

# 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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**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

1

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 I<sup>2</sup> (54, 55). A random-effects model was used when the I<sup>2</sup> 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 (I<sup>2</sup> > 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 (I<sup>2</sup> = 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/mm²)
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/ ADCmin	500, 1,000
Saito et al. (14)	2012	Japan	Retrospective	42	Grade	Siemens1.5	ADCmean	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
Le moigne et al. (17)	2014	France	Prospective	62	Grade	Siemens1.5	ADCmean	50, 400, 800
Woo et al. (18)	2014	Korea	Retrospective	42	Grade	Siemens3.0	ADCmean/ D/D*/f	0, 25, 50, 75, 100, 200, 500, 800
Guo et al. (19)	2015	China	Prospective	27	Grade	GE3.0	ADCmean	0, 600
Tang et al. (20)	2016	China	Retrospective	74	Grade	GE3.0	ADCmean	0, 800
Iwasa 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/ D/D*/f	0, 50, 100, 200, 400, 600, 800
Shankar et al. (23)	2016	India	Prospective	20	Grade	Siemens3.0	ADCmean	0, 100, 500, 1,000
Li et al. (24)	2016	China	Retrospective	241	Grade	GE1.5	ADCmean/	0, 800
Shan et al. (25)	2017	China	Retrospective	109	Grade	GE3.0	ADCmean/	0, 30, 50, 100, 150, 200, 300, 500, 800, 1,000, 1,500
Jing et al. (26)	2017	China	Retrospective	254	Grade	GE1.5	ADCmean/	0, 600
Marine at al $(27)$	2017	lonon	Dotroopootivo	56	Crada	Sigmono 1 5	ADCmin	100 800
Nonya et al. $(27)$	2017	Japan	Retrospective	20	Grade	Siemens I.S	ADCMIN	100, 800
Derived at al. $(20)$	2010	Varaa	Retrospective	42	Grade	GET.5/3.0 Sigmonol F	ADCmean	0, 800, 1,000
Park et al. (29) $\mathbf{Z}_{\rm but}$ at al. (29)	2018	Oleirea	Retrospective	141	Grade	Siemens I.S	ADCineari	50, 800
Zhu et al. (30)	2018	Gnina	Retrospective	62	Grade	GE3.0	D/D*/f	10, 20, 40, 80, 100, 150, 200, 400, 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
Lee et al. (36)	2018	Korea	Retrospective	114	Grade/MVI	Philips3.0	ADCmean/	0, 100, 800
Kim et al. (37)	2019	Korea	Retrospective	143	Grade/MVI	Philips3.0	ADCmean/	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
Wei 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
Xu et al. (41)	2014	China	Retrospective	92	MVI	Siemens1.5	ADCmean	0, 500
Okamura et al. (42)	2016	Japan	Retrospective	75	MVI	Siemens1.5	ADCmean	0, 1,000
Huang et al. (43)	2016	China	Retrospective	51	MVI	Siemens1.5	ADCmean	0, 500
Lee 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
Li et al. (46)	2018	China	Prospective	41	MVI	Philips3.0	ADCmean/ D/D*/f	0, 10, 20, 40, 80, 200, 400, 600, 1,000
Zhao et al. (47)	2018	China	Retrospective	51	MVI	GE3.0	ADCmean/ D/D*/f	0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 1,000
Chuang et al. (48)	2019	China	Retrospective	97	MVI	GE1.5	ADCmean/ ADCmin	0, 400

(Continued)

#### TABLE 1 | Continued

Author	Published year	Country	Study design	Sample size	Research direction	Machine type	Parameters	b-values (s/mm <sup>2</sup> )
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 I<sup>2</sup> 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 Oranala V2016 Guo W2015 Heo SH2010 Image T2017 Image T2017 Image T2017 Image T2017 Image T2017 Image T2018 Le molinge F2014 Lee S2018 Li X2016 Ogihara Y2018 Ogihara Y2018 Ogihara Y2018 Ogihara Y2018 Ogihara Y2018 Shankar S2016 Taray 1H2016 Shankar S2016 Taray 1H2016 Wei Y2019 Wei Y2019 Wei Y2019 Wei Y2019 Total (95% CI) Helteropenely, Tar <sup>2</sup> Test for overall effect Study of Subforcement Study of Subforcement Study of Subforcement Chang Wc2014	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	
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Heo SH2010 Wasa Y2016 Jiang T2017 Kim J02019 Kim J02019 Kim J02019 Lee S2018 Lix2016 Moriya T2017 Moriya T2017 Moriya T2017 Moriya Y2018 Park IL2018 Salio X2012 Shan G2017 Shan G2017 Shan G2017 Shan G2017 Shan G2017 Shan G2017 Shan G2017 Shan G2017 Tang YH2016 Wei Y2019 Wei Y2019 Wei Y2019 Wei Y2019 Total (95% C) Total (95% C) Total (95% C) Study or Subtrough Chang WC2014 Chang WC2014 C	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	
Hang T2017 Hang T2017 Kim J20219 Le mojane F2014 Lee S2018 Ll x2016 Ll x2016 Ogihare Y2018 Ogihare Y2018 Ogihare Y2018 Ogihare Y2018 Ogihare Y2018 Shankar S2016 Taray 14/2016 Wei Y2019 Wei Y2019 Wei Y2019 Wei Y2019 Wei Y2019 Wei Y2019 Total (95% CI) Heteropenely, Tau*= Test for overall effect Study of Subforces	157         0.13         29           1.14         0.37         1           1.05         0.19         3           1.19         0.233         1           1.119         0.233         1           1.13         0.32         1           1.14         0.32         1           1.19         0.233         1           1.11         0.12         3           1.13         0.18         1           1.33         0.19         1           1.20         0.15         1           1.33         0.15         1           1.46         0.24         1.16           0.224         0.165         1           1.46         0.24         1           1.46         0.24         1           1.46         0.24         1           1.46         0.24         1           1.46         0.23         1           1.46         0.21         1           1.46         0.21         1           1.46         0.31         1           1.490         0.312         1           1.490         0.312 <t< td=""><td><math display="block">\begin{array}{cccccccccccccccccccccccccccccccccccc</math></td><td><math display="block">\begin{array}{c} 4.08 \\ - 2.511 \\ \pm 0.02 \\ - 2.56 \\ - 5.01 \\ \pm 0.02 \\ - 5.05</math></td><td></td></t<>	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{c} 4.08 \\ - 2.511 \\ \pm 0.02 \\ - 2.56 \\ - 5.01 \\ \pm 0.02 \\ - 5.05$	
kim J62019 Lem 00jpe 72014 Lee 52016 Moriya 72017 Muti A2006 Nishie A2011 Ogihara Y2018 Ogihara Y2018 Ogihara Y2018 Saha 002017 Shahara 52016 Wang 022020 Wang 022020 Wang 022020 Wang 022020 Wang 20210 Wang 022020 Wang 20210 Wang 20210 Wang 20210 Wang 20210 Wang 20211 Wang 20211 Zhu 352018 Wang 2021 Zhu 352018 State of the State of the State Test for overall effect State of Subtrough Chang Wc2014 Chang Wc2014	1.14         0.37           1.14         0.23           1.119         0.233           1.131         0.231           1.131         0.232           1.131         0.232           1.131         0.232           1.131         0.231           1.131         0.232           1.21         0.11           1.33         0.19           1.12         0.15           1.23         0.19           1.24         0.15           1.25         0.25           1.24         0.15           1.25         0.26           1.240         0.315           1.25         0.26           1.24         0.315           1.25         0.26           1.24         0.315           1.25         0.26           1.26         0.28           1.27         0.28           1.48         0.312           1.496         0.312           1.496         0.312           1.496         0.312           1.494         0.47           0.44         0.47	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	
Lee \$2016 Lix2016 Moriya 72017 Muhin 22006 Northal 22017 Noglinae 72018 Oglinae 72018 Park II:2018 Salio 5/2012 Shan 6/2012 Shan 6/2012 Tang 1/4/2016 Wang 0/2/2020 Wal 7/2019 Wal 7/2019 Wal 7/2019 Wal 7/2019 Wal 7/2019 Wal 7/2019 Total (05% Ct) Heterogenety, Tau*= Test for overall effect Study of Subforcing Chang Wc/2014	1.119 0.233 1. 1.13 0.232 2. 1.051 0.203 1. 0.91 0.25 3. 1.21 0.11 2. 1.33 0.19 1. 1.33 0.19 1. 1.33 0.19 1. 1.33 0.19 1. 1.35 0.25 1. 1.34 0.15 2. 1.32 0.15 1. 1.34 0.31 2. 1.35 0.25 1. 1.36 0.23 1. 1.36 0.23 1. 1.36 0.23 1. 1.36 0.23 1. 1.36 0.25 1. 1.37 0.22 1. 1.36 0.306 1. 47. 0.44; Ch <sup>2</sup> = 14.91,44 0. 47. 0.44; Ch <sup>2</sup> = 14.91,44 0. 47. 1.44 0.21 2. 47. 1.44 0. 1.45 0.	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	
Li A.2017 D017 Mubin 7.2009 Nishie A2011 Ogihara Y 2018 Ogihara Y 2018 Ogihara Y 2018 Satio K.2012 Satio K.2012 Mang 0.22020 Wei Y 2019 Wei Y 2019 Wei Y 2019 Wei Y 2019 Wei Y 2019 Wei Y 2019 Wei Y 2019 Zhu SC 2018 Zhu SC 2018 Zhu SC 2018 Zhu SC 2018 Zhu SC 2018 Zhu SC 2018 Zhu SC 2018 Chang WC 2014 Chang WC 2014 Chang WC 2014 Chang WC 2014	1.13         0.22         2           1.1651         0.220         1           0.21         0.21         0.11           1.108         0.15         1           1.23         0.15         1           1.33         0.19         1           1.26         0.15         1           1.33         0.19         1           1.11         0.18         1           1.26         0.25         1           1.27         0.24         1           1.24         0.15         1           1.46         0.28         1           1.46         0.26         1           1.46         0.26         1           1.46         0.26         1           1.46         0.26         1           1.46         0.312         1           1.409         0.306         1           1.500         0.306         1           47.7         24.48         60.0000	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	3 4% 0.04 {0.04 {0.04 {0.05 {0	
Muh X2009 Nishie X2011 Oginan Y 2018 Ogina Y 2018 Salio K2012 Shan G22017 Shankar S2016 Wang G22020 Wang G22020 Wang G22020 Wang G22020 Wang G22019 Wai Y2019 Wai Y2019 Wai Y2019 Wai Y2019 Total (95% CI) Heterogeneity, Tau* Test for overall effect Study or Subarroun Chang Wc2014 Chang Wc2014	0.91 0.25 33 1.21 0.11 1 1.21 0.11 1 1.33 0.19 11 1.11 0.18 11 1.25 0.25 1 1.22 0.15 1 1.22 0.25 1 1.22 0.25 1 1.22 0.25 1 1.32 0.15 1 1.32 0.15 1 1.32 0.26 1 1.32 0.26 1 1.35 0.26 1 1.35 0.26 1 1.35 0.25 - 1.35 0.31 2 1.46 0.31 2 1.46 0.31 2 1.450 0.306 1 1.35 0.306 1 47. 0.44; Ch <sup>2</sup> = 149.14, 2.4.85 (\$ 0.0000		3.9%         0.78 [0.30, 1.26]           2.9%         0.34 [0.58, 1.26]           3.2%         0.65 [-1.28, 0.29]           3.2%         0.50 [-1.28, 0.29]           3.8%         0.24 [-0.78, 0.29]           3.8%         0.54 [-0.78, 0.29]           3.8%         0.54 [-0.42, 0.22]           3.8%         0.10 [-0.42, 0.62]           3.4%         1.07 [0.36, 1.77]           3.7%         0.75 [0.21, 1.30]           3.7%         1.76 [0.21, 1.37]           3.7%         1.76 [0.21, 1.37]           3.6%         1.44 [0.08, 2.11]           3.5%         1.38 [0.73, 2.03]           2.6%         0.76 [-0.55]	
