% Weight 11.4% 13.7%	-0.24 [-1.10, 0.63] Std. Mean Difference IV, Random, 95% CI -1.58 [-2.25, -0.91] 0.21 [-0.25, 0.67]	Favours [experimental] Favours [control] Std. Mean Difference
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y 2019	= 1.34; Cl : Z = 0.54 <u>Mean</u> 31.49 31.55 30	ni ² = 69. (P = 0.5 md-F SD 17.6 66.28 13	115 86, df = 59) ICC <u>Total</u> 30 66 41	• 7 (P < <u>Mean</u> 54.08 19.35 31	0.00001 pd-HC0 SD 2.96 16.18 13	163); I ² = 9 <u>Total</u> 18 25 23	100.0% 00% Weight 11.4% 13.7% 13.2%	-0.24 [-1.10, 0.63] Std. Mean Difference <u>IV, Random, 95% CI</u> -1.58 [-2.25, -0.91] 0.21 [-0.25, 0.67] -0.08 [-0.59, 0.43]	Favours [experimental] Favours [control] Std. Mean Difference
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y 2019 Wei Y20 19	= 1.34; Cl Z = 0.54 <u>Mean</u> 31.49 31.55 30 29	ni² = 69. (P = 0.5 md-F <u>SD</u> 17.6 66.28 13 13	115 86, df = 59) ICC <u>Total</u> 30 66	• 7 (P < <u>Mean</u> 54.08 19.35 31 32	0.00001 pd-HC0 <u>SD</u> 2.96 16.18 13 15	163); I ² = 9 <u>Total</u> 18 25	100.0% 00% Weight 11.4% 13.7% 13.2% 13.2%	-0.24 [-1.10, 0.63] Std. Mean Difference IV, Random, 95% CI -1.58 [-2.25, -0.91] 0.21 [-0.25, 0.67]	Favours [experimental] Favours [control] Std. Mean Difference
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y 2019	= 1.34; Cl : Z = 0.54 <u>Mean</u> 31.49 31.55 30	ni ² = 69. (P = 0.5 md-F SD 17.6 66.28 13	115 86, df = 59) ICC <u>Total</u> 30 66 41	• 7 (P < <u>Mean</u> 54.08 19.35 31	0.00001 pd-HC0 SD 2.96 16.18 13	163); I ² = 9 <u>Total</u> 18 25 23	100.0% 00% Weight 11.4% 13.7% 13.2%	-0.24 [-1.10, 0.63] Std. Mean Difference <u>IV, Random, 95% CI</u> -1.58 [-2.25, -0.91] 0.21 [-0.25, 0.67] -0.08 [-0.59, 0.43]	Favours [experimental] Favours [control] Std. Mean Difference
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y 2019 Wei Y20 19	= 1.34; Cl Z = 0.54 <u>Mean</u> 31.49 31.55 30 29	ni² = 69. (P = 0.5 md-F <u>SD</u> 17.6 66.28 13 13	115 86, df = 59) ICC <u>Total</u> 30 66 41 41	• 7 (P < <u>Mean</u> 54.08 19.35 31 32	0.00001 pd-HC0 <u>SD</u> 2.96 16.18 13 15	163); ² = 9 Total 18 25 23 23	100.0% 00% 11.4% 13.7% 13.2% 13.2% 13.2%	-0.24 [-1.10, 0.63] Std. Mean Difference <u>IV, Random, 95% Cl</u> -1.58 [-2.25, -0.91] 0.21 [-0.25, 0.67] -0.08 [-0.59, 0.43] -0.22 [-0.73, 0.30]	Favours [experimental] Favours [control] Std. Mean Difference
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y 2019 Wei Y2019 Wei Y2019	= 1.34; Cl Z = 0.54 <u>Mean</u> 31.49 31.55 30 29 30	ni ² = 69. (P = 0.5 md-F 5D 17.6 66.28 13 13 13	115 86, df = 59) ICC <u>Total</u> 30 66 41 41 41	Mean 54.08 19.35 31 32 33 21	0.00001 pd-HC(<u>SD</u> 2.96 16.18 13 15 14	163); ² = 9 <u>Total</u> 18 25 23 23 23 23	100.0% 00% 11.4% 13.7% 13.2% 13.2% 13.2%	-0.24 [-1.10, 0.63] Std. Mean Difference <u>IV, Random, 95% Cl</u> -1.58 [-2.25, -0.91] 0.21 [-0.25, 0.67] -0.08 [-0.59, 0.43] -0.22 [-0.73, 0.30] -0.24 [-0.76, 0.27]	Favours [experimental] Favours [control] Std. Mean Difference
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Wei Y2019 Woo S2014	= 1.34; Cl Z = 0.54 <u>Mean</u> 31.49 31.55 30 29 30 24.1	ni ² = 69. (P = 0.5 17.6 66.28 13 13 11 12.1	115 86, df = 59) ICC Total 30 66 41 41 41 41 20	Mean 54.08 19.35 31 32 33 21	0.00001 pd-HCC <u>SD</u> 2.96 16.18 13 15 14 12.2	163); ² = 9 Total 18 25 23 23 23 23 14	100.0% 00% 11.4% 13.7% 13.2% 13.2% 13.2% 13.2% 13.2%	-0.24 [-1.10, 0.63] Std. Mean Difference <u>IV, Random, 95% CI</u> -1.58 [-2.25, -0.91] 0.21 [-0.25, 0.67] -0.08 [-0.59, 0.43] -0.22 [-0.73, 0.30] -0.24 [-0.76, 0.27] 0.25 [-0.44, 0.94]	Favours [experimental] Favours [control] Std. Mean Difference
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y 2019 Wei Y2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021	= 1.34; Cl Z = 0.54 31.49 31.55 30 29 30 24.1 26.35	ni ² = 69. (P = 0.5 17.6 66.28 13 13 11 12.1 6.24	115 86, df = 59) ICC Total 30 66 41 41 41 20 30	Mean 54.08 19.35 31 32 33 21 23.69	0.00001 pd-HCC <u>SD</u> 2.96 16.18 13 15 14 12.2 7.79	163); I ² = 9 Total 18 25 23 23 23 23 14 28 9	100.0% 00% 11.4% 13.7% 13.2% 13.2% 13.2% 13.2% 13.3% 13.1%	-0.24 [-1.10, 0.63] Std. Mean Difference <u>IV, Random, 95% CI</u> -1.58 [-2.25, -0.91] 0.21 [-0.25, 0.67] -0.08 [-0.59, 0.43] -0.22 [-0.73, 0.30] -0.24 [-0.76, 0.27] 0.25 [-0.44, 0.94] 0.37 [-0.15, 0.89]	Favours [experimental] Favours [control] Std. Mean Difference
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y 2019 Wei Y2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 Total (95% CI)	= 1.34; Cl Z = 0.54 31.49 31.55 30 29 30 24.1 26.35 23	ni² = 69. (P = 0.5 17.6 66.28 13 13 13 12.1 6.24 8	115 86, df = 59) ICC Total 30 66 41 41 41 20 30 46 315	Mean 54.08 19.35 31 32 33 21 23.69 18	0.00001 pd-HC0 2.96 16.18 13 15 14 12.2 7.79 7	163); I ² = 9 Total 18 25 23 23 23 23 14 28 9 163	100.0% Weight 11.4% 13.7% 13.2% 13.2% 13.2% 13.3% 10.9% 100.0%	-0.24 [-1.10, 0.63] Std. Mean Difference IV, Random, 95% CI -1.58 [-2.25, -0.91] 0.21 [-0.25, 0.67] -0.08 [-0.59, 0.43] -0.22 [-0.73, 0.30] -0.24 [-0.76, 0.27] 0.25 [-0.44, 0.94] 0.37 [-0.15, 0.89] 0.63 [-0.10, 1.35]	Favours [experimental] Favours [control] Std. Mean Difference IV, Random, 95% CI
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 Total (95% CI) Heterogeneity: Tau ² =	= 1.34; Cl Z = 0.54 31.49 31.55 30 29 30 24.1 26.35 23 = 0.25; C	hi ² = 69. (P = 0.5 17.6 66.28 13 13 11 12.1 6.24 8 hi ² = 28.	115 86, df = 59) ICC Total 30 66 41 41 41 20 30 46 315 74, df =	Mean 54.08 19.35 31 32 33 21 23.69 18	0.00001 pd-HC0 2.96 16.18 13 15 14 12.2 7.79 7	163); I ² = 9 Total 18 25 23 23 23 23 14 28 9 163	100.0% Weight 11.4% 13.7% 13.2% 13.2% 13.2% 13.3% 10.9% 100.0%	-0.24 [-1.10, 0.63] Std. Mean Difference IV, Random, 95% CI -1.58 [-2.25, -0.91] 0.21 [-0.25, 0.67] -0.08 [-0.59, 0.43] -0.22 [-0.73, 0.30] -0.24 [-0.76, 0.27] 0.25 [-0.44, 0.94] 0.37 [-0.15, 0.89] 0.63 [-0.10, 1.35]	Favours [experimental] Favours [control]
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y 2019 Wei Y2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 Total (95% CI)	= 1.34; Cl Z = 0.54 31.49 31.55 30 29 30 24.1 26.35 23 = 0.25; C	hi ² = 69. (P = 0.5 17.6 66.28 13 13 11 12.1 6.24 8 hi ² = 28.	115 86, df = 59) ICC Total 30 66 41 41 41 20 30 46 315 74, df =	Mean 54.08 19.35 31 32 33 21 23.69 18	0.00001 pd-HC0 2.96 16.18 13 15 14 12.2 7.79 7	163); I ² = 9 Total 18 25 23 23 23 23 14 28 9 163	100.0% Weight 11.4% 13.7% 13.2% 13.2% 13.2% 13.3% 10.9% 100.0%	-0.24 [-1.10, 0.63] Std. Mean Difference IV, Random, 95% CI -1.58 [-2.25, -0.91] 0.21 [-0.25, 0.67] -0.08 [-0.59, 0.43] -0.22 [-0.73, 0.30] -0.24 [-0.76, 0.27] 0.25 [-0.44, 0.94] 0.37 [-0.15, 0.89] 0.63 [-0.10, 1.35]	Favours [experimental] Favours [control] Std. Mean Difference IV, Random, 95% CI
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 Total (95% CI) Heterogeneity: Tau ² =	= 1.34; Cl Z = 0.54 31.49 31.55 30 29 30 24.1 26.35 23 = 0.25; C	hi ² = 69. (P = 0.5 17.6 66.28 13 13 11 12.1 6.24 8 hi ² = 28.	115 86, df = 59) ICC Total 30 66 41 41 41 20 30 46 315 74, df =	Mean 54.08 19.35 31 32 33 21 23.69 18	0.00001 pd-HC0 2.96 16.18 13 15 14 12.2 7.79 7	163); I ² = 9 Total 18 25 23 23 23 23 14 28 9 163	100.0% Weight 11.4% 13.7% 13.2% 13.2% 13.2% 13.3% 10.9% 100.0%	-0.24 [-1.10, 0.63] Std. Mean Difference IV, Random, 95% CI -1.58 [-2.25, -0.91] 0.21 [-0.25, 0.67] -0.08 [-0.59, 0.43] -0.22 [-0.73, 0.30] -0.24 [-0.76, 0.27] 0.25 [-0.44, 0.94] 0.37 [-0.15, 0.89] 0.63 [-0.10, 1.35]	Favours [experimental] Favours [control]
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 Total (95% CI) Heterogeneity: Tau ² = Test for overall effect:	= 1.34; Cl Z = 0.54 31.49 31.55 30 24.1 26.35 23 = 0.25; C : Z = 0.37	hi ² = 69. (P = 0.5 17.6 66.28 13 13 11 12.1 6.24 8 hi ² = 28.	115 86, df = 59) ICC Total 30 66 41 41 41 20 30 46 315 74, df =	Mean 54.08 19.35 31 32 33 21 23.69 18 = 7 (P =	0.00001 pd-HC0 2.96 16.18 13 15 14 12.2 7.79 7	163); I ² = 9 Total 18 25 23 23 23 23 14 28 9 163	100.0% 11.4% 13.7% 13.2% 13.2% 13.2% 13.3% 10.9% 100.0% 3%	-0.24 [-1.10, 0.63] Std. Mean Difference IV, Random, 95% CI -1.58 [-2.25, -0.91] 0.21 [-0.25, 0.67] -0.08 [-0.59, 0.43] -0.22 [-0.73, 0.30] -0.24 [-0.76, 0.27] 0.25 [-0.44, 0.94] 0.37 [-0.15, 0.89] 0.63 [-0.10, 1.35]	Favours [experimental] Favours [control]