Total and 2010           Oglinar 2011           Oglinar 2011           Park IK/2018           Salko K/2012           Shan Go2017           Shan Kar 2016           Tang M*2016           Wein 2017           Wein 2018           Wein 2019           Wein 2019           Wein 2019           Wein 2019           Wein 2019           Wein 2020           Zhu SC 2018           Zhu SC 2018           Zhu SC 2018           Study or Subgroup           Chang Wc2014           Chang Wc2014           Chang Wc2014           Chang Wc2014           Chang Wc2014	L.1 0.11 5 1.08 0.15 1 1.33 0.19 11 1.25 0.25 1 1.11 0.18 11 1.25 0.25 1 1.19 0.24 11 0.924 0.165 1 1.32 0.15 11 1.46 0.31 2 1.70 0.29 11 1.55 0.26 11 1.55 0.26 11 1.55 0.26 11 1.55 0.26 11 1.55 0.32 11 1.55 0.32 14 1.55 0.32 14 1.55 0.30 14 1.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	2.3%         0.5.4         [1.0]         [1.0]           3.2%         0.62         [1.16]         1.0]           3.2%         0.62         [1.16]         1.0]           3.2%         0.62         [1.16]         1.0]           3.8%         0.24         [1.78]         0.3]           3.6%         0.54         [1.14]         1.22]           2.9%         0.42         [0.53]         1.6]           3.4%         1.07         [1.36]         1.77]           3.7%         0.75         [1.71]         1.7]           3.5%         1.46         [0.00]         1.11]           3.5%         1.71         1.32         2.9]           3.5%         1.71         1.33         1.07           3.5%         1.71         1.03         2.83           3.5%         1.71         1.03         2.83           3.5%         1.71         1.03         2.83           3.5%         1.71         1.03         2.83           2.6%         0.75         1.03         1.27           2.6%         0.75         1.03         1.38	
Ogihari Y2018 Ogihari Y2018 Sato K2012 Sato K2012 Jana Oc2021 Wei Y2019 Wei Y2019 Wei Y2019 Wei Y2019 Wei Y2019 Wei Y2019 Wei Y2019 Zhu SC2018 Zhu SC2018 Zhu SC2018 Total (95% CI) Heterogeneti, Tau*= Test for overall effect. Study or Subarcoun Chang Wc2014 Chang Wc2014	1.33         0.19         11           1.11         0.18         11           1.25         0.25         1           1.19         0.34         11           0.924         0.165         11           1.32         0.15         11           1.46         0.312         11           1.46         0.32         11           1.55         0.26         11           1.56         0.26         11           1.50         0.302         11           1.46         0.312         11           1.503         0.306         1           447         1.603         0.312           1.24         2.4.85 (Pr < 0.0000	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	3.2% 0.62 [-0.16, 1.40] 3.8% -0.24 [-0.78, 0.29] 3.5% 0.54 [-0.14, 1.22] 3.8% 0.10 [-0.42, 0.62] 3.8% 0.42 [-0.53, 1.36] 3.4% 1.07 [10.36, 1.77] 3.7% 0.42 [-0.53, 1.36] 3.5% 1.46 [0.80, 2.11] 3.5% 1.38 [0.73, 2.03] 3.5% 0.75 [-0.35, 1.87]	
Sabia C2012 Shan Q32017 Shankar S2016 Tang YH2016 Wang Q22020 Wei Y2019 Wei Y2019 Wei Y2019 Wei Y2019 Zhou Y2021 Zhou Y2021 Zhou Y2021 Zhou S2018 Zhu S2018 Zhu S2018 Chang WC2014 Chang WC2014 Chang WC2014 Chang WC2014	1.25 0.25 1 1.19 0.34 11 1.924 0.165 : 1.32 0.15 1 1.46 0.31 2 1.46 0.31 2 1.46 0.28 11 1.55 0.26 1 1.77 0.29 11 1.55 0.26 1 1.77 0.29 11 1.35 0.26 1 1.70 0.29 11 1.36 0.12 1 1.466 0.312	1.12         0.22         18           8         1.07         1.32         66           0.866         0.1         10         1.13         0.18         51           2         1.28         0.18         51         2         2.28         1.18         51           2         1.28         0.18         51         2         2.24         0.15         11         5         1.22         0.21         41           5         1.42         0.21         41         5         2.05         20         3         1.41         0.19         3         1.41         0.17         46         4         1.22         0.16         21         41         1.25         2.15         20         3         1.41         0.17         46         4         1.22         0.16         21         1.41         0.19         3         4.11         0.17         46         4         1.21         0.166         24         4         1.21         0.168         24         4.21         0.168         24         4         1.21         0.168         24         1.21         0.168         24         1.21         0.168         24         1.21         0.168	3.5%         0.54          0.14, 1.22           3.8%         0.10          0.42, 0.62           2.9%         0.42          0.53, 1.36           3.4%         1.07          0.36, 1.77           3.7%         0.75          0.21, 1.30           3.5%         1.46          0.80, 2.11           3.5%         1.71          1.03, 2.38           3.5%         1.78          0.72, 0.23           3.5%         1.73          0.73, 5.18	
Shan Go2017 Shankar S2016 Tang YH2016 Wei Y2019 Wei Y2019 Wei Y2019 Wei Y2019 Wei Y2019 Wei Y2019 Zhu S2020 Zhu S2021 Total (95% CI) Heteropeneity, Tau <sup>e</sup> = Testopeneity, Tau <sup>e</sup> Study or Subarroup Chang Wc2014 Chang Wc2016	1.19 0.34 1: 0.924 0.165 : 1.32 0.15 1: 1.46 0.28 1: 1.46 0.28 1: 1.56 0.26 1: 1.77 0.29 1: 1.35 0.25 . 1.7 0.23 1: 1.35 0.17 1: 1.496 0.312 1: 1.496 0.312 1: 1.496 0.312 1: 1.496 0.312 1: 1.496 0.312 1: 1.496 0.312 1: 1.496 0.412 1: 1.4	8         1.07         1.32         66           8         0.866         0.1         10           0         1.13         0.18         51           2         1.28         0.18         51           5         1.12         0.21         41           5         1.24         0.15         41           5         1.47         0.18         41           4         1.22         0.15         20           9         1.41         0.17         46           4         1.21         0.186         24           4         0.124         0.17         46	3.8% 0.10 [-0.42, 0.62] 2.9% 0.42 [-0.53, 1.36] 3.4% 1.07 [0.36, 1.77] 3.7% 0.75 [0.21, 1.30] 3.5% 1.46 [0.00, 2.11] 3.5% 1.71 [1.03, 2.38] 3.6% 1.38 [0.73, 2.03] 2.6% 0.75 [-0.35, 1.87]	
Tang Wr42016           Wang 02/2020           Wei Y 2019           Wei Y2019           Wei Y2019           Woo S2014           Wu S2020           Zhou Y 2021           Zhu SC 2018           Total (95%CI)           Heterogeneity, Tau*=           Test for overall effect           Viruly or Subgroup           Chang Wc2014           Oranata Y2016	1.32 0.15 11 1.46 0.31 22 1.46 0.28 11 1.56 0.26 11 1.57 0.29 11 1.35 0.25 1.35 0.325 1.35 0.325 1.35 0.312 11 1.496 0.312 11 1.496 0.312 11 1.503 0.306 11 477 :0.44; Chi <sup>µ</sup> = 149.14, 2 = 4.85 (P < 0.0000)	0 1.13 0.18 51 2 1.28 0.18 37 5 1.12 0.21 41 5 1.24 0.15 41 5 1.47 0.18 41 4 1.22 0.15 20 9 1.41 0.19 30 5 1.16 0.17 46 4 1.21 0.186 24	3.4% 1.07 [0.38, 1.77] 3.7% 0.75 [0.21, 1.30] 3.5% 1.46 [0.80, 2.11] 3.5% 1.38 [0.73, 2.03] 3.5% 1.38 [0.73, 2.03] 2.6% 0.75 [-0.35, 1.8%]	
Wang 02/2020 Wei Y2019 Wei Y2019 Wei Y2019 Woo S2014 Woo S2014 Woo S2014 Zhu SC2018 Zhu SC2018 Zhu SC2018 Total (95% C) Heterogenety, Tau" = Test for overall effect: Study or Subgroup Chang WC2014 Chang WC2014	1.46 0.31 2: 1.46 0.28 1: 1.56 0.26 1: 1.77 0.29 1: 1.35 0.25 . 1.7 0.32 1: 1.35 0.17 1: 1.496 0.312 1: 1.496 0.312 1: 1.503 0.306 1: 2.044; Chi#=149.14, Z=4.85 (P < 0.0000)	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	3.7% 0.75 [0.21, 1.30] 3.5% 1.46 [0.80, 2.11] 3.5% 1.71 [1.03, 2.38] 3.5% 1.38 [0.73, 2.03] 2.6% 0.75 [-0.35, 1.85]	
Wei Y20 19 Wei Y2019 Wei Y2019 Zhou Y2021 Zhou Y2021 Zhou Y2021 Zhou SC2019 Total (95% CI) Heterogeneity: Tau <sup>x</sup> = Test for overall effect Study or Subgroup Chang Wc2014 Chang Wc2014	1.56 0.26 1: 1.77 0.29 1: 1.35 0.25 . 1.7 0.32 1: 1.35 0.17 1: 1.496 0.312 1: 1.503 0.306 1: 1.503 0.306 1: 2.044; Chi#=149.14, Z=4.85 (P < 0.0000)	5         1.24         0.15         41           5         1.47         0.18         41           4         1.22         0.15         20           9         1.41         0.19         30           5         1.16         0.17         46           4         1.21         0.186         24	3.5% 1.71 [1.03, 2.38] 3.5% 1.38 [0.73, 2.03] 2.6% 0.75 [-0.35, 1.84]	
Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 Zhu SC 2018 Zhu SC 2018 Total (95% CI) Heterogeneity, Tau*= Test for overall effect: Study or Subgroup Chang WC 2014 Granata V2016	1.77 0.29 1: 1.35 0.25 1: 1.35 0.17 1: 1.496 0.312 1: 1.503 0.306 1: 47: 0.44; Chi <sup>2</sup> = 149.14, Z = 4.85 (P < 0.0000)	5 1.47 0.18 41 4 1.22 0.15 20 9 1.41 0.19 30 5 1.16 0.17 46 4 1.21 0.186 24	3.5% 1.38 [0.73, 2.03] 2.6% 0.75 (-0.35, 1.85)	
Wu B2020 Zhou Y2021 Zhu SC 2018 Zhu SC 2018 Total (95% CI) Heterogeneily, Tau*= Test for overall effect: Study or Subproup Chang WC2014 Granata V2016	1.7 0.32 11 1.35 0.17 11 1.496 0.312 1- 1.503 0.306 1- 472 0.44; Chi <sup>2</sup> = 149.14, Z = 4.85 (P < 0.0000	9 1.41 0.19 30 5 1.16 0.17 46 4 1.21 0.186 24		
Zhou Y2021 Zhu SC 2018 Zhu SC 2018 Total (95% CI) Heterogeneity: Tau*= Test for overall effect: Study or Subproup Chang WC2014 Granata V2016	1.35 0.17 1: 1.496 0.312 1: 1.503 0.306 1: 47: 0.44; Chi <sup>p</sup> = 149.14, Z = 4.85 (P < 0.0000)	5 1.16 0.17 46 4 1.21 0.186 24	3.6% 1.15 [0.53, 1.77]	
Zhu SC2018 Total (95% CI) Heterogeneity, Tau <sup>2</sup> = Test for overall effect: Study or Subgroup Chang WC2014 Granata V2016	1.503 0.306 1 47: 0.44; Chi <sup>p</sup> = 149.14, Z = 4.85 (P < 0.0000	1 4 04 4 0 100	3.6% 1.10 [0.49, 1.72] 3.4% 1.17 [0.45, 1.89]	
Total (95% CI) Heterogeneity: Tau <sup>#</sup> = Test for overall effect: Study or Subgroup Chang WC2014 Granata V2016	47: 0.44; Chi <sup>2</sup> = 149.14, Z = 4.85 (P < 0.0000	4 1.214 U.186 24	3.4% 1.20 [0.48, 1.91]	
Heterogeneity: Tau <sup>a</sup> = Test for overall effect: Study or Subgroup Chang WC2014 Granata V2016	0.44; Chi <sup>2</sup> = 149.14, Z = 4.85 (P < 0.0000	2 1443	100.0% 0.67 [0.40, 0.95]	•
Study or Subgroup Chang WC2014 Granata V2016	Z = 4.85 (P < 0.0000	df = 28 (P < 0.00001); I <sup>2</sup>	= 81%	-4 -2 0 2 4
Study or Subgroup Chang WC2014 Granata V2016		U .		Favours [experimental] Favours [control]
Study or Subgroup Chang WC2014 Granata V2016				
Chang WC2014 Granata V2016	wd-HCC Mean SD Tota	pd -HCC al Mean SD Total	Sto. mean Difference Weight IV, Random, 95% Cl	N. Random, 95% Cl
cratiata v2016	2.04 0.41 3	4 1.26 0.21 43	4.1% 2.46 [1.86, 3.06]	
Guo W2015	1.43 0.09	6 1.16 0.16 11	3.2% 1.82 [0.61, 3.04]	——