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 Total (95% CI) Heterogeneity: Tau ² = Test for overall effect:	= 1.34; Cl Z = 0.54 31.49 31.55 30 24.1 26.35 23 = 0.25; C : Z = 0.37	hi ² = 69. (P = 0.5 17.6 66.28 13 13 12.1 6.24 8 hi ² = 28. (P = 0.7	115 86, df = 59) ICC Total 30 66 41 41 41 20 30 46 315 74, df =	Mean 54.08 19.35 31 32 33 21 23.69 18 = 7 (P =	0.00001 pd-HCC <u>SD</u> 2.96 16.18 13 15 14 12.2 7.79 7 0.0002)	163); ² = § <u>Total</u> 18 25 23 23 23 14 28 9 163 9 163	100.0% 11.4% 13.7% 13.2% 13.2% 13.2% 13.3% 10.9% 100.0% 3%	-0.24 [-1.10, 0.63] Std. Mean Difference IV, Random, 95% CI -1.58 [-2.25, -0.91] 0.21 [-0.25, 0.67] -0.08 [-0.59, 0.43] -0.22 [-0.73, 0.30] -0.24 [-0.76, 0.27] 0.25 [-0.44, 0.94] 0.37 [-0.15, 0.89] 0.63 [-0.10, 1.35] -0.08 [-0.48, 0.33]	Favours [experimental] Favours [control] Std. Mean Difference IV, Random, 95% Cl
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Wei Y2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup	= 1.34; Cl Z = 0.54 31.49 31.55 30 24.1 26.35 23 = 0.25; C : Z = 0.37	hi ² = 69. (P = 0.5 17.6 66.28 13 13 12.1 6.24 8 hi ² = 28. (P = 0.7 ///(-) SD	115 86, df= 59) ICCC Total 30 66 41 41 41 20 30 46 315 74, df= 71)	Mean 54.08 19.35 31 32 33 21 23.69 18 = 7 (P = Mean	0.00001 pd-HCC SD 2.96 16.18 13 15 14 12.2 7.79 7 0.0002) M(+) SD	163); ² = § <u>Total</u> 18 25 23 23 23 23 14 28 9 163 9 163 5, ² = 7€	100.0% 10% Weight 11.4% 13.7% 13.2% 13.2% 13.2% 13.3% 10.9% 100.0% 3% Weight	-0.24 [-1.10, 0.63] Std. Mean Difference <u>IV, Random, 95% Cl</u> -1.58 [-2.25, -0.91] 0.21 [-0.25, 0.67] -0.08 [-0.59, 0.43] -0.22 [-0.73, 0.30] -0.24 [-0.76, 0.27] 0.25 [-0.44, 0.94] 0.37 [-0.15, 0.89] 0.63 [-0.10, 1.35] -0.08 [-0.48, 0.33] Std. Mean Difference IV, Fixed, 95% Cl	Favours [experimental] Favours [control] Std. Mean Difference IV, Random, 95% Cl
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Wei Y2019 Wei Y2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Li H2018	= 1.34; Cl Z = 0.54 31.49 31.55 30 24.1 26.35 23 = 0.25; C : Z = 0.37	$hi^2 = 69.$ (P = 0.5) 17.6 66.28 13 13 11 12.1 6.24 8 $hi^2 = 28.$ (P = 0.5) IVI(-) 9.7	115 86, df = 39) ICCC Total 30 66 41 41 41 20 30 46 315 74, df = 71) Total 20	Mean 54.08 19.35 31 23.69 18 = 7 (P = Mean 19.3	0.00001 pd-HC(SD 2.96 16.18 13 15 14 12.2 7.79 7 0.0002) VI(+) SD 7.9	163); ² = 9 Total 18 25 23 23 23 14 28 9 163 163 163 163 163 21	100.0% 11.4% 13.2% 13.2% 13.2% 13.2% 13.3% 10.9% 100.0% 3%	-0.24 [-1.10, 0.63] Std. Mean Difference <u>IV, Random, 95% CI</u> -1.58 [-2.25, -0.91] 0.21 [-0.25, 0.67] -0.08 [-0.59, 0.43] -0.22 [-0.73, 0.30] -0.24 [-0.76, 0.27] 0.25 [-0.44, 0.94] 0.37 [-0.15, 0.89] 0.63 [-0.10, 1.35] -0.08 [-0.48, 0.33] Std. Mean Difference <u>IV, Fixed, 95% CI</u> 0.12 [-0.49, 0.74]	Favours [experimental] Favours [control] Std. Mean Difference IV, Random, 95% Cl
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Li H2018 Wei Y2019	= 1.34; Cl Z = 0.54 <u>Mean</u> 31.49 31.55 30 29 30 24.1 26.35 23 = 0.25; C : Z = 0.37 <u>Mean</u> 20.4 36	$hi^{2} = 69.$ (P = 0.5) 17.6 66.28 13 13 11 12.1 6.24 8 $hi^{2} = 28.$ (P = 0.5) IVVI(-) SD 9.7 14	115 86, df = 39) 1000 1000 1000 1000 1000 1000 1000 10	Mean 54.08 19.35 32 33 21 23.69 18 = 7 (P = M Mean 19.3 36	0.00001 pd-HCC SD 2.96 16.18 13 15 14 12.2 7.79 7 0.0002) VI(+) SD 7.9 16	163); ² = 9 <u>Total</u> 18 25 23 23 23 14 28 9 163 6 163 16 3 27 27 55	100.0% 10% Weight 11.4% 13.2% 13.2% 13.2% 13.2% 13.2% 13.3% 13.3% 10.9% 100.0%	-0.24 [-1.10, 0.63] Std. Mean Difference <u>IV, Random, 95% CI</u> -1.58 [-2.25, -0.91] 0.21 [-0.25, 0.67] -0.08 [-0.59, 0.43] -0.22 [-0.73, 0.30] -0.24 [-0.76, 0.27] 0.25 [-0.44, 0.94] 0.37 [-0.15, 0.89] 0.63 [-0.10, 1.35] -0.08 [-0.48, 0.33] Std. Mean Difference <u>IV, Fixed, 95% CI</u> 0.12 [-0.49, 0.74] 0.00 [-0.34, 0.34]	Favours [experimental] Favours [control] Std. Mean Difference IV, Random, 95% Cl
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Wei Y2019 Wei Y2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Li H2018	= 1.34; Cl Z = 0.54 31.49 31.55 30 24.1 26.35 23 = 0.25; C : Z = 0.37	$hi^{2} = 69.$ (P = 0.5) 17.6 66.28 13 13 11 12.1 6.24 8 $hi^{2} = 28.$ (P = 0.5) IVVI(-) SD 9.7 14	115 86, df = 39) 1000 1000 1000 1000 1000 1000 1000 10	Mean 54.08 19.35 31 23.69 18 = 7 (P = Mean 19.3	0.00001 pd-HCC SD 2.96 16.18 13 15 14 12.2 7.79 7 0.0002) VI(+) SD 7.9 16	163); ² = 9 Total 18 25 23 23 23 14 28 9 163 163 163 163 163 21	100.0% 11.4% 13.2% 13.2% 13.2% 13.2% 13.3% 10.9% 100.0% 3%	-0.24 [-1.10, 0.63] Std. Mean Difference <u>IV, Random, 95% CI</u> -1.58 [-2.25, -0.91] 0.21 [-0.25, 0.67] -0.08 [-0.59, 0.43] -0.22 [-0.73, 0.30] -0.24 [-0.76, 0.27] 0.25 [-0.44, 0.94] 0.37 [-0.15, 0.89] 0.63 [-0.10, 1.35] -0.08 [-0.48, 0.33] Std. Mean Difference <u>IV, Fixed, 95% CI</u> 0.12 [-0.49, 0.74]	Favours [experimental] Favours [control] Std. Mean Difference IV, Random, 95% Cl
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Li H2018 Wei Y2019 Zhao W2018	= 1.34; Cl Z = 0.54 <u>Mean</u> 31.49 31.55 30 29 30 24.1 26.35 23 = 0.25; C : Z = 0.37 <u>Mean</u> 20.4 36	$hi^{2} = 69.$ (P = 0.5) 17.6 66.28 13 13 11 12.1 6.24 8 $hi^{2} = 28.$ (P = 0.5) IVVI(-) SD 9.7 14	115 86, df = i9) 10CC <u>Total</u> 30 66 41 41 20 30 46 315 74, df = 71) 70 80 33	Mean 54.08 19.35 32 33 21 23.69 18 = 7 (P = M Mean 19.3 36	0.00001 pd-HCC SD 2.96 16.18 13 15 14 12.2 7.79 7 0.0002) VI(+) SD 7.9 16	163); ² = 9 <u>Total</u> 18 25 23 23 14 28 9 163 ; ² = 76 163 ; ² = 76 163 55 18	100.0% 11.4% 13.7% 13.2% 13.2% 13.2% 13.2% 13.3% 13.1% 10.9% 100.0% 20.0% 21.2%	-0.24 [-1.10, 0.63] Std. Mean Difference <u>IV, Random, 95% CI</u> -1.58 [-2.25, -0.91] 0.21 [-0.25, 0.67] -0.08 [-0.59, 0.43] -0.22 [-0.73, 0.30] -0.24 [-0.76, 0.27] 0.25 [-0.44, 0.94] 0.37 [-0.15, 0.89] 0.63 [-0.10, 1.35] -0.08 [-0.48, 0.33] Std. Mean Difference <u>IV, Fixed, 95% CI</u> 0.12 [-0.49, 0.74] 0.00 [-0.34, 0.34] 0.32 [-0.26, 0.89]	Favours [experimental] Favours [control] Std. Mean Difference IV, Random, 95% Cl
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Wei Y2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Li H2018 Wei Y2019 Zhao W2018 Total (95% CI)	= 1.34; Cl Z = 0.54 31.49 31.55 30 29 30 24.1 26.35 23 = 0.25; C Z = 0.37 Mean 20.4 36 29.67	$hi^{2} = 69.$ (P = 0.5) 17.6 66.28 13 11 12.1 6.24 8 $hi^{2} = 28.$ (P = 0.5) IVI(-) SD 9.7 14 18.9	115 86, df = i9) 10CC <u>Total</u> 30 66 41 41 20 30 46 315 74, df = 71) Total 20 80 33 33 133	Mean 54.08 19.35 31 32 23.69 18 7 (P = M Mean 19.3 36 24.17	0.000001 pd-HCC 2.96 16.18 13 15 14 12.2 7.79 7 0.00002) M(+) SD 7.9 16 13.32	163); ² = 9 <u>Total</u> 18 25 23 23 14 28 9 163 ; ² = 76 163 ; ² = 76 163 55 18	100.0% 10% Weight 11.4% 13.2% 13.2% 13.2% 13.2% 13.2% 13.3% 13.3% 10.9% 100.0%	-0.24 [-1.10, 0.63] Std. Mean Difference <u>IV, Random, 95% CI</u> -1.58 [-2.25, -0.91] 0.21 [-0.25, 0.67] -0.08 [-0.59, 0.43] -0.22 [-0.73, 0.30] -0.24 [-0.76, 0.27] 0.25 [-0.44, 0.94] 0.37 [-0.15, 0.89] 0.63 [-0.10, 1.35] -0.08 [-0.48, 0.33] Std. Mean Difference <u>IV, Fixed, 95% CI</u> 0.12 [-0.49, 0.74] 0.00 [-0.34, 0.34]	Favours [experimental] Favours [control] Std. Mean Difference IV, Random, 95% CI
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Granata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Study or Subgroup Li H2018 Wei Y2019 Zhao W2018	= 1.34; Cl Z = 0.54 31.49 31.55 30 29 30 24.1 26.35 23 = 0.25; C Z = 0.37 Mean 20.4 36 29.67 = 0.86, df	$hi^{2} = 69.$ (P = 0.5) 17.6 66.28 13 13 11 12.1 6.24 8 $hi^{2} = 28.$ (P = 0.3) IVI(-) 9.7 14 18.9 = 2 (P = 0.5)	115 86, df= 59) 1000 1000 1000 1000 1000 1000 1000 10	Mean 54.08 19.35 31 32 23.69 18 7 (P = M Mean 19.3 36 24.17	0.000001 pd-HCC 2.96 16.18 13 15 14 12.2 7.79 7 0.00002) M(+) SD 7.9 16 13.32	163); ² = 9 <u>Total</u> 18 25 23 23 14 28 9 163 ; ² = 76 163 ; ² = 76 163 55 18	100.0% 11.4% 13.7% 13.2% 13.2% 13.2% 13.2% 13.3% 13.1% 10.9% 100.0% 20.0% 21.2%	-0.24 [-1.10, 0.63] Std. Mean Difference <u>IV, Random, 95% CI</u> -1.58 [-2.25, -0.91] 0.21 [-0.25, 0.67] -0.08 [-0.59, 0.43] -0.22 [-0.73, 0.30] -0.24 [-0.76, 0.27] 0.25 [-0.44, 0.94] 0.37 [-0.15, 0.89] 0.63 [-0.10, 1.35] -0.08 [-0.48, 0.33] Std. Mean Difference <u>IV, Fixed, 95% CI</u> 0.12 [-0.49, 0.74] 0.00 [-0.34, 0.34] 0.32 [-0.26, 0.89]	Favours [experimental] Favours [control] Std. Mean Difference IV, Random, 95% Cl