Heo SH2010 Iwasa Y2016	1.2 0.22	9 0.9 0.13 9 4 0.9 0.2 10	3.4% 1.58 [0.49, 2.67] 3.7% 1.16 [0.27, 2.04]	
Jiang T2017	1.67 0.13 3	9 1.08 0.11 29	3.6% 4.78 [3.83, 5.74]	
KIM JG2019 Lee S2018	1.14 0.37 1	9 1.02 0.28 12 4 0.947 0.131 7	3.7% 0.36 [-0.51, 1.23] 3.6% 0.80 [-0.15, 1.75]	T
Li X2016	1.13 0.32 2	0 0.92 0.17 23	4.0% 0.82 [0.20, 1.45]	<u>_</u>
monya 12017 Muhi A2009	0.91 0.203 1	2 0.964 0.167 9 9 0.68 0.19 14	3.7% U.44 [-0.43, 1.32] 4.0% 0.96 [0.32, 1.60]	1-
Nishie A2011	1.21 0.11	5 0.902 0.162 26	3.4% 1.92 [0.84, 3.01]	
Ogihara Y2018 Ogihara Y2018	1.33 0.19 1	0 1.06 0.39 12	3.7% 0.82 [-0.06, 1.70]	
Park IK2018 Saito K2012	1.11 0.18 1	8 1.05 0.16 42 7 1.13 0.23 7	4.1% 0.36 [-0.22, 0.94] 3.7% 0.47 L0.42 1 271	<u>+-</u>
Shan QG2017	1.19 0.34 1	8 0.855 0.56 25	4.0% 0.68 [0.06, 1.31]	
Shankar S2016 Tang YH2016	0.924 0.165	8 0.695 0.122 2 0 0.92 0.21 13	2.5% 1.29 [-0.42, 3.00] 3.4% 2.07 [1.01. 3.12]	T
Wang GZ2020	1.46 0.31 2	2 1.1 0.13 69	4.1% 1.89 [1.34, 2.45]	
Wei Y 2019 Wei Y20 19	1.46 0.28 1	5 1.03 0.2 23 5 1.16 0.2 23	3.6% 1.80 [1.02, 2.57] 3.8% 1.74 [0.97, 2.51]	
Wei Y2019	1.77 0.29 1	5 1.31 0.14 23	3.8% 2.13 [1.31, 2.95]	
Wu B2020	1.7 0.32 1	9 1.31 0.27 28	4.0% 1.32 [0.67, 1.96]	
Zhou Y2021 Zhu SC 2010	1.35 0.17 1	5 0.98 0.21 9	3.5% 1.93 [0.91, 2.94]	
Zhu SC2018 Zhu SC2018	1.503 0.306 1	4 1.003 0.247 24	3.8% 1.87 [1.07, 2.66]	
Total (95% CI)	43	5 568	100.0% 1.32 [0.91, 1.74]	•
Heterogeneity: Tau <sup>2</sup> =	1.02; Chi <sup>2</sup> = 184.55,	df = 27 (P < 0.00001); P	= 85%	-4 -2 0 2 4
Control overall ellect.	2 - 0.23 (* * 0.0000	<i></i>		Favours [experimental] Favours [control]
,	md-HCC	pd-HCC	Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean SD Tota	al Mean SD Total	Weight IV, Random, 95% Cl	IV, Random, 95% Cl
Chang WC2014 Granata V2016	1.62 0.3 6 1.03 0.31 3	4 1.26 0.21 43 30 2.44 0.04 18	4.0% 1.34 [0.91, 1.76] 2.1% -5.61 [-6.92, -4.30]	←   <sup></sup>
Guo W2015	1.34 0.19 1	0 1.16 0.16 11	2.9% 0.99 [0.07, 1.91]	<u> </u>
heo sh2010 Iwasa Y2016	1.1 0.1	9 0.9 0.13 9 8 0.9 0.2 10	2.5% 1.64 [U.54, 2.75] 3.1% 0.91 [0.10, 1.73]	
Jiang T2017	1.31 0.16 18	6 1.08 0.11 29	4.0% 1.48 [1.07, 1.90]	<del>_</del>
Lee S2018	1.081 0.25 12	2 1.02 0.28 12 5 0.947 0.131 7	3.2% -0.04 [-0.63, 0.55] 3.2% 0.67 [-0.11, 1.45]	
Li X2016 Moriva T2017	1.12 0.23 19	8 0.92 0.17 23	4.0% 0.89 [0.45, 1.33]	
Muhi A2009	0.71 0.26 3	3 0.68 0.19 14	3.6% 0.12 [-0.50, 0.75]	+-
Nakanishi M2012 Nishie 42011	1.29 0.21 2	9 1.07 0.15 18	3.6% 1.14 [0.51, 1.78]	
Ogihara Y 2018	1.19 0.220 5	1 1.01 0.19 19	3.6% 0.82 [0.23, 1.42]	
Ogihara Y2018 Park IK2018	1.2 0.21 2 1.16 0.21 0	0 1.06 0.39 12	3.3% 0.47 [-0.25, 1.20] 4.1% 0.56 0.18 0.041	1
Saito K2012	1.12 0.22 1	8 1.13 0.23 7	3.0% -0.04 [-0.92, 0.83]	
snan QG2017 Shankar S2016	1.07 1.32 6 0.866 0.1 1	ь U.855 0.56 25 0 0.695 0.122 ?	3.9% 0.18 [-0.28, 0.64] 1.6% 1.54 [-0.15. 3 24]	Ţ
Tang YH2016	1.13 0.18 5	1 0.92 0.21 13	3.5% 1.11 [0.47, 1.75]	
wang 022020 Wei Y 2019	1.28 0.18 3	1 1.1 0.13 69 1 1.03 0.2 23	4.0% 1.20 [0.77, 1.63] 3.8% 0.43 [-0.09, 0.95]	+
Wei Y20 19	1.24 0.15 4	1 1.16 0.2 23	3.8% 0.47 [-0.05, 0.98]	<u> </u>
Woo S2014	1.22 0.15 2	0 1.02 0.13 14	3.2% 0.95 [0.41, 1.48] 3.2% 1.37 [0.61, 2.14]	
Wu B2020	1.41 0.19 3	0 1.31 0.27 28	3.8% 0.43 [-0.10, 0.95]	t <del></del>
Zhu SC 2018	1.21 0.186 2	4 1.003 0.247 24	3.6% 0.93 [0.33, 1.53]	
	1.214 0.186 2	4 1.001 0.236 24	3.6% 0.99 [0.38, 1.59]	
Zhu SC2018	144	6 586	100.0% 0.66 [0.40, 0.93]	•
Zhu SC2018 Total (95% CI)		df = 28 (P < 0.00001): I <sup>2</sup>	= 82%	-4 -2 0 2 4
Zhu SC2018 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect	0.40; Chi <sup>2</sup> = 154.55, Z = 4.92 (P < 0.0000	1)		Favours [experimental] Favours [control]
Zhu SC2018 Total (95% Cl) Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	0.40; Chi <sup>2</sup> = 154.55, Z = 4.92 (P < 0.0000	1)		
Zhu SC2018 Total (95% Cl) Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	0.40; Chi <sup>2</sup> = 154.55, Z = 4.92 (P < 0.0000	1)	Std Mean Difference	Stid Mean Difference
Zhu SC2018 Total (95% CI) Heterogeneity: Tau <sup>®</sup> = Test for overall effect: Study or Subgroup	0.40; Chi <sup>2</sup> = 154.55, Z = 4.92 (P < 0.0000 MVI(-) Mean SD Tota	1) MVI(+) Il Mean SD Total	Std. Mean Difference Weight IV, Fixed, 95% CI	Std. Mean Difference IV, Fixed, 95% Cl
Zhu SC2018 Total (95% CI) Heterogeneity: Tau <sup>a</sup> = Test for overall effect: <u>Study or Subgroup</u> Cao L2019 Chon J025	0.40; Chi <sup>2</sup> = 154.55, Z = 4.92 (P < 0.0000 MVI(-) <u>Mean SD Tota</u> 1.29 0.17 3 2.00 7	1) MVI(+) <u>al Mean SD Total</u> 6 1.22 0.16 38 2 1.39 0.49 0.20	Std. Mean Difference           Weight         IV. Fixed, 95% CI           4.7%         0.42 [-0.04, 0.88]           2.4%         4.47 (0.02, 0.72)	Std. Mean Difference IV. Fixed, 95% Cl
Zhu SC2018 Total (95% CI) Heterogeneih; Tau <sup>2</sup> = Test for overall effect: Study or Subgroup Cao L2019 Chen J2021 Chuang YH2019	0.40; Chi <sup>2</sup> = 154.55; Z = 4.92 (P < 0.0000 MVI(-) Mean SD Tote 1.29 0.17 3 2.09 0.7 3 1.42 0.32 7	MVI(+) <u>al Mean SD Total</u> 6 1.22 0.16 38 3 1.38 0.46 30 9 1.47 0.22 18	Std. Mean Difference           Weight         V, Fixed, 95% CI           4.7%         0.42 [-0.04, 0.88]           3.4%         1.17 [0.83, 1.71]           3.8%         -0.16 [-0.68, 0.35]	Std. Mean Difference N. Fixed, 95% Cl
Zhu SC2018 Total (95% CI) Heterogeneity: Tau*= Test for overall effect: Study or Subgroup Cao L2019 Chaang YH2019 Huang YH2019 Huang YH2019	0.40; ChP = 154.55, Z = 4.92 (P < 0.0000 MVI(-) 1.29 0.17 3 2.09 0.7 3 1.42 0.32 7 1.488 0.35 2 1.05 0.24 7	1) MVI(+) <u>el Mean SD Total</u> 6 1.22 0.16 38 3 1.38 0.46 30 9 1.47 0.22 18 5 1.288 0.245 26 4 1 0.29	Std. Mean Difference           Weight         IV. Fixed, 95% CI           4.7%         0.42 (-0.04, 0.88)           3.4%         1.17 (0.63, 1.71)           3.8%         -0.16 (-0.68, 0.35)           3.1%         0.65 (0.09, 1.22)           9.2%         0.14 (-0.14, 0.57)	Std. Mean Difference IV. Fixed, 95% CI
Zhu SC2018 Total (95% CI) Heterogeneih; Tau <sup>2</sup> = Test for overall effect: Study or Subgroup Cao L2019 Chao J2021 Chuang YH2019 Huang Y02016 Kim J62019 Lee S2017	0.40; Chi <sup>a</sup> = 154.55, Z = 4.92 (P < 0.0000 MVI(-) Mean SD Tote 1.29 0.17 3 2.09 0.7 3 1.42 0.32 7 1.498 0.35 2 1.05 0.24 7 1.09 0.23 13	MVI(+)           Mean         SD         Total           6         1.22         0.16         38           3         1.38         0.46         30           9         1.47         0.22         18           5         1.288         0.245         26           4         1         0.28         69           4         0.18         63         4	Std. Mean Difference           Weight         IV. Fixed, 95% C1           4.7%         0.42 [0.04, 0.88]           3.4%         1.17 [0.63, 1.71]           3.8%         -0.16 [-0.68, 0.35]           3.1%         0.65 [0.09, 1.22]           9.2%         0.19 [-0.14, 0.52]           11.0%         0.32 [0.02, 0.62]	Std. Mean Difference N. Fixed, 95% Cl
Zhu SC2018 Total (95% C) Heterogeneity, Tau*= Test for overall effect: Study or Subgroup Cao L2019 Chen J2021 Chuang YH2019 Huang YC2016 Kim J62019 Lee S2017 Lee S2017 Lee S2018	0.40; Chi <sup>P</sup> = 154.55, Z = 4.92 (P < 0.0000 MV1(-) Mean SD Tote 1.29 0.17 3 2.09 0.7 3 1.42 0.32 7 1.488 0.35 2 1.05 0.24 7 1.09 0.23 13 1.13 0.208 7 1.47 2 1.67 2 1.77 2	NVI(+) <u>11</u> Mean SD Total 6 1.22 0.16 38 3 1.38 0.46 38 9 1.47 0.22 18 5 1.288 0.245 26 4 1 0.245 26 4 1.02 0.18 63 7 0.986 0.15 37 0.466 0.53 27	Std. Mean Difference           Weight         N. Fixed, 95% CI           4.7%         0.42 [0.04, 0.08]           3.4%         1.17 [0.83, 1.71]           3.8%         -0.16 [1.68, 0.35]           3.1%         0.65 [0.09, 1.22]           9.2%         0.19 [-0.14, 0.52]           1.10%         0.32 [0.02, 0.62]           6.1%         0.75 [0.34, 1.15]           2.5%         0.09 (0.02)	Std. Mean Difference 
Zhu SC2018 Total (95% Ct) Heterogenety, Tau*a Test for overall effect: Study of Subgroup Cao L2019 Chen J2021 Chuang VH2019 Lem J20216 Kim J02018 Lem S2017 Lee S2017 Lee S2018 Li H2018 Okamura S2016	0.40; ChP = 154.55, Z = 4.92 (P < 0.0000 MV/(-) 1.29 0.17 3 1.42 0.32 7 1.488 0.35 2 1.05 0.24 7 1.09 0.23 13 1.13 0.208 7 1.74 0.57 2 1.31 0.487 4	MVI(+)           Mean         SD         Total           6         1.22         0.16         38           3         1.38         0.46         30           9         1.47         0.22         18           5         1.288         0.245         26           4         1.028         69         4         1.028         69           7         0.966         0.15         37         0         1.46         0.322         21           1         1.08         0.2421         33         3         1.082         1.21         33	Std. Mean Difference           Weight         N. Fixed, 95% CI.           4.7%         0.42 [-0.04, 0.88]           3.4%         1.17 [0.63, 1.71]           3.5%         0.65 [0.09, 1.22]           9.2%         0.14 [-0.14, 0.52]           1.1%         0.65 [0.09, 1.22]           9.2%         0.65 [0.09, 1.22]           0.2%         0.75 [0.34, 1.15]           2.5%         0.60 [-0.03, 1.23]           4.6%         0.50 [0.03, 0.96]	Std. Mean Difference N. Fixed, 55% CI
Zhu SC2018 Total (95% CI) Heterogeneik/, Tau*a Test for overall effect: Study or Subgroup Chen J2021 Chuang VH2019 Huang V20118 Lee S2017 Lee S2017 Lee S2017 Lee S2017 Lee S2017 Lee S2017 Mang GV 2021 Wang GV 2021	0.40; Chi <sup>2</sup> = 154.55, Z = 4.92 (P < 0.0000 MM/(.) Mean SD Totz 1.29 0.77 3 1.42 0.32 7 1.09 0.23 13 1.48 0.35 2 1.05 0.24 7 1.13 0.208 7 1.74 0.57 2 1.31 0.487 4 1.856 0.418 3 2.029 0.47	Image         MVI(+)           Mean         SD         Total           6         1.22         0.16         38           3         1.38         0.46         30           9         1.47         0.22         18           5         1.288         0.245         26           4         1         0.28         69           4         1.02         0.18         63           7         0.46         0.32         21           7         1.46         0.32         21           1.08         0.421         33         6           6         1.735         0.535         4.10	Std. Mean Difference           Weinht         M. Fixed, 95% CI.           4.7%         0.42 [+0.04, 0.80]           3.4%         1.17 [0.83, 1.71]           3.8%         -0.16 [+0.68, 0.35]           3.1%         0.05 [0.09, 1.22]           9.2%         0.19 [+0.14, 0.52]           1.1%         0.27 [0.34, 1.15]           2.5%         0.60 [+0.03, 1.23]           4.5%         0.26 [+0.36, 0.77]           2.5%         0.60 [+0.03, 1.23]           4.7%         0.26 [+0.36, 0.77]           2.4%         0.60 [+0.03, 1.23]	Std. Mean Difference M. Fized 95% Cl 