FIGURE 7 | (A–C) Forest plot of the f values distinguished wdHCC, mdHCC, and pdHCC. The SMDs indicated that there was no significant difference for grades in HCC. (D) Forest plot of the f values between MVI- and MVI+. The SMD indicated that there was no significant difference for MVI in HCC. wd-HCC, well differentiated hepatocellular carcinoma; md-HCC, moderately differentiated hepatocellular carcinoma; pd-HCC, poorly differentiated hepatocellular carcinoma; MVI, microvascular invasion; SMD, standardized mean difference

0.92), respectively, as shown in **Figures 10E**, **F**. Deek's test suggested no publication bias (P = 0.178, P = 0.066). Furthermore, the AUCs of the D and ADCmean for preoperative prediction of MVI+ HCC were 0.87 (95% CI: 0.83–

0.89) and 0.78 (95% CI: 0.74–0.81), respectively (Z = -2.208, P = 0.027; **Figures 10G, H**). Deek's test suggested no publication bias in terms of D (P = 0.331), but there was a certain publication bias regarding ADCmean (P = 0.024).

	n	onpd-H	ICC		pd-H	ICC	5	Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% CI
Cao L2019	1.54	0.22	45	1.34	0.18	29	17.4%	0.96 [0.47, 1.46]	
Nang GZ 2020	0.95	0.24	59	0.81	0.22	69	33.5%	0.61 [0.25, 0.96]	+
Nang GZ2020	0.96	0.24	59	0.82	0.23	69	33.5%	0.59 [0.24, 0.95]	+
Wu B2020	1.35	0.36	30	1.2	0.35	28	15.6%	0.42 [-0.10, 0.94]	+
fotal (95% CI)			193			195	100.0%	0.63 [0.43, 0.84]	•
Heterogeneity: Chi ² =	2.46, df	= 3 (P =	0.48);	1= 0%					
Test for overall effect	:Z= 6.04	(P < 0.	00001)						
Test for overall effect	:Z=6.04	(P < 0.	00001)						Favours [experimental] Favours [control]
Test for overall effect	: Z = 6.04	(P < 0.	00001)						
Test for overall effect		(P < 0. ₩11/1(-)	00001)		/ī√l(+)		•	Std. Mean Difference	-4 -2 0 2 4 Favours [experimental] Favours [control] Std. Mean Difference
			00001) <u>Total</u>	,	/IVI(+) SD	Total		Std. Mean Difference IV, Fixed, 95% Cl	
Study or Subgroup	ı	VIVI(-)		,		<u>Total</u> 38			Std. Mean Difference
Study or Subgroup Cao L2019	Mean 1.51	VIVI(-) SD	Total	N Mean	SD		Weight	IV, Fixed, 95% CI	Std. Mean Difference
Study or Subgroup Cao L2019 Wang WT 2020	I <u>Mean</u> 1.51 1.59	VTVI(-) SD 0.22	Total 36	Mean 1.41 1.46	SD 0.22	38	Weight 29.0% 35.7%	IV, Fixed, 95% Cl 0.45 [-0.01, 0.91]	Std. Mean Difference
Fest for overall effect Study or Subgroup Cao L2019 Wang WT 2020 Wang WT2020 Fotal (95% CI)	I <u>Mean</u> 1.51 1.59	MVI(-) SD 0.22 0.398	<u>Total</u> 36 52	Mean 1.41 1.46	SD 0.22 0.219	38 40 40	Weight 29.0% 35.7%	IV, Fixed, 95% Cl 0.45 [-0.01, 0.91] 0.39 [-0.03, 0.80]	Std. Mean Difference
<mark>Study or Subgroup</mark> Cao L2019 Wang WT 2020 Wang WT2020	Mean 1.51 1.59 1.7	VIVI(-) SD 0.22 0.398 0.504	Total 36 52 52 52 140	Mean 1.41 1.46 1.48	SD 0.22 0.219	38 40 40	Weight 29.0% 35.7% 35.3%	IV, Fixed, 95% Cl 0.45 [-0.01, 0.91] 0.39 [-0.03, 0.80] 0.50 [0.08, 0.92]	Std. Mean Difference

FIGURE 8 | (A) Forest plot of the MD values between non-pdHCC and pdHCC. The SMD indicated significantly lower MD values in pdHCC than those in non-pdHCC. (B) Forest plot of MD values between MVI- and MVI+. The SMD indicated significantly lower MD values in MVI+ HCC than those in MVI- HCC. pd-HCC, poorly differentiated hepatocellular carcinoma; MVI, microvascular invasion; SMD, standardized mean difference.

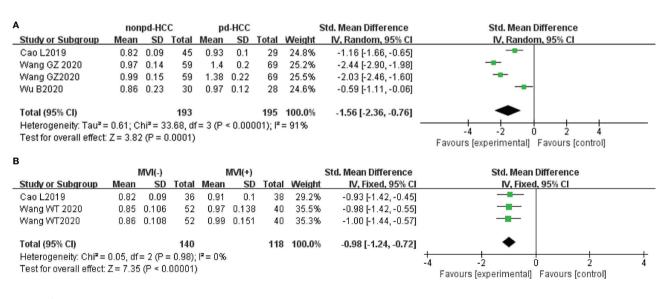


FIGURE 9 | (A) Forest plot of the MK values between non-pdHCC and pdHCC. The SMD indicated significantly higher MK values in pdHCC than those in non-pdHCC. (B) Forest plot of MK values between MVI- and MVI+. The SMD indicated significantly higher MK values in MVI+ HCC than those in MVI- HCC. pd-HCC, poorly differentiated hepatocellular carcinoma; MVI, microvascular invasion; SMD, standardized mean difference.

Subgroup Analysis of the Mean Apparent Diffusion Coefficient Value for Preoperative Diagnosis of Microvascular Invasion-Positive and Poorly Differentiated Hepatocellular Carcinoma

Due to differences in the study design, the number of included samples, and the examination equipment, clinical and methodological heterogeneity was inevitable. The results of the subgroup analysis are listed in **Table 3**. Interestingly, after grouping by subgroup (study design, sample size, machine type, number of b value, and maximum b value), the heterogeneity of the sensitivity and specificity decreased to varying degrees, suggesting that the subgroup might have been the source of heterogeneity. In addition, after grouping by maximum b value (\leq 800) and sample size (\leq 90), the AUC of the ADCmean for the diagnosis of pdHCC increased

TABLE 2	The diagnostic	performance	assessed	by the	parameters.

Indicators	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)
Poorly differentiated HCC						
MK	0.89 (0.86, 0.91)	0.69 (0.56, 0.80)#	0.94 (0.84, 0.98)&	10.7 (4.4, 26.0)	0.33 (0.23, 0.48)	32 (13, 80)
D	0.89 (0.86, 0.92)	0.87 (0.75, 0.93)#	0.80 (0.72, 0.86)#	4.4 (2.9, 6.5)	0.17 (0.08, 0.33)	26 (10, 68)
ADCmean	0.86 (0.83, 0.89)	0.82 (0.75, 0.88)#	0.75 (0.68, 0.82)#	3.4 (2.5, 4.5)	0.23 (0.17, 0.33)	14 (8, 24)
ADCmin	0.81 (0.78, 0.84)	0.83 (0.67, 0.92)&	0.64 (0.51, 0.75)#	2.3 (1.7, 3.1)	0.27 (0.13, 0.52)	9 (4, 20)
Well-differentiated HCC						
ADCmean	0.90 (0.87, 0.92)	0.82 (0.73, 0.89)#	0.88 (0.75, 0.95)#	7.0 (3.0, 16.2)	0.20 (0.12, 0.34)	34 (10, 120)
D	0.92 (0.89, 0.94)	0.87 (0.76, 0.93)&	0.83 (0.78, 0.87)&	5.1 (3.8, 6.9)	0.16 (0.08, 0.30)	32 (14, 73)
MVI(+) vs. MVI(-)						
ADCmean	0.78 (0.74, 0.81)	0.74 (0.68, 0.79)&	0.71 (0.61, 0.80)#	2.6 (1.9, 3.5)	0.37 (0.30, 0.45)	7 (5, 11)
D	0.87 (0.83, 0.89)	0.80 (0.72, 0.86)&	0.80 (0.73, 0.85)&	3.9 (2.9, 5.3)	0.25 (0.18, 0.36)	15 (9, 27)

&, the fixed effect model; #, the random effect model; ADCmean, mean apparent diffusion coefficient; ADCmin, minimum apparent diffusion coefficient; MK, mean kurtosis; MVI, microvascular invasion; AUC, area under the curve; PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odds ratio; HCC, hepatocellular carcinoma.

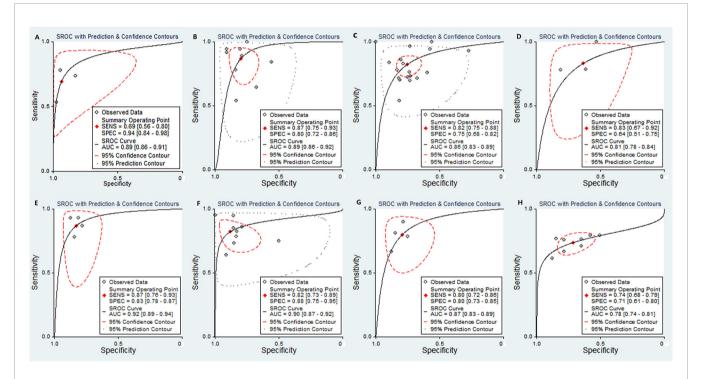


FIGURE 10 | SROC plots of the MK value (A), D value (B), ADCmean (C), and ADCmin (D) for discriminating pdHCC. SROC plots of the D value (E) and ADC mean (F) for discriminating wdHCC. SROC plots of the D value (G) and ADC mean (H) for discriminating MVI+ in HCC. SROC, summary receiver operating characteristic; AUC, area under curve; pdHCC, poorly differentiated hepatocellular carcinoma; wdHCC, well differentiated hepatocellular carcinoma; MVI, microvascular invasion; HCC, hepatocellular carcinoma

from0.86 to 0.93, and the AUC of the MVI+ HCC increased from 0.78 to 0.81. Overall, each subgroup analysis had a good prediction effect.