Zhu SC2018 Total (95% CI) Heterogeneity, Tau*= Test for overall effect: Study or Subgroup Cao L2019 Cao L2019 Cao L2019 Chen J201 Chen J2019 Lee S2017 Lee S2017 Lee S2017 Lee S2018 LH2018 Okamura S2016 Okamura S2016 Wang (972021 Wang 072021	0.40; Ch <sup>2</sup> = 154.55 Z = 4.92 (P < 0.0000 MVI(-) Mean SD Totz 1.29 0.17 3 2.09 0.7 3 1.42 0.32 7 1.48 0.35 2 1.15 0.24 7 1.09 0.23 13 1.13 0.208 7 1.13 0.208 7 1.13 0.208 7 1.13 0.208 7 1.14 0.57 2 1.31 0.487 4 1.866 0.418 3 2.029 0.709 2	NV1(+) <u>1 Mean SD Total</u> 6 1.22 0.16 30 9 1.47 0.22 18 5 1.288 0.245 26 4 1 0.228 69 1 1.02 18 63 7 0.986 0.15 37 0 1.46 0.32 21 2 1.08 0.421 33 1 1.644 0.285 19 1 1.644 0.285 19 2 0.929 0.144 40	Weint         N. Fixed, 95% CI           4.7%         0.42 fo 0.4.085           4.7%         0.42 fo 0.4.085           3.4%         1.71 0.80,171           3.8%         -0.16 fo 0.80, 0.91           3.1%         0.65 (0.90, 1.22)           3.1%         0.65 (0.90, 1.22)           3.1%         0.65 (0.00, 1.23)           5.5%         0.80 (0.00, 1.23)           5.5%         0.50 (0.03, 1.23)           6.5%         0.50 (0.03, 1.23)           6.5%         0.50 (0.03, 1.23)           5.5%         0.80 (0.05, 1.33)           5.6%         0.50 (0.12, 0.89)	Std. Mean Difference N. Fixed. 95% CL 
Zhu SC2018 Total (95% CI) Heterogeneik, Tau*= Test for overall effect: Study of Subgroup Chen J2021 Chen J2021 Chang (¥12019 Huang V2016 Kim J62019 Lee S2016 LH 2010 S2016 Oxfang (¥2021) Wang (¥72011) Wang (¥72018	0.40; Ch <sup>2</sup> = 154.55, Z = 4.92 (P < 0.0000 MV/(-) Mean SD Totz 1.29 0.17 3 2.09 0.7 3 1.42 0.27 7 1.48 0.35 2 1.05 0.24 7 1.09 0.23 13 1.13 0.208 7 1.74 0.57 2 1.31 0.487 4 1.74 0.57 2 1.31 0.487 4 1.65 0.418 3 2.029 0.70 9 1.31 0.487 4 1.355 0.418 3 2.029 0.70 9 1.37 0.487 5 1.37 0.77 2 1.37 0.487 4 1.37 0.487 4 1.37 0.487 4 1.37 0.487 4 1.37 0.487 4 1.37 0.77 2 1.37 0.77 2 1.3	MV(t)           Il Mean         SD         Total           6         1.22         0.16         38           3         3.80         0.46         30           9         1.47         0.22         18           5         1.280         0.245         26           4         1.02         0.18         63           7         0.966         0.15         37           1.08         0.34         1.32         21           1.08         0.41         3.32         21           1.128         0.424         3.55         24           1         1.64         0.255         24           1         1.64         0.255         24           1         0.84         0.255         24           1         0.84         0.28         19.49           2         0.929         0.149         40           2         0.929         0.149         40           0         0.107         0.77         65	Weight         N. Fixed, 95%; Cl.           4.7%         0.42 (10.4, 0.9%; Cl.           3.6%         -0.16 (10.8, 0.71)           3.6%         -0.16 (10.8, 0.72)           3.6%         -0.16 (10.8, 0.72)           3.6%         -0.16 (10.8, 0.72)           3.6%         -0.16 (10.8, 0.72)           3.6%         -0.16 (10.8, 0.72)           3.6%         -0.16 (10.8, 0.72)           3.6%         -0.16 (10.1, 0.72)           10.6%         0.32 (0.02, 0.81)           5.6%         0.80 (0.03, 0.88)           3.7%         0.26 (10.2, 0.73)           4.6%         0.50 (0.3, 0.88)           3.7%         0.26 (10.2, 0.57)           4.6%         0.56 (0.57, 1.33)           5.6%         0.56 (0.57, 1.33)           5.6%         0.56 (0.57, 1.33)           5.6%         0.56 (0.75, 1.33)           5.6%         0.56 (0.75, 1.33)	Std. Mean Difference Nr. Pixed, 95% CI
Zhu SC2018 Total (95% CI) Hetkrogenetik, Tau*a Test for overall effect. Study or Subgroup Cao L2019 Chona J2021 Chuang VH2019 Lee S2017 Lee S2017 Lee S2017 Lee S2017 Lee S2017 Wang WY 2018 Wang WY 2018 Wang WY 2018 Wang WY 2018 Wang WY 2019 Wei Y2019 Wei Y2019 Wei Y2019 Su P2014.	$\begin{array}{c} 0.40; {\rm ch}^{2}=154.85;\\ {\rm Z}=4.92({\rm P}<0.0000\\\\\hline \\ \hline \\ {\rm Mean} \qquad {\rm SD} \ {\rm Totz}\\ 1.29\ 0.17\ 3\\ 2.09\ 0.7\ 3\\ 1.42\ 0.22\ 7\\ 1.48\ 0.35\ 2\\ 1.42\ 0.22\ 7\\ 1.48\ 0.35\ 2\\ 1.13\ 0.248\ 7\\ 1.13\ 0.248\ 7\\ 1.13\ 0.248\ 7\\ 1.13\ 0.248\ 7\\ 1.13\ 0.248\ 7\\ 1.13\ 0.268\ 7\\ 1.13\ 0.268\ 7\\ 1.13\ 0.268\ 7\\ 1.37\ 0.37\ 8\\ 1.37\ 0.37\ 8\\ 1.37\ 0.37\ 8\\ 1.33\ 0.38\ 7\\ 1.33\ 0.38\ 1.33\ 0.38\ 1.33$	MM(r)           I Mean         SD         Total           0         122         0.16         38           0         120         0.16         38           0         147         0.22         16           5         1.28         0.46         32           4         10.22         16         34           7         0.46         0.15         37           0         1.46         0.32         21           1         0.28         0.55         24           1         1.28         0.55         24           1         1.28         0.55         24           1         1.46         0.32         21           2         0.32         0.149         40           0         0.40         0.17         0.27           0         1.46         0.27         55           2         0.328         0.38         39           0         1.22         0.38         39	Sid. Mean Difference           Weinin IV. Fixed. 55:5:1           4.%         17.10, 83.1711           3.6%         1.10, 10.83, 10.91           3.6%         0.15, 10.86, 0.39           3.1%         0.85, 10.94, 12.92           3.1%         0.10, 10.22, 0.51           2.5%         0.69, 10.94, 0.52           2.5%         0.69, 10.94, 0.52           2.5%         0.69, 10.93, 12.33           4.6%         0.50, 10.33, 0.36           5.6%         0.59, 10.30, 0.37           2.4%         0.89, 10.54, 13.02           5.6%         0.59, 10.30, 0.37           7.%         0.26, 10.31, 0.39           7.%         0.90, 10.54, 13.02           7.%         0.90, 10.54, 13.02           7.%         0.90, 10.54, 13.02           7.%         0.90, 10.54, 13.02           7.%         0.90, 10.47, 13.7	Std. Mean Difference M. Fized 95% Cl 
Zhu Sc2018 Total (95:0) Test for overall effect Situdy of Subgroup Cao L2019 Cao L2019 Cao L2019 Chanago V12019 Huang V20216 Lee S2018 Lee S2018 Lee S2018 Lee S2018 Lee S2018 Lee S2018 Wang 0Y2021 Wang 0Y2019 Wang 0Y2019	$\begin{array}{c} 0.40; \ \ chr^m=154, \ \ s5, \\ \mathbb{Z}=4, 92 \ (P < 0.0000 \\ \mathbb{W} M(t) \\ \hline \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \$	MV(r)           Mean         SD         Total           0         122         0.16         38           1.38         0.48         30         1.80         0.48           1.47         0.22         18         4           4         1.28         0.48         30         1.80           7         0.86         0.45         37         1.86         94           4         1.20         0.16         32         12         1.08         0.42         12           1         1.44         0.22         12         1.08         0.42         12         1.08         0.42         12           2         0.80         0.144         0.255         24         1         1.44         0.26         10         0.26         0.149         40         2         0.918         0.149         40         2         0.918         0.149         40         0.12         0.26         0.149         40         0         1.20         0.26         0.26         0.26         0.26         0.26         0.26         0.26         0.26         0.26         0.26         0.26         0.26         0.26         0.26         0.26	Weight         Nr. Faced, 35%; Cl.           4,7%         0.42; (10,4,6); (10,4	Std. Mean Difference M. Fized 95% CL 
Zhu SC018 Total (95% C) Helerogeneily: Tay*s Test for overall effect: Study or Subgroup Cao L2019 Chang (H12019 Chang (H12019 Chang (H12019 Chang (H12019 Chang (H12019 Chang (H12019 Chang (H12019) Chang (H1201	$\begin{array}{c} 0.40; \ \ (n + 1 \le 4 \le 5; \\ Z = 4.92 \ (P < 0.0000 \\ \hline \\ \hline$	NV(+)           1         Mean         SD         Total           0         1.22         0.16         38           1.80         0.46         30         1.80         0.46           9         1.47         0.22         18           5         1.28         0.14         0.22         18           4         10         0.28         63         4         0.02         17           1.00         0.46         0.02         21         1.06         0.41         31         1.55         24         1.02         21         1.06         0.41         31         1.55         24         1.02         25         1.0         1.735         0.555         24         1.1735         0.555         24         1.16         40         0.20         0.90         0.149         40         0.010         0.07         5.7         0         1.22         0.38         39         0         1.07         0.16         21         3         1.50         0.22         1.06         211         3         1.50         0.22         1.08         0.01         0.01         0.07         0.77         55         0         1.22         0.38         30<	Weight         Nr. Fixed, 95%; Cl.           4.7%         0.42 (10.43, 171)           3.6%         -0.16 (10.83, 171)           3.6%         -0.16 (10.83, 171)           3.6%         -0.16 (10.84, 172)           3.6%         -0.16 (10.84, 172)           3.6%         -0.16 (10.84, 172)           3.6%         -0.16 (10.84, 172)           0.5%         0.16 (10.93, 174)           0.5%         0.05 (10.33, 174)           2.5%         0.60 (10.03, 123)           3.7%         0.26 (10.23, 174)           4.6%         0.60 (10.30, 123)           3.7%         0.26 (10.32, 123)           4.6%         0.60 (10.30, 123)           5.6%         0.56 (10.30, 023)           6.6%         0.56 (10.30, 024)           6.6%         0.56 (10.30, 024)           6.6%         0.56 (10.30, 024)           7.7%         0.09 (10.96, 123)           7.7%         0.09 (10.96, 123)           7.3%         0.73 (10.96, 123)           7.3%         0.73 (10.93, 024)           7.3%         0.73 (10.93, 024)           9.0%         0.57 (10.02, 115)	Std. Mean Difference M. Fized 95% Cl 

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.

	N	vd-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	0.865	0.198	14	0.837	0.197	75	23.9%	0.14 [-0.43, 0.71]	
Li X2016	1.04	0.36	20	0.98	0.24	198	36.7%	0.24 [-0.22, 0.70]	
Moriya T2017	0.585	0.388	12	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% CI)			58			459	100.0%	0.39 [0.12, 0.67]	◆
Heterogeneity: Chi <sup>2</sup> =	= 3.32, df	= 4 (P =	0.51);	$l^2 = 0\%$				-	-4 -2 0 2 4
Fest for overall effect	: Z = 2.77	(P = 0.1	006)						Favours [experimental] Favours [control]
						~		Std. Moon Difforonco	Std Moon Difference
Study or Subgroup	Moan	SD-PCC	Total	Moan	pa -nu	Total	Mojaht	Stu. Wean Difference	Std. Mean Difference
July of Subgroup	1.04	0.25		0.70	0.00	10101	40.00	0.05 ( 0.06 4 70)	
Kim JG2019	1.01	0.35	9	0.76	0.22	12	19.0%	0.85 [-0.06, 1.76]	
Lee 52018	0.865	0.198	14	0.624	0.24		10.4%	1.09 [0.11, 2.07]	
LI A2016	1.04	0.36	20	0.78	0.2	23	39.5%	0.89 [0.26, 1.53]	
Monya 12017 Nelvenieki MOOAC	0.585	0.388	12	0.235	0.102	9	17.8%	1.11 [0.17, 2.05]	
Nakanishi M2012	1.15	U.1	3	0.69	0.19	18	7.3%	2.42 [0.95, 3.89]	
Total (95% CI)			58	17 000		69	100.0%	1.07 [0.67, 1.46]	
Heterogeneity: Chir =	= 3.77, df	= 4 (P =	0.44);	1*= 0%				-	-4 -2 0 2 4
l est for overall effect	: Z = 5.28	(P < U.	00001)						Favours [experimental] Favours [control]
		md-H	ICC		nd-HC	C		Std. Mean Difference	Std. Mean Difference
Study or Subaroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Random, 95% Cl	IV. Random, 95% Cl
<im. ig2019<="" td=""><td>0.82</td><td>0.24</td><td>122</td><td>0.76</td><td>0.22</td><td>12</td><td>21.4%</td><td>0.25 [-0.34_0.84]</td><td></td></im.>	0.82	0.24	122	0.76	0.22	12	21.4%	0.25 [-0.34_0.84]	
ee S2018	0.837	0 197	75	0.624	0.24	7	15.9%	1.05 [0.26, 1.84]	_ <b>_</b>
i X2016	0.98	0.24	198	0.78	0.2	23	26.8%	0.84 [0.40, 1.28]	
Moriva T2017	0.411	0.278	35	0.235	0.102	9	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]	
Fotal (95% CI)			459			69	100.0%	0.86 [0.44, 1.27]	•
Heterogeneity: Tau <sup>2</sup> =	= 0.11; CI	ni² = 8.5	3. df =	4 (P = 0	.07); I <sup>2</sup> =	53%		-	
Test for overall effect	Z= 4.07	(P < 0.0	0001)						-4 -2 0 2 4
			,						Favours [experimental] Favours [control]
I					/I\/I(+)			Std. Mean Difference	Std Mean Difference
Study or Subaroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Random 95% Cl	IV. Random, 95% CI
Chuang YH2010	1 02	0.22	70	0.85	0.24	1.9	20.5%	0.86 (0.22 1.20)	
kim 162019	0.85	0.23	74	0.03	0.24	60	26.5%	0.00 [0.00, 1.00]	+
002013	0.00	0.24	77	0.0	0.20	27	20.0%	1 1 / [0 72 1 66]	
Lee 02010 7boo 12017	0.090	0.172	107	0.007	0.199	214	20.1%	0.70 (0.65, 1.00)	
21180 32017	1.00	0.17	107	0.92	0.18	211	23.1%	0.79 [0.00, 1.03]	
Total (95% CI)			337			335	100.0%	0.73 [0.34, 1.12]	-
Heterogeneity: Tau <sup>2</sup> :	= 0.12; C	hi² = 14.	02, df:	= 3 (P =	0.003);	<sup>2</sup> = 799	%	-	
Test for overall effect	: Z = 3.67	(P = 0.)	0002)						-z -i U i Z
									Favours (experimental) Favours (control)

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

	١	vd-HCC			md-ł	ICC		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	0.81	0.49	30	10.4%	0.12 [-0.52, 0.75]	
Shan QG2017	1.01	0.36	18	0.91	1.44	66	11.0%	0.08 [-0.44, 0.60]	7
Vei Y 2019	1.2	0.17	15	0.96	0.16	41	10.3%	1.45 [0.80, 2.11]	
Vei Y20 19	1.33	0.17	15	1.13	0.13	41	10.4%	1.39 [0.74, 2.04]	
Vei Y2019	1.47	0.04	15	1.23	0.09	41	9.4%	2.95 [2.14, 3.77]	
Noo 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	1.186	0.214	14	0.91	0.151	24	9.8%	1.53 [0.78, 2.28]	
Zhu SC2018	1.193	0.226	14	0.91	0.148	24	9.8%	1.54 [0.78, 2.29]	
fotal (95% CI)			143			363	100.0%	1.17 [0.67, 1.68]	•
Heterogeneity: Tau <sup>2</sup> :	= 0.52; C	hi² = 48.	.49, df :	= 9 (P <	0.0000	1); l² = 8	31%		-4 -2 0 2 4
Fest for overall effect	t: Z = 4.58	8 (P < 0.)	00001)						Favours [experimental] Favours [control]
	v	vd -HCC			pd -HCC	2	5	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	0.86	0.09	14	1.51	0.11	18	8.7%	-6.22 [-7.99, -4.45]	- <b>-</b>
3han 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]	
Voo S2014	1.3	0.28	4	1.02	0.13	14	9.7%	1.58 [0.33, 2.84]	
Vu B2020	1.18	0.33	19	0.79	0.2	28	10.6%	1.48 [0.81, 2.14]	+
hou Y2021	1.06	0.17	15	0.76	0.18	9	10.2%	1.67 [0.69, 2.64]	
hu SC 2018	1.186	0.214	14	0.775	0.187	24	10.4%	2.04 [1.22, 2.86]	
		0.000				~ 1	4.0.40/	2 06 14 22 2 061	
(hu SC2018	1.193	0.226	14	0.771	0.187	24	10.4%	2.05 [1.25, 2.60]	
(hu SC2018	1.193	0.220	14	0.771	0.187	24	10.4%	2.05 [1.25, 2.60]	
(hu SC2018 (otal (95% Cl)	1.193	U.220	14 143	0.771	0.187	24 211	10.4%	1.59 [0.44, 2.74]	◆
(hu SC2018 f <b>otal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> =	1.193 = 3.13; Cl	0.226 hi <sup>2</sup> = 14(	14 143 0.49, df	0.771 (P <	0.187 < 0.0000	24 <b>211</b> 01); I <sup>2</sup> =	10.4% 100.0% 94%	1.59 [0.44, 2.74]	-10 -5 0 5 10
(hu SC2018 f <b>otal (95% Cl)</b> Heterogeneity: Tau <sup>2</sup> = fest for overall effect	1.193 = 3.13; Cl : Z = 2.71	0.226 hi <sup>2</sup> = 14( (P = 0.0	14 143 0.49, df 007)	0.771 (= 9 (P <	0.187 < 0.0000	24 <b>211</b> 01); I <sup>2</sup> =	10.4% 100.0% 94%	1.59 [0.44, 2.74] -	-10 -5 0 5 10 Favours [experimental] Favours [control]
(hu SC2018 f <b>otal (95% Cl)</b> leterogeneity: Tau <sup>2</sup> = fest for overall effect	1.193 = 3.13; Cl : Z = 2.71	0.226 hi <sup>2</sup> = 14( (P = 0.0	14 143 0.49, df 007)	0.771 f= 9 (P <	0.187 < 0.0000	24 <b>211</b> 01); I <sup>2</sup> =	10.4% 100.0% 94%	1.59 [0.44, 2.74]	-10 -5 0 5 10 Favours [experimental] Favours [control]
(hu SC2018 iotal (95% CI) leterogeneity: Tau <sup>2</sup> = est for overall effect	1.193 = 3.13; Ci : Z = 2.71 Mean	0.226 hi <sup>2</sup> = 14( (P = 0.0 <b>md-</b> H	14 143 0.49, df 007) ICC Total	0.771 (= 9 (P <	0.187 < 0.0000 pd-HC(	24 211 01); I <sup>2</sup> = C Total	10.4% 100.0% 94%	1.59 [0.44, 2.74]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference
(hu SC2018 iotal (95% CI) leterogeneity: Tau <sup>2</sup> = est for overall effect <u>study or Subgroup</u>	1.193 = 3.13; Cl : Z = 2.71 <u>Mean</u>	0.228 hi <sup>2</sup> = 14( (P = 0.0 <b>md-H</b> <u>SD</u>	14 143 0.49, df 007) ICC <u>Total</u>	0.771 (= 9 (P < <u>Mean</u>	0.187 < 0.0000 pd-HC( SD	24 211 01); I <sup>2</sup> = C <u>Total</u>	10.4% 100.0% 94% <u>Weight</u>	1.59 [0.44, 2.74] Std. Mean Difference IV, Random, 95% Cl -1.74 (2.42, -1.06)	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV, Random, 95% Cl
(hu SC2018 iotal (95% Cl) leterogeneity: Tau <sup>2</sup> = iest for overall effect itudy or Subgroup Standta V2016 bran 062047	1.193 = 3.13; Cl : Z = 2.71 <u>Mean</u> 0.81	0.226 hi <sup>2</sup> = 14( (P = 0.( <b>md-H</b> <u>SD</u> 0.49	14 143 0.49, df 007) ICC <u>Total</u> 30	0.771 f= 9 (P < <u>Mean</u> 1.51	0.187 < 0.0000 pd-HC( <u>SD</u> 0.11 0.57	24 211 )1); I <sup>2</sup> = C <u>Total</u> 18	10.4% 100.0% 94% <u>Weight</u> 9.7%	1.59 [0.44, 2.74] 1.59 [0.44, 2.74] Std. Mean Difference <u>IV, Random, 95% Cl</u> -1.74 [-2.43, -1.06] 0.07 (-0.29.0.552)	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV, Random, 95% Cl
(hu SC2018 iotal (95% Cl) leterogeneity: Tau <sup>2</sup> = iest for overall effect istudy or Subgroup Sranata V2016 Shan QG2017 Shan QG2017	1.193 = 3.13; Cl : Z = 2.71 <u>Mean</u> 0.81 0.91	0.228 hi <sup>2</sup> = 14( (P = 0.( <b>md-H</b> <u>SD</u> 0.49 1.44 0.16	14 143 0.49, df 007) ICC Total 30 66	0.771 (= 9 (P < <u>Mean</u> 1.51 0.82	0.187 < 0.0000 pd-HC( <u>SD</u> 0.11 0.57 0.11	24 <b>211</b> )1); I <sup>2</sup> = C <u>Total</u> 18 25 22	10.4% 100.0% 94% <u>Weight</u> 9.7% 10.5% 10.2%	1.59 [0.44, 2.74] 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] 0.99 [0.26, 4, 42]	-10 -5 0 5 10 Favours (experimental) Favours (control) Std. Mean Difference IV, Random, 95% Cl
(hu SC2018 <b>iotal (95% CI)</b> leterogeneity: Tau <sup>2</sup> = <b>iest for overall effect</b> <b>itudy or Subgroup</b> Sranata V2016 Shan QG2017 Vei Y 2019 Vei Y 2019	1.193 = 3.13; CI : Z = 2.71 <u>Mean</u> 0.81 0.91 0.96 1.12	0.228 hi² = 14( (P = 0.0 md-H <u>SD</u> 0.49 1.44 0.16 0.12	14 143 0.49, df 007) ICC <u>Total</u> 30 66 41	0.771 (= 9 (P < <u>Mean</u> 1.51 0.82 0.83 0.96	0.187 < 0.0000 pd-HC( SD 0.11 0.57 0.11 0.1	24 211 21); I <sup>2</sup> = C Total 18 25 23 22	10.4% 100.0% 94% <u>Weight</u> 9.7% 10.5% 10.3% 10.3%	<b>1.59 [0.44, 2.74]</b> <b>1.59 [0.44, 2.74]</b> <b>5td. Mean Difference</b> <b>IV, Random, 95% CI</b> -1.74 [-2.43, -1.06] 0.07 [-0.39, 0.53] 0.89 [0.36, 1.43] 1.40 [0.92, 4.97]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV, Random, 95% Cl
(hu SC2018 <b>iotal (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = iest for overall effect <b>Study or Subgroup</b> Stanata V2016 Shan QG2017 Vei Y 2019 Vei Y 2019 Vei Y2019	1.193 = 3.13; C : Z = 2.71 <u>Mean</u> 0.81 0.91 0.96 1.13	0.228 hi² = 140 (P = 0.0 md-H <u>SD</u> 0.49 1.44 0.16 0.13 0.09	14 143 0.49, df 007) ICC Total 30 66 41 41	0.771 (= 9 (P < <u>Mean</u> 1.51 0.82 0.83 0.96 1.07	0.187 < 0.00000 pd-HC( SD 0.11 0.57 0.11 0.1 0.1	24 211 21); I <sup>2</sup> = C Total 18 25 23 23 23 23	10.4% 100.0% 94% <u>Weight</u> 9.7% 10.5% 10.3% 0.3% 0.2%	1.59 [0.44, 2.74] 1.59 [0.44, 2.74] Std. Mean Difference IV. Random, 95% Cl -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 [1.24, 2.59]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference N. Random, 95% Cl
thu SC2018 iotal (95% CI) leterogeneity: Tau <sup>2</sup> = iest for overall effect itudy or Subgroup Stanata V2016 Shan QG2017 Vei Y2019 Vei Y2019 Vei Y2019 Vei Y2014	1.193 = 3.13; C : Z = 2.71 0.81 0.91 0.96 1.13 1.15	0.228 $hi^2 = 14($ (P = 0.0) md-H SD 0.49 1.44 0.16 0.13 0.09 0.42	14 143 0.49, df 007) ICC Total 30 66 41 41 41 20	0.771 (= 9 (P < <u>Mean</u> 1.51 0.82 0.83 0.96 1.07	<pre>0.187 &lt; 0.00000 pd-HC(     SD     0.11     0.57     0.11     0.10     0.12 </pre>	24 <b>211</b> D1); I <sup>2</sup> = C Total 18 25 23 23 23 23 14	10.4% 100.0% 94% <u>Weight</u> 9.7% 10.5% 10.3% 10.1% 9.9%	<b>1.59 [0.44, 2.74]</b> <b>1.59 [0.44, 2.74]</b> <b>5td. Mean Difference</b> <b>IV. Random, 95% CI</b> -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] 0.09 [0.25, 4, 70]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV, Random, 95% Cl
(hu SC2018 <b>otal (95% CI)</b> leterogeneity: Tau <sup>≈</sup> = <b>est for overall effect</b> <b>Study or Subgroup</b> Stanata V2016 Shan QG2017 Vei Y 2019 Vei Y2019 Vei Y2019 Vei Y2019 Vei Y2019 Vei Y2019	1.193 = 3.13; C : Z = 2.71 <u>Mean</u> 0.81 0.91 0.96 1.13 1.23 1.15	0.228 hi <sup>2</sup> = 14( (P = 0.0 <b>md-H</b> 0.49 1.44 0.16 0.13 0.09 0.13 0.28	14 143 0.49, df 007) ICC Total 30 66 41 41 41 20 20	0.771 (= 9 (P < <u>Mean</u> 1.51 0.82 0.83 0.96 1.07 1.02 0.7	<pre>0.187 &lt; 0.00000 pd-HC(     SD     0.11     0.57     0.11     0.1     0.13     0.13     0.2 </pre>	24 <b>211</b> D1);   <b>r</b> <sup>2</sup> = C Total 18 25 23 23 23 23 23 23 23 23 23 23	10.4% 100.0% 94% Weight 9.7% 10.5% 10.3% 10.1% 9.9% 9.9% 9.5%	<b>1.59 [0.44, 2.74]</b> <b>1.59 [0.44, 2.74]</b> <b>5td. Mean Difference</b> <b>I.74 [2.43, -1.06]</b> 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] 0.58 [0.22, 1.02]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV, Random, 95% Cl
thu SC2018 iotal (95% CI) leterogeneity: Tau <sup>≈</sup> = iest for overall effect itudy or Subgroup Stanata V2016 Shan QG2017 Vei Y2019 Vei Y2019 Vei Y2019 Voo S2014 Vu B2020 Dou X2021	1.193 = 3.13; C1 : Z = 2.71 0.81 0.96 1.13 1.23 1.15 0.92	0.226 hi² = 14( (P = 0.0 0.49 1.44 0.16 0.13 0.09 0.13 0.26 0.16	14 143 0.49, df 007) ICC Total 30 66 41 41 41 20 30 41 41 20 30 41 41 20 30 41 41 41 41 41 41 41 41 41 41	0.771 = 9 (P < <u>Mean</u> 1.51 0.82 0.83 0.96 1.07 1.02 0.79 0.79	0.187 ► 0.00000 ► 0.00000 ► 0.11 0.11 0.11 0.11 0.11 0.11 0.13 0.12 0.12	24 <b>211</b> D1);   <sup>2</sup> = C <u>Total</u> 18 25 23 23 23 14 28 0	10.4% 100.0% 94% <u>Weight</u> 9.7% 10.5% 10.3% 10.3% 9.5% 10.3% 9.5% 10.3%	1.59 [0.44, 2.74] 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 L0.00 1 45]	-10 -5 0 5 10 Favours (experimental) Favours (control) Std. Mean Difference IV, Random, 95% Cl
thu SC2018 otal (95% CI) leterogeneity: Tau <sup>2</sup> = Test for overall effect est for overall effect an QG2017 Vei Y2019 Vei Y2019 Vei Y2019 Voo S2014 Vu B2020 thou Y2021 thu SC 2012	1.193 = 3.13; Cl : Z = 2.71 0.81 0.96 1.13 1.23 1.15 0.92 0.88	0.226 hi² = 14( (P = 0.0 0.49 1.44 0.16 0.13 0.09 0.13 0.26 0.151	14 143 0.49, df 007) ICC Total 30 66 41 41 20 30 30 30 24	0.771 f= 9 (P < <u>Mean</u> 1.51 0.82 0.83 0.96 1.07 1.02 0.79 0.76 0.776	<pre>0.187 &lt;0.00000 pd-HC(     SD     0.11     0.57     0.11     0.16     0.13     0.2     0.18 </pre>	24 <b>211</b> D1);   <sup>2</sup> = C Total 18 25 23 23 23 14 28 9 24	10.4% 100.0% 94% Weight 9.7% 10.5% 10.3% 9.9% 9.5% 10.3% 9.5%	1.59 [0.44, 2.74] 1.59 [0.44, 2.74] Std. Mean Difference IV, Random, 95% CI -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] 0.72 [-0.00, 1.45]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV, Random, 95% Cl
thu SC2018 teterogeneity: Tau <sup>≈</sup> = test for overall effect tudy or Subgroup than QG2017 Vei Y2019 Vei Y2019 Vei Y2019 Voo S2014 Vu B2020 thou Y2021 thou SC2018 thu SC2018	1.193 = 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	0.226 hi <sup>2</sup> = 14( (P = 0.0 0.49 0.44 0.16 0.13 0.09 0.13 0.26 0.151 0.151 0.148	14 143 0.49, df 007) ICC Total 30 66 41 41 41 20 30 46 24 24 24	Mean (= 9 (P < Mean 1.51 0.82 0.83 0.96 1.07 1.02 0.79 0.76 0.775	<pre>0.187 &lt;0.0000 pd-HC( SD 0.11 0.57 0.11 0.1 0.06 0.13 0.2 0.18 0.187 0.187</pre>	24 211 01);   <sup>2</sup> = C Total 18 25 23 23 23 23 14 28 9 24 24	10.4% 100.0% 94% Weight 9.7% 10.5% 10.5% 10.1% 9.5% 10.3% 9.5% 10.3% 9.5% 10.3%	1.59 [0.44, 2.74] 1.59 [0.44, 2.74] Std. Mean Difference IV, Random, 95% Cl -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]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV, Random, 95% CI
thu SC2018 <b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = rest for overall effect <b>Study or Subgroup</b> Stranata V2016 Shan QG2017 Vei Y 2019 Vei Y2019 Vei Y2019 Vei Y2019 Voo S2014 Vu B2020 Chou Y2021 Chou SC 2018 Chou SC2018 Chou SC2018 Cho	1.193 = 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	0.226 hi <sup>2</sup> = 14( (P = 0.0 0.49 1.44 0.16 0.13 0.09 0.13 0.26 0.16 0.151 0.148	14 143 0.49, df 007) ICC Total 30 66 41 41 41 20 30 46 24 24 24	Mean (= 9 (P < 1.51 0.82 0.83 0.96 1.07 1.02 0.79 0.76 0.775 0.771	■ 0.187 ■ 0.00000 ■ 0.11 0.11 0.11 0.11 0.11 0.13 0.2 0.18 0.187 0.187	24 211 21);   <sup>2</sup> = C Total 18 25 23 23 23 23 23 23 23 24 24 24 24 24 24 24	10.4% 100.0% 94% 94% 97% 10.5% 10.3% 10.1% 9.9% 9.5% 10.3% 10.3% 10.3% 10.3% 10.3% 10.3% 10.3% 10.3% 10.3% 10.3% 10.3% 10.3% 10.3% 10.3% 10.5% 10.3% 10	1.59 [0.44, 2.74] 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 [0.02, 1.02]	-10 -5 0 5 10 Favours (experimental) Favours (control) Std. Mean Difference IV, Random, 95% Cl
thu SC2018 teterogeneity: Tau <sup>2</sup> = test for overall effect tudy or Subgroup than Q62017 Vei Y 2019 Vei Y 2019 Vei Y2019 Vei Y2019 Voo S2014 Vu B2020 thou Y2021 thou Y2021 thou SC2018 thu SC2018 thu SC2018	1.193 = 3.13; CI : Z = 2.71	0.226 hi <sup>2</sup> = 14( (P = 0.0 0.49 1.44 0.16 0.13 0.09 0.13 0.26 0.16 0.151 0.148	14 143 0.49, df 007) ICC Total 66 41 41 41 20 30 46 24 24 363 24 24	Mean (= 9 (P < Mean 1.51 0.82 0.83 0.96 1.07 1.02 0.79 0.76 0.775 0.771	<ul> <li>0.187</li> <li>0.0000</li> <li>pd-HC(</li> <li>SD</li> <li>0.11</li> <li>0.57</li> <li>0.11</li> <li>0.16</li> <li>0.13</li> <li>0.2</li> <li>0.18</li> <li>0.187</li> <li>0.187</li> </ul>	24 211 21); F= C Total 25 23 23 23 23 23 23 23 23 24 24 24 24 24 24 24 24 24 24	10.4% 100.0% 94% 94% <u>Weight</u> 9.7% 10.5% 10.5% 10.1% 10.1% 10.1% 10.1%	1.59 [0.44, 2.74] 1.59 [0.44, 2.74] Std. Mean Difference IV. Random, 95% Cl -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]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV. Random, 95% CI
thu SC2018 otal (95% CI) leterogeneity: Tau <sup>2</sup> = rest for overall effect est for overall est est	1.193 = 3.13; CI : Z = 2.71 Mean 0.91 0.96 1.13 1.23 1.15 0.92 0.88 0.91 0.91 = 0.70; CI	0.226 $hi^2 = 14($ (P = 0.0) 0.49 1.44 0.16 0.13 0.26 0.151 0.148 $hi^2 = 78.$	14 143 0.49, dti 007) HCC Total 300 66 41 41 41 41 20 30 46 24 24 363 356, dt=	0.771 (= 9 (P < 1.51 0.82 0.83 0.96 1.07 1.02 0.79 0.76 0.775 0.771 = 9 (P <	<pre>0.187 &lt; 0.0000 pd-HC( SD 0.11 0.57 0.11 0.16 0.13 0.2 0.18 0.187 0.187 0.00001</pre>	24 211 11);  F = Total 18 25 23 23 23 23 23 14 28 9 24 24 24 24 24 21 ();  F = 23 23 23 23 23 23 23 23 23 24 24 25 23 23 23 23 24 25 24 25 23 23 23 24 25 24 25 23 23 23 24 25 23 23 23 24 25 24 25 23 23 23 24 25 24 25 23 23 23 24 25 24 25 24 25 23 23 24 25 24 25 24 25 24 25 25 25 25 25 25 25 25 25 25	10.4% 100.0% 94% 94% 9.7% 10.5% 10.3% 10.3% 9.5% 10.3% 9.5% 10.1% 10.1% 10.1% 100.0% 9%	1.59 [0.44, 2.74] 1.59 [0.44, 2.74] Std. Mean Difference IV, Random, 95% CI -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]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV, Random, 95% CI
thu SC2018 otal (95% CI) leterogeneity: Tau <sup>2</sup> = cest for overall effect est for overall effect canata V2016 chan QG2017 Vei Y2019 Vei Y2019 Vei Y2019 Vei Y2019 Voo S2014 Vu B2020 chou Y2021 chou SC2018 chu SC2018 otal (95% CI) leterogeneity: Tau <sup>2</sup> = cest for overall effect	1.193 = 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	0.226 $hi^2 = 14($ (P = 0.0) 0.49 1.44 0.16 0.13 0.26 0.151 0.148 $hi^2 = 78.$ (P = 0.0)	14 143 0.49, dt 007) ACC <u>Total</u> 30 66 41 41 20 30 46 24 24 363 356, dt= 02)	Mean (= 9 (P < 1.51 0.82 0.83 0.96 1.07 1.02 0.79 0.76 0.775 0.771 = 9 (P <	<ul> <li>0.187</li> <li>0.0000</li> <li>sD</li> <li>0.11</li> <li>0.57</li> <li>0.11</li> <li>0.16</li> <li>0.13</li> <li>0.2</li> <li>0.18</li> <li>0.187</li> <li>0.187</li> <li>0.00001</li> </ul>	24 211 21);   <sup>2</sup> = C Total 18 25 23 23 23 23 23 14 28 9 24 24 24 24 24 24 24 24 24 24	10.4% 100.0% 94% 94% 9.7% 10.5% 10.5% 10.3% 9.9% 9.5% 10.3% 9.5% 10.1% 10.1% 10.1% 100.0% 9%	1.59 [0.44, 2.74] 1.59 [0.44, 2.74] Std. Mean Difference IV. Random, 95% CI -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 [0.34, 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]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV, Random, 95% CI -4 -2 0 2 4 Favours [experimental] Favours [control]
thu SC2018 <b>iotal (95% CI)</b> leterogeneity: Tau <sup>≈</sup> = est for overall effect <b>itudy or Subgroup</b> Stanata V2016 Shan QG2017 Vei Y 2019 Vei Y2019 Vei Y2019 Vei Y2019 Voo S2014 Vu B2020 Chou Y2021 Chou Y2021 Chou SC 2018 Chou SC 2018 <b>iotal (95% CI)</b> leterogeneity: Tau <sup>≈</sup> = est for overall effect	1.193 = 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	0.226 $hi^2 = 14($ (P = 0.0) 0.49 1.44 0.13 0.09 0.13 0.26 0.161 0.148 $hi^2 = 78.$ (P = 0.0)	14 143 0.49, df 1007) ACC <u>Total</u> 30 66 41 41 20 30 46 24 24 363 56, df = 502)	Mean 1.51 0.82 0.83 0.96 1.07 1.02 0.79 0.76 0.775 0.771 = 9 (P <	<ul> <li>0.187</li> <li>0.0000</li> <li>9d-HC0</li> <li>SD</li> <li>0.11</li> <li>0.57</li> <li>0.11</li> <li>0.16</li> <li>0.13</li> <li>0.2</li> <li>0.18</li> <li>0.187</li> <li>0.187</li> <li>0.187</li> <li>0.00001</li> </ul>	24 211 21);   <sup>2</sup> = C Total 18 25 23 23 23 23 14 28 9 24 21 28 9 24 21 28 9 24 21 28 9 24 24 21 28 29 24 24 28 29 24 29 24 29 24 24 24 25 23 23 23 23 23 23 23 24 24 24 24 24 24 24 24 24 24	10.4% 100.0% 94% 94% 9.7% 10.5% 10.5% 10.3% 9.5% 10.3% 9.5% 10.3% 9.5% 10.1% 10.1% 10.1% 10.1%	1.59 [0.44, 2.74] 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]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV, Random, 95% CI -4 -2 0 2 4 Favours [experimental] Favours [control]
thu SC2018 otal (95% CI) leterogeneity: Tau <sup>2</sup> = est for overall effect otal y2016 branata V2016 bran QG2017 Vei Y 2019 Vei Y2019 Vei Y2019 Vei Y2019 Vos S2014 Vu B2020 chou Y2021 thu SC 2018 cotal (95% CI) leterogeneity: Tau <sup>2</sup> = est for overall effect	1.193 = 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	0.226 $hi^2 = 14($ (P = 0.0) 0.49 1.44 0.16 0.13 0.09 0.13 0.26 0.151 0.148 $hi^2 = 78.$ I (P = 0.0) VVI(-)	14 143 0.49, df 1007) ACC <u>Total</u> 30 66 41 41 20 30 46 24 363 56, df = 12) 22)	0.771 <sup>(=</sup> 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 Macaria	<ul> <li>0.187</li> <li>0.0000</li> <li>sD</li> <li>0.11</li> <li>0.57</li> <li>0.11</li> <li>0.13</li> <li>0.2</li> <li>0.18</li> <li>0.187</li> <li>0.187</li> <li>0.187</li> <li>0.00001</li> <li>VI(+)</li> </ul>	24 211 21);   <sup>2</sup> = C Total 18 25 23 23 23 14 28 9 24 211 28 9 24 211 ();   <sup>2</sup> =	10.4% 100.0% 94% 94% 9.7% 10.5% 10.5% 10.1% 9.5% 10.3% 9.5% 10.3% 9.5% 10.3% 9.5% 10.1% 10.1% 10.1% 10.0% 9%	1.59 [0.44, 2.74] 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] 	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV, Random, 95% CI -4 -2 0 2 4 Favours [experimental] Favours [control] Std. Mean Difference
thu SC2018 iotal (95% CI) leterogeneity: Tau <sup>2</sup> = iest for overall effect est for overall effect est for overall effect in QG2017 Vei Y2019 Vei Y2019 Vei Y2019 Vei Y2019 Voo S2014 Vu B2020 thu SC 2018 iotal (95% CI) leterogeneity: Tau <sup>2</sup> = iest for overall effect itudy or Subgroup	1.193 = 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 I Mean	0.226 $hi^2 = 14($ (P = 0.0) 0.49 1.44 0.16 0.13 0.26 0.151 0.148 $hi^2 = 78.$ (P = 0.0) VIVI(-) SC	14 143 0.49, dt 007) 4CC <u>Total</u> 30 66 41 41 20 30 46 24 24 24 24 363 56, dt= 02) <u>Total</u>	0.771 (= 9 (P < 1.51 0.82 0.83 0.96 1.07 0.76 0.775 0.771 = 9 (P < Mean	<ul> <li>0.187</li> <li>0.0000</li> <li>sD</li> <li>0.11</li> <li>0.57</li> <li>0.11</li> <li>0.57</li> <li>0.11</li> <li>0.13</li> <li>0.2</li> <li>0.18</li> <li>0.187</li> <li>0.187</li> <li>0.00001</li> <li>VI(+)</li> <li>SD</li> <li>1</li> </ul>	24 211 211);   <sup>2</sup> = C Total 18 25 23 23 23 23 23 23 23 23 24 24 24 24 24 24 21 ();   <sup>2</sup> = () () () () () () () () () ()	10.4% 100.0% 94% 94% 9.7% 10.5% 10.5% 10.3% 9.5% 10.3% 9.5% 10.1% 10.1% 10.1% 100.0% 9% St Weight	1.59 [0.44, 2.74] 1.59 [0.44, 2.74] Std. Mean Difference IV. Random, 95% CI -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 [0.34, 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] d. Mean Difference IV. Fixed, 95% CI	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV, Random, 95% Cl -4 -2 0 2 4 Favours [experimental] Favours [control] Std. Mean Difference IV, Fixed, 95% Cl
thu SC2018 otal (95% CI) leterogeneity: Tau <sup>2</sup> = rest for overall effect Standy or Subgroup Granata V2016 Shan QG2017 Vei Y 2019 Vei Y2019 Vei Y2019 Vei Y2019 Vei Y2019 Vei S2014 Vu B2020 Chou Y2021 thu SC 2018 Stat (95% CI) leterogeneity: Tau <sup>2</sup> = rest for overall effect Study or Subgroup Chen J2021	1.193 = 3.13; CI : Z = 2.71	0.226 $hi^{2} = 14($ (P = 0.0) 0.49 1.44 0.16 0.13 0.26 0.151 0.148 $hi^{2} = 78.$ (P = 0.0) <b>MVI(-)</b> <u>SD</u> 0.13	14 143 0.49, dt 007) 4CC Total 30 66 41 41 41 41 20 30 46 24 24 363 56, dt= 02) Total 33	0.771 (= 9 (P < 1.51 0.82 0.83 0.96 1.07 0.79 0.76 0.775 0.771 = 9 (P < M Mean 0.84	<pre>0.187 </pre> pd-HC( SD 0.11 0.57 0.11 0.13 0.13 0.13 0.187 0.187 0.187 0.00001 VI(+) SD I 0.11	24 211 211);   <sup>2</sup> = C Total 18 25 23 23 23 23 23 23 23 23 23 23	10.4% 100.0% 94% 94% 9.7% 10.5% 10.3% 9.5% 10.1% 10.1% 10.1% 10.1% 10.1% 10.1% 10.1% 10.2% St Veight	1.59 [0.44, 2.74] 1.59 [0.44, 2.74] Std. Mean Difference IV, Random, 95% CI -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] d. Mean Difference IV, Fixed, 95% CI 1.55 [0.98, 2.12]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV, Random, 95% CI -4 -2 0 2 4 Favours [experimental] Favours [control] Std. Mean Difference IV, Fixed, 95% CI
thu SC2018 iotal (95% CI) leterogeneity: Tau <sup>2</sup> = iest for overall effect istudy or Subgroup granata V2016 Shan QG2017 Vei Y2019 Vei Y2019 Vei Y2019 Vei Y2019 Vei Y2019 Vei Y2019 Vei S2014 Vu B2020 thu SC 2018 inu SC 2018 inu SC2018 inu SC2	1.193 = 3.13; CI : Z = 2.71 Mean 0.81 0.91 0.96 1.13 1.15 0.92 0.88 0.91 0.91 = 0.70; CI : Z = 2.30 Mean 1.03 0.98	0.226 $hi^2 = 14($ (P = 0.0) 0.49 1.44 0.13 0.26 0.151 0.151 0.148 $hi^2 = 78.$ I(P = 0.0) VIVI(-) <u>SD</u> 0.13 0.28	14 143 0.49, dt 007) HCC <u>Total</u> 30 66 41 41 41 20 30 46 24 24 24 24 363 556, dt= 02) <u>Total</u> 33 20	0.771 (= 9 (P ≪ 1.51 0.82 0.83 0.96 1.02 0.79 0.76 0.775 0.771 = 9 (P ≪ M Mean 0.84 0.79	<pre>v.187 v.0.0000 v.0.0000 v.0.00001 v.0.0000 v.0000 v.0</pre>	24 211 21); P = C Total 18 25 23 23 23 23 23 23 23 23 23 23	10.4% 100.0% 94% 94% 9.7% 10.5% 10.3% 10.1% 9.5% 10.3% 9.5% 10.1% 10.1% 10.1% 10.1% 10.1% 10.1% 10.1% 10.5% 10.1% 10.5% 10.3% 10.5% 10.3% 10.3% 10.5% 10.3% 10.5% 10.3% 10.5% 10.3% 10.5% 10.3% 10.5% 10.3% 10.5% 10.3% 10.5% 10.3% 10.5% 10.3% 10.5% 10.3% 10.5% 10.3% 10.5% 10.3% 10.3% 10.5% 10.3% 10.5% 10.3% 10.3% 10.1% 9.5% 10.1% 9.5% 10.1% 10.1% 9.5% 10.1	1.59 [0.44, 2.74] 1.59 [0.44, 2.74] Std. Mean Difference IV, Random, 95% CI -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] d. Mean Difference IV, Fixed, 95% CI 1.55 [0.98, 2.12] 0.86 [0.22, 1.50]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV. Random, 95% CI -4 -2 0 2 4 Favours [experimental] Favours [control] Std. Mean Difference IV. Fixed, 95% CI
thu SC2018 iotal (95% CI) leterogeneity: Tau <sup>2</sup> = iest for overall effect istudy or Subgroup branata V2016 Shan QG2017 Vei Y2019 Vei Y2019 Vei Y2019 Vei Y2019 Vei Y2019 Vei S2014 Vu S2020 thou SC2018 inu SC 2018 inu SC2018 interogeneity: Tau <sup>2</sup> = iest for overall effect itudy or Subgroup then J2021 i H2018 Vei Y2019	1.193 = 3.13; CI : Z = 2.71	0.226 $hi^{2} = 14($ (P = 0.0) 0.49 1.44 0.16 0.13 0.26 0.151 0.151 0.148 $hi^{2} = 78.$ I(P = 0.0) MVI(-) <u>SD</u> 0.13 0.28 0.34	14 143 0.49, df 1007) ACC <u>Total</u> 30 66 41 41 41 20 30 46 24 24 24 24 363 56, df = 202) <u>Total</u> 33 20 80	0.771 (= 9 (P ≪ 1.51 0.82 0.83 0.96 1.02 0.79 0.76 0.775 0.771 = 9 (P ≪ Mean 0.84 0.79 0.77	<pre>0.187 </pre> pd-HC(     SD     0.11     0.57     0.11     0.16     0.13     0.13     0.16	24 211 21);   <sup>2</sup> = C Total 18 25 23 23 23 14 28 9 24 21 24 21 21 21 23 23 23 14 28 9 24 24 21 23 23 23 23 23 23 23 23 23 23	10.4% 100.0% 94% 94% 9.7% 10.5% 10.3% 9.5% 10.3% 9.5% 10.3% 9.5% 10.1% 10.1% 10.1% 10.1% 10.1% 10.1% 10.1% 10.5% 10.3% 10.3% 9.5% 10.3% 10.3% 9.5% 10.3% 10.3% 9.5% 10.3% 10.3% 9.5% 10.3% 10.3% 9.5% 10.3% 10.3% 9.5% 10.3% 10.3% 9.5% 10.3% 10.3% 9.5% 10.3% 10.3% 9.5% 10.3% 10.3% 9.5% 10.3% 10.3% 9.5% 10.3% 10.3% 9.5% 10.3% 10.1% 9.5% 10.3% 10.1% 9.5% 10.3% 10.3% 10.1% 10.1% 10.1% 10.1% 10.1% 10.1% 10.1% 10.1% 10.1% 10.1% 10.3% 10.1% 10.3% 10.3% 10.1% 10.3% 10.3% 10.3% 10.3% 10.1% 10.3% 10	1.59 [0.44, 2.74] 1.59 [0.44, 2.74] 5td. 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] 4d. Mean Difference <u>IV, Fixed, 95% Cl</u> 1.55 [0.98, 2.12] 0.88 [0.22, 1.50] 1.06 [0.69, 1.43]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV, Random, 95% CI -4 -2 0 2 4 Favours [experimental] Favours [control] Std. Mean Difference IV, Fixed, 95% CI
thu SC2018 total (95% CI) teterogeneity: Tau <sup>2</sup> = test for overall effect total v2016 than QG2017 Vei Y 2019 Vei Y 2019 Vei Y 2019 Vei Y 2019 Vei Y 2019 Vei Y 2019 total SC2014 thu SC 2018 thu SC 2018 thu SC 2018 total (95% CI) teterogeneity: Tau <sup>2</sup> = test for overall effect total (95% CI) teterogeneity: Tau <sup>2</sup> = test for overall effect thu SC 2018 total (95% CI) teterogeneity: Tau <sup>2</sup> = test for overall effect thu SC 2018 total (95% CI) teterogeneity: Tau <sup>2</sup> = test for overall effect total (95% CI) teterogeneity: Tau <sup>2</sup> = test for overall effect thu SC 2018 total (95% CI) teterogeneity: Tau <sup>2</sup> = test for overall effect total (95% CI) teterogeneity: Tau <sup>2</sup> = test for overall effect test for overall effect t	1.193 = 3.13; CI : Z = 2.71 0.81 0.91 0.96 1.13 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	0.226 $hi^{2} = 14($ (P = 0.0) 0.49 1.44 0.16 0.13 0.26 0.151 0.148 $hi^{2} = 78.$ I(P = 0.0) MVI(-) <u>SD</u> 0.13 0.28 0.34 0.29	14 143 0.49, dt 007) HCC Total 30 66 41 41 41 41 20 30 46 24 24 363 356, dt= 02) Total 33 20 80 33	0.771 (= 9 (P ≪ 1.51 0.82 0.83 0.96 1.02 0.79 0.76 0.775 0.771 = 9 (P ≪ Mean 0.84 0.79 0.77 0.99	<pre>0.187 </pre> pd-HC(     SD     0.11     0.57     0.11     0.13     0.22     0.18     0.187     0.187     0.187     0.00001  VI(+)     SD     1     0.11     0.13     0.16     0.21	24 211 21);   <sup>2</sup> =	10.4% 100.0% 94% 94% 9.7% 10.5% 10.3% 9.5% 10.3% 9.5% 10.3% 9.5% 10.3% 9.5% 10.1% 10.1% 10.1% 10.0% 9% SI Veight 10.7% 10.3% 1	1.59 [0.44, 2.74] 1.59 [0.44, 2.74] 5td. 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] 0.89 [0.36, 1.43] 0.89 [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] 4d. Mean Difference <u>IV, Fixed, 95% CI</u> 1.55 [0.98, 2.12] 0.88 [0.22, 1.50] 1.06 [0.69, 1.43] 0.82 [0.22, 1.42]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV, Random, 95% CI -4 -2 0 2 4 Favours [experimental] Favours [control] Std. Mean Difference IV, Fixed, 95% CI
thu SC2018 iotal (95% CI) leterogeneity: Tau <sup>2</sup> = iest for overall effect: itudy or Subgroup Granata V2016 Shan QG2017 Vei Y2019 Vei Y2019 Vei Y2019 Vei Y2019 Vei Y2019 Vei Y2019 Vei SC2014 Vu B2020 thu SC 2018 inu SC 2018 inu SC 2018 inu SC2018 inu	1.193 = 3.13; CI : Z = 2.71 	$hi^2 = 14($ (P = 0.0 0.49 1.44 0.16 0.13 0.26 0.16 0.151 0.16 0.151 0.148 hi^2 = 78. (P = 0.0 <b>VIVI(-)</b> <b>SD</b> 0.13 0.28 0.34 0.29	14 143 0.49, dt 007) HCC Total 30 66 41 41 41 20 30 46 24 24 24 363 55, dt= 02) Total 33 20 80 33 166	0.771 (= 9 (P < 1.51 0.82 0.83 0.96 1.02 0.79 0.76 0.775 0.771 = 9 (P < M Mean 0.84 0.79 0.77 0.99	<pre>0.187 </pre> pd-HC( SD 0.11 0.57 0.11 0.13 0.2 0.18 0.187 0.187 0.00001  VI(+) SD I 0.11 0.13 0.16 0.21	24 2111 211); P = Total 18 25 23 23 23 23 23 23 23 23 23 23	10.4% 100.0% 94% 94% 9.7% 10.5% 10.3% 10.1% 9.5% 10.3% 9.5% 10.1% 10.1% 10.1% 10.1% 10.1% 10.1% 10.1% 10.5% 10.3% 10.3% 10.5% 10.3% 10.3% 10.3% 10.5% 10.3% 10.5% 10.3% 10.5% 10.3% 10.5% 10.3% 10.3% 10.5% 10.3% 10.5% 10.3% 10.5% 10.3% 10.3% 10.5% 10.3% 10.5% 10.3% 10.5% 10.3% 10.5% 10.3% 10.5% 10.3% 10.5% 10.3% 10.5% 10.3% 10.5% 10.3% 10.5% 10.3% 10.5% 10.3% 10.5% 10.3% 10.1% 10.5% 10.1% 10.5% 10.1% 10.5% 10.1% 10.5% 10.1% 10.5% 10.1% 10.5% 10.1% 10.5% 10.1% 10.5% 10.1% 10.2% 10.1% 10.2% 10.1% 10.2% 10.1% 10.2% 10.1% 10.2% 10.1% 10.2% 10.1% 10.2% 10.1% 10.2% 10.1% 10.2% 10.1% 10.2% 10.1% 1	1.59 [0.44, 2.74] 1.59 [0.44, 2.74] 5td. 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] 0.89 [0.36, 1.43] 0.89 [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] 1.08 [0.83, 1.34]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV, Random, 95% CI -4 -2 0 2 4 Favours [experimental] Favours [control] Std. Mean Difference IV, Fixed, 95% CI
thu SC2018 iotal (95% CI) leterogeneity: Tau <sup>2</sup> = iest for overall effect istudy or Subgroup Franata V2016 Shan QG2017 Vei Y2019 Vei Y2019 Vei Y2019 Vei Y2019 Vei Y2019 Vei S2014 Vu S2020 Chou Y2021 Chou SC2018 int SC	1.193 = 3.13; CI : Z = 2.71 Mean 0.81 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 = 3.85 d <sup>4</sup>	0.226 $hi^2 = 14($ (P = 0.0) 0.49 1.44 0.13 0.09 0.13 0.26 0.151 0.151 0.151 0.151 0.151 0.151 0.151 0.151 0.151 0.151 0.151 0.151 0.28 0.34 0.29 = 3.(P - 1)	143 0.49, dt 007) ACC Total 30 66 41 41 41 20 30 46 24 24 363 56, df 24 363 20 80 33 20 80 33 166 6 9 28 <sup>1</sup>	0.771 (= 9 (P < 1.51 0.82 0.83 0.96 1.07 1.02 0.79 0.775 0.771 = 9 (P < M Mean 0.84 0.77 0.99	<pre></pre>	24 211 21);  ² = <u>Total</u> 18 25 23 23 23 23 14 28 9 24 21 ();  ² = 8 <b>C</b> <b>C</b> <b>Total</b> 12 18 23 23 23 23 23 23 23 23 23 23	10.4% 100.0% 94% 94% 9.7% 10.5% 10.5% 10.3% 9.5% 10.3% 9.5% 10.3% 9.5% 10.1% 10.1% 10.1% 10.1% 10.1% 10.5% 10.5% 10.5% 10.3% 9.5% 10.3% 10.5% 10.3% 9.5% 10.1% 10.1% 10.5	1.59 [0.44, 2.74] 1.59 [0.44, 2.74] 5td. 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] 4d. Mean Difference <u>IV, Fixed, 95% CI</u> 1.55 [0.98, 2.12] 0.86 [0.22, 1.50] 1.06 [0.69, 1.43] 0.82 [0.22, 1.42] 1.08 [0.83, 1.34]	-10 -5 0 5 10 Favours [experimental] Favours [control] Std. Mean Difference IV, Random, 95% CI -4 -2 0 2 4 Favours [experimental] Favours [control] Std. Mean Difference IV, Fixed, 95% CI -4 -2 0 2 4 Favours [experimental] Favours [control]

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.

Α	v	vd-HCC			md-HO	C		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl
Granata V2016	54.69	83.62	14	44.49	70.15	30	11.6%	0.13 [-0.50, 0.77]	
Shan QG2017	19.7	21.96	18	25.25	64.14	66	17.2%	-0.09 [-0.62, 0.43]	
Wei Y 2019	22.21	10.98	15	17.99	10.23	41	13.1%	0.40 [-0.20, 1.00]	+
Wei Y20 19	18.21	9.21	15	18.54	9.62	41	13.4%	-0.03 [-0.63, 0.56]	
Wei Y2019	20.75	12.74	15	18.62	8.86	41	13.3%	0.21 [-0.38 0.80]	
Woo S2014	34.7	21	4	38.8	15	20	4.0%	-0.25 [-1.32 0.83]	
100 02014 1000 B2020	134 32	51 93	19	120 72	44 18	30	14.0%	0.28 [-0.29   0.86]	
7hou Y2021	37.87	147	15	41.68	17 9	46	13.4%	-0.51 [-1.10, 0.08]	
21100 12021	52.01	14.1	15	41.00	11.5	40	10.470	0.01[1.10, 0.00]	
Total (95% CI)			115			315	100.0%	0.04 [-0.18, 0.25]	
Heterogeneity Chi <sup>2</sup> =	635 df=	7 (P =	0.501	<sup>2</sup> = 0%		0.0			
Test for overall effect	7 = 0.33	(P = 0.7)	4)	- 0 /0					-4 -2 0 2 4
restion overall effect.	. 2 - 0.55	ų – 0.7	-/						Favours [experimental] Favours [control]
Р									
D C	v	vd-HCC			pd -HCC			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
Granata V2016	54.69	83.62	14	13.7	7.39	18	11.5%	0.72 [-0.00, 1.45]	
Shan QG2017	19.7	21.96	18	128.1	221.49	25	15.6%	-0.63 [-1.250.00]	
Wei Y 2019	22.21	10.98	15	16.5	12.73	23	13.9%	0.46 [-0.20, 1.12]	+
Wei Y20 19	18 21	9 21	15	14 39	7 73	23	13.9%	0 45 [-0 21 1 11]	+
Wei Y2019	20.75	12.74	15	1619	11.66	23	14 0%	0.37 [-0.29, 1.03]	
Woo S2014	34.7	2.14	13	30.7	18.4	14	1 9.0 %	0.20 [-0.23, 1.03]	
W00 32014	124.22	61 02	10	114.24	10.4	20	4.570	0.20[-0.31, 1.32]	<b></b>
7hou V2021	134.32	147	19	24 54	49.10	20	0.00%	0.39 [-0.20, 0.90]	
2000 12021	32.07	14.7	15	34.34	10.0	9	0.070	-0.10 [-0.95, 0.75]	
Total (95% CI)			115			163	100.0%	0 23 [ 0 01 0 48]	•
Hotorogonoity Chiz-	11.04 46	- 7 /0 -	0.1.43	18 - 270		105	100.070	0.25 [-0.01, 0.40]	<b>*</b> /
Telefoyenelly. Chir =	7 - 1 06	- / (F -	· U. 14), 6\	1 - 37 %					-4 -2 0 2 4
rest for overall effect.	2 = 1.80	(P = 0.0	6)						Favours [experimental] Favours [control]
с									
-		md-H	CC		pd-HCC			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Granata V2016	44 49	70.15	30	13.7	7.39	18	12.0%	0.54 (-0.05, 1.14)	
Shan QG2017	25.25	64 14	66	128.1	221 49	25	14.0%	-0.80[-1.280.33]	
Wei Y 2019	17 99	10.23	41	16.5	12.73	23	13.4%	0.13 [-0.38 0.64]	
Wei Y2010	18.54	9.62	41	14 39	7 73	23	13 3%	0.46[-0.06]0.97]	
Vici Y2019	18.62	8.86	41	16.19	11.66	23	13 3%	0.24 [-0.27 0.75]	
Woo S2014	38.9	15	20	30.7	18/	14	10.5%	0.24 [-0.27, 0.75]	+
Mu B2020	120.72	44.19	20	114.24	49.19	20	13 3%	0.40[0.21, 1.17]	
7hou V2020	A1 60	17.0	46	34.54	106	20 0	10.3%	0.14 [-0.30, 0.03]	
21100 12021	41.00	17.3	40	54.54	10.0	9	10.2 %	0.03 [0.00, 1.11]	
Total (95% CI)			315			163	100.0%	0.17 [-0.16. 0.50]	•
Heterogeneity Tau <sup>2</sup> =	0.15: Ch	i <sup>2</sup> = 197	5 df=	7 (P = 0 0	106): I <sup>2</sup> = I	65%			
Test for overall effect:	7=1.02	(P = 0.3)	1)	= 0.0					-4 -2 0 2 4
reactor overall effect.	2 - 1.021	0.5	.,						Favours [experimental] Favours [control]
D									
-		/IVI(-)		M	VI(+)		S	td. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD T	otal V	Veight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Li H2018	68	38	20	64	34	21	19.0%	0.11 (-0.50, 0.72)	
Wei Y2019	17.88	12.68	80	14.38	11.4	55	59.9%	0.29 [-0.06 0.63]	+
7han W/2018	58 99	35.13	33	45.59	21.68	18	21.1%	0.42[-0.16 1.00]	+ <del>-</del>
2.130 112010	50.55	55.15	55	40.00	21.00	10	21.170	0.42 [[0.10, 1.00]	
Total (95% CI)			133			94 1	00.0%	0.28 [0.01, 0.55]	•
Hotorogeneity Ohiz-	-064 46	- 2/0-	0.763	<b>IZ</b> = 0.0%		34	00.070		
Tect for everall effect	- 0.04, di: F 7 - 2.07	- 2 (F = (P = 0.0	0.70),	1 - 0 %					-2 -1 0 1 2
rest for overall effect	L Z = 2.07	(== 0.0	54)						Favours [experimental] Favours [control]

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–

Α	v	vd -HCC	:		md-H	ICC		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	14.48	7.38	14	31.49	17.6	30	12.3%	-1.10 [-1.78, -0.42]	
Shan QG2017	26	20.35	18	31.55	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	131%	0.32 [-0.27 0.92]	
10/ei Y2019	33	12	15	30	11	41	131%	0.26 [-0.33, 0.86]	
Vici 12013	100	37	1.5	24.1	121	20	9.0%	-0.36 [-1.44 0.72]	
Web 02014	27 12	0.12	10	29.1	6 24	20	12 6%		
7hou V2020	37.13	5.15	15	20.33	0.24	46	12.0%	0.12[0.77, 2.00]	
21100 12021	22	'	15	25	0	40	13.2%	-0.13 [-0.71, 0.40]	
Total (95% CI)			115			315	100.0%	0.09 [-0.38, 0.56]	◆
Heterogeneity: Tau <sup>2</sup> =	= 0.35; CI	hi² = 30	.84. df =	= 7 (P <	0.0001)	$ ^2 = 77$	%		
Test for overall effect:	Z = 0.37	(P = 0)	71)	,	,				-4 -2 0 2 4
									Favours (experimental) Favours (control)
В		11100			- 1.1100			Ctd Maan Differense	Ctd Mean Difference
Chuche or Cubarow	Maar	Vd-HCC	Total	Mean	pd-HCC	Tetal	Mainht	Sta. mean Difference	Sta. Mean Difference
Study of Subgroup	mean	SD	Total	mean	SD	rotal	weight	IV, Random, 95% Cl	IV, Kandom, 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]	T
Wei Y 2019	33	12	15	31	13	23	13.5%	0.16 [-0.50, 0.81]	T
Wei Y20 19	33	10	15	32	15	23	13.5%	0.07 [-0.58, 0.72]	
Wei Y2019	33	12	15	33	14	23	13.5%	0.00 [-0.65, 0.65]	-
Woo S2014	19.9	3.7	4	21	12.2	14	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	7	15	18	7	9	12.8%	0.55 [-0.29, 1.40]	+
Total (95% CI)			115			163	100.0%	-0.24 [-1.10, 0.63]	•
Heterogeneity: Tau <sup>2</sup> =	1.34: CI	hi² = 69.	.86. df=	= 7 (P <	0.00001	); $ ^2 = 9$	0%	-	
Test for overall effect:	Z=0.54	(P = 0.9)	59)						-4 -2 0 2 4
									Favours (experimental) Favours (control)
С		md-l	нсс		pd -HC	C		Std. Mean Difference	Std. Mean Difference
Study or Subgroup					CD	Total	Woight		
	Mean	SD	Total	mean	50	Total	wweight	IV, Random, 95% Cl	IV, Random, 95% Cl
Granata V2016	Mean 31.49	SD 17.6	<u>Total</u> 30	54.08	2.96	18	11.4%	<u>IV, Random, 95% Cl</u> -1.58 (-2.25, -0.91)	<u>IV, Random, 95% Cl</u>
Granata V2016 Shan QG2017	Mean 31.49 31.55	SD 17.6 66.28	<u>Total</u> 30 66	54.08 19.35	2.96 16.18	18 25	11.4% 13.7%	<u>IV, Random, 95% Cl</u> -1.58 [-2.25, -0.91] 0.21 [-0.25, 0.67]	IV, Random, 95% Cl
Granata V2016 Shan QG2017 Wei Y 2019	Mean 31.49 31.55 30	SD 17.6 66.28 13	<u>Total</u> 30 66 41	54.08 19.35 31	2.96 16.18 13	18 25 23	11.4% 13.7% 13.2%	<u>IV, Random, 95% Cl</u> -1.58 [-2.25, -0.91] 0.21 [-0.25, 0.67] -0.08 [-0.59, 0.43]	IV, Random, 95% Cl
Granata V2016 Shan QG2017 Wei Y 2019 Wei Y20 19	Mean 31.49 31.55 30 29	SD 17.6 66.28 13 13	Total 30 66 41 41	меан 54.08 19.35 31 32	2.96 16.18 13 15	18 25 23 23	11.4% 13.7% 13.2% 13.2%	V, Random, 95% Cl -1.58 [-2.25, -0.91] 0.21 [-0.25, 0.67] -0.08 [-0.59, 0.43] -0.22 [-0.73, 0.30]	IV, Random, 95% Cl
Granata V2016 Shan QG2017 Wei Y 2019 Wei Y20 19 Wei Y2019	Mean 31.49 31.55 30 29 30	SD 17.6 66.28 13 13 13 11	Total 30 66 41 41 41	54.08 19.35 31 32 33	2.96 16.18 13 15 14	18 25 23 23 23	11.4% 13.7% 13.2% 13.2% 13.2%	IV, Random, 95% Cl -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 0.77]	IV, Random, 95% Cl
Granata V2016 Shan QG2017 Wei Y 2019 Wei Y20 19 Wei Y2019 Woo S2014	Mean 31.49 31.55 30 29 30 24 1	SD 17.6 66.28 13 13 13 11 121	Total 30 66 41 41 41 20	Mean 54.08 19.35 31 32 33 21	2.96 16.18 13 15 14 12 2	18 25 23 23 23 23 14	11.4% 13.7% 13.2% 13.2% 13.2% 13.2% 11.3%	IV, Random, 95% Cl -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]	IV, Random, 95% Cl
Granata V2016 Shan QG2017 Wei Y 2019 Wei Y20 19 Wei Y2019 Woo S2014 Wu B2020	Mean 31.49 31.55 30 29 30 24.1 26 35	SD 17.6 66.28 13 13 13 11 12.1 6.24	Total 30 66 41 41 41 20 30	Mean 54.08 19.35 31 32 33 21 23.69	2.96 16.18 13 15 14 12.2 7 70	18 25 23 23 23 23 14 28	11.4% 13.7% 13.2% 13.2% 13.2% 13.2% 13.2% 13.2% 13.2%	N, Random, 95% Cl -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]	IV, Random, 95% Cl
Granata