DISCUSSION

Hepatectomy and liver transplantation are currently the preferred treatment methods for HCC. Due to the invasive nature of surgery and the limited availability of organ transplantation, it is extremely important to determine the possibility of postoperative recovery and recurrence rate in patients before surgery. The HCC pathological grade and MVI are independent risk factors for recurrence and metastasis after hepatectomy or liver transplantation (56, 57). Therefore, preoperative prediction of pathological grade or MVI in HCC is crucial. The DKI is based on the non-Gaussian distribution model, which can better and more accurately reflect the subtle changes of tissue microstructure (58). IVIM adopts a multi-b-value scan and double exponential model fitting, which can more accurately reflect the diffusion of water molecules in tissues and microvascular blood perfusion, thereby better reflecting the heterogeneity of tumors (59). However, there are controversies as

TABLE 3 Subgroup analysis of the ADCmean value for diagnosis of MVI+ and poorly differentiated	d HCC.
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Indicators/Sub-	Groups (Studios)	AUC (95%CI)	Sensitivity (95% CI)	Specificity	PLR	NLR (95%	DOR		1 ²
group	(Studies)			(95% CI)	(95% CI)	CI)	(95% CI)	Sensitivity (%)	Specificity (%)
Poorly differentiated HCC									
Study design	Retrospective (n = 13)	0.87 (0.84, 0.90)	0.84 (0.76, 0.89)	0.75 (0.64, 0.84)	3.3 (2.2, 5.1)	0.22 (0.14, 0.33)	15 (7, 32)	57.32	85.14
	Prospective (n = 3)	0.84 (0.80, 0.87)	0.81 (0.61, 0.92)	0.78 (0.71, 0.84)	3.7 (2.8, 4.9)	0.24 (0.12, 0.51)	15 (7, 35)	75.69	28.46
Sample size	>90 (n = 7)	0.88 (0.85, 0.90)	0.86 (0.78, 0.91)	0.73 (0.62, 0.82)	3.2 (2.3, 4.5)	0.19 (0.13, 0.29)	16 (10, 27)	57.57	86.91
	≤90 (n = 9)	0.85 (0.82, 0.88)	0.78 (0.65, 0.88)	0.79 (0.67, 0.87)	3.7 (2.1, 6.5)		13 (5, 39)	63.23	73.56
Machine type	3.0T (n = 7)	0.82 (0.78, 0.85)	0.81 (0.71, 0.88)	0.73 (0.66, 0.79)	3.0 (2.5, 3.6)	0.26 (0.17, 0.39)	12 (7, 18)	74.27	59.89
	1.5T (n = 9)	0.88 (0.85, 0.91)	0.84 (0.74, 0.91)	0.79 (0.62, 0.90)	4.0 (2.0, 8.0)	0.20 (0.11, 0.37)	20 (6, 63)	54.30	89.78
Number of b value	>3 (n = 7)	0.86 (0.83, 0.89)	0.78 (0.67, 0.86)	0.80 (0.70, 0.87)	3.9 (2.3, 6.4)	0.27 (0.16, 0.46)	14 (5, 37)	62.24	70.21
	≤3 (n = 9)	0.87 (0.84, 0.90)	0.87 (0.78, 0.93)	0.71 (0.58, 0.81)	3.0 (2.1, 4.3)	0.18 (0.10, 0.31)	17 (9, 32)	61.7	86.33
Maximum b value	>800 (n = 9)	0.81 (0.78, 0.85)	0.76 (0.68, 0.83)	0.73 (0.64, 0.81)	,	,	9 (6, 13)	34.64	79.08
	≤800 (n = 7)	0.93 (0.90, 0.95)	0.91 (0.78, 0.97)	0.80 (0.63, 0.90)	,	0.11 (0.04, 0.30)	40 (10, 169)	78.23	87.92
MVI(+) vs. MVI(-)									
Study design	Retrospective (n = 5)	0.78 (0.74, 0.81)	0.73 (0.65, 0.80)	0.72 (0.57, 0.83)	2.6 (1.7, 3.9)	0.38 (0.30, 0.48)	7 (4, 12)	34.54	85.96
	Prospective (n = 3)	0.77 (0.74, 0.81)	0.74 (0.64, 0.82)	0.71 (0.59, 0.81)	2.6 (1.7, 4.0)	0.37 (0.25, 0.54)	7 (3, 15)	0	36.7
Sample size	>90 (n = 4)	0.76 (0.72, 0.80)	0.74 (0.67, 0.81)	0.63 (0.52, 0.73)	2.0 (1.6, 2.6)	0.40 (0.32, 0.51)	5 (3, 8)	25.48	79.83
	≤90 (n = 4)	0.81 (0.78, 0.85)	0.74 (0.64, 0.81)	0.80 (0.72, 0.87)	3.8 (2.6, 5.5)	0.33 (0.24, 0.46)	11 (6, 21)	0	36.13
Machine type	3.0T (n = 5)	0.77 (0.73, 0.80)	0.73 (0.65, 0.80)	0.73 (0.60, 0.83)	2.7 (1.8, 4.0)	0.37 (0.28, 0.49)	7 (4, 13)	0	70.66
	1.5T (n = 3)	0.78 (0.74, 0.81)	0.74 (0.65, 0.81)	0.70 (0.52, 0.83)	2.4 (1.5, 3.9)	0.37 (0.28, 0.49)	7 (3, 12)	20.9	84.49
Number of b value	>3 (n = 4)	0.73 (0.69, 0.77)	0.72 (0.63, 0.79)	0.76 (0.63, 0.86)	3.0 (1.9, 4.9)	0.37 (0.27, 0.51)	8 (4, 17)	0	68.92
	≤3 (n = 4)	0.78 (0.74, 0.81)	0.75 (0.68, 0.81)	0.67 (0.53, 0.78)	2.3 (1.6, 3.2)	0.37 (0.29, 0.47)	6 (4, 10)	12.73	84.8
Maximum b value	>800 (n = 5)	0.74 (0.70, 0.78)	0.73 (0.65, 0.79)	0.77 (0.67, 0.84)	,	,	9 (5, 16)	0	61.19
	≤800 (n = 3)	0.77 (0.73, 0.80)	0.75 (0.67, 0.82)	0.63 (0.47, 0.76)	,	0.39 (0.30, 0.51)	5 (3, 9)	3.42	78.99

ADCmean, mean apparent diffusion coefficient; MVI, microvascular invasion; AUC, area under the curve; PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odds ratio; HCC, hepatocellular carcinoma.

to whether the parameters of DKI and IVIM-DWI can be employed in the preoperative distinguishing of pathological grades and MVI in individuals with HCC. Therefore, 42 original studies were strictly included in this analysis to expand the sample size, and they were objectively and comprehensively evaluated to determine the diagnostic value of the DKI and IVIM-DWI parameters.

Based on SMDs, we showed that there were significant differences in the MK, MD, D, ADCmean, and ADCmin for preoperative prediction of the pathological grade or MVI in individuals with HCC. The D, ADCmean, and ADCmin positively correlated with the degree of differentiation of HCC. However, these findings are inconsistent with the conclusion of the meta-analysis by Surov et al. (60) that the ADCmean could not predict pathological grade and MVI in HCC. The reason may be that we included new studies (33–35, 38, 49, 50) and expanded the sample size. Moreover, various combination methods contributed to the differences. Surov et al. (60) combined the means of grades 1, 2, and 3 and MVI+/- and then compared whether there was an overlap between the combined means. In contrast, the SMDs were used as the effective index to distinguish well-, moderately, and poorly differentiated HCC and MVI+/- in our study. Similarly, the MK and MD could be used for preoperative distinguishing between pdHCC and non-pdHCC and between MVI+ and MVI-, with significant differences. The SMDs and 95% CIs were significantly away from the 0 reference line, which

suggested that the MK and MD values were of great value in the identification of grades/MVI in HCC. The MK and MD values were the most representative parameters in DKI, which were able to reflect the complexity of tumor tissue microstructure and had potential correlation with tumor invasive biological behavior (38). Compared with non-pdHCC, pdHCC had greater heteromorphism, and the proliferation capacity of cancer tissues was more vigorous, which led to complex tissue structure and non-Gaussian distribution of the water molecule movement, thereby resulting in a higher MK value and a lower MD value.

Interestingly, some studies (22, 25, 34) have suggested that the D^{*} or f values could predict HCC pathological grades, while other studies (18, 35, 39) did not confirm such conclusions. Our study suggested that there was no significant benefit of D^{*} or f values in predicting HCC pathological grades. The reason may be that the D^{*} value is mainly related to microcirculation blood flow velocity; thus, this can lead to inaccurate measurements under subjective dynamics. In addition, the D^{*} value could not truthfully reflect the real value of cancer focus because the D^{*} value is easily affected by the changes of machine signal and noise. Similarly, the f value indicates the microcirculation perfusion fraction, and the repeatability of measurement is poor because the microcirculation blood flow is dynamic at all times.

Importantly, our study suggested that the MK, D, ADCmean, and ADCmin had a higher diagnostic efficacy to predict pdHCC. Compared with the ADCmean and ADCmin, the D value had higher sensitivity, specificity, and AUC. Similarly, the AUC of the pdHCC predicted by the MK value was 0.89, which was higher than that predicted by the ADCmean and ADCmin, and the specificity was as high as 94%. The reason might be that the MK value is based on a non-Gaussian model; thus, it could reflect the diffusion characteristics of water molecules in vivo as a whole and could more truly reflect the movement state of water molecules in the lesion. Compared with the meta-analysis of Yang et al. (52), our study latest suggested that the D value had excellent diagnostic efficacy in predicting wdHCC, with a sensitivity of 87%, specificity of 83%, and AUC of 0.92; moreover, our study subdivided the ADC value into the mean and minimum ADC value on the basis of expanding the sample size, thereby making the combined results more reliable.

Furthermore, compared with the ADCmean, our study suggested that the D value had higher sensitivity (80%) and specificity (80%) in predicting MVI+ HCC, and the summary AUC of the D value was significantly higher than that of the ADCmean (Z = -2.208, P = 0.027), indicating that the D value was better and more sensitive in predicting MVI+ HCC. The reason might be that the ADC value ignores the influence of microcirculation perfusion in the cancer focus; thus, the D value is more realistic than the ADC value, given that the D value distinguishes the diffusion of pure water molecules and microcirculation perfusion in the tissue by changes in the b value (61).

Our study comprehensively and systematically evaluated the power of the DKI, IVIM, and DWI parameters for preoperative prediction of the pathological grade and MVI in HCC. The quality of the included studies was acceptable, and there was no publication bias in the studies according to Egger's or Begg's test. Moreover, we performed the subgroup analysis of the ADCmean value for the diagnosis of MVI+ HCC and pdHCC. Interestingly, after grouping by maximum b value (\leq 800) and sample size (\leq 90), the AUC of the ADCmean for the diagnosis of pdHCC increased from 0.86 to 0.93, and the AUC of the MVI+ HCC increased from 0.78 to 0.81. Overall, each subgroup analysis had a good prediction effect.

However, our study had some limitations. First, most studies were retrospective studies, which increased the risk of confusion bias to a certain extent. Second, the sample size of the MK, MD, D*, and f values was not large enough. Therefore, further studies with a larger sample size and of prospective nature are needed to prove our results. Finally, most studies were conducted in Asia, which introduced a certain regional bias.

CONCLUSION

Our meta-analysis showed that the DKI parameters (MD and MK) and the IVIM-DWI parameters (D value, ADCmean, and ADCmin) can be used as a noninvasive and simple preoperative examination method to predict the pathological grade and MVI in HCC. Compared with the ADCmean and ADCmin, the MD and D values showed a higher diagnostic efficacy in predicting the grades of HCC, and the D value had superior diagnostic efficacy to the ADCmean in predicting MVI+ in HCC. However, f values cannot be used as an effective parameter to predict the grades and MVI in HCC. It is quite helpful when making a clinical treatment plan, preoperative prognosis evaluation, and follow-up research.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/ **Supplementary Material**.

AUTHOR CONTRIBUTIONS

Research route design: FW, CYY, and DZ. Draft of the article: FW. Data acquisition: CHW, CYY, and FW. Data analysis: FW and CYY. Review and editing of the article: DZ and YY. All authors contributed substantially to the preparation of the article.

FUNDING

This work was supported by Talent project of Chongqing (Dong Zhang, CQYC202103075).

ACKNOWLEDGMENTS

We thank LetPub (www.letpub.com) for its linguistic assistance during the preparation of this article.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.884854/ full#supplementary-material

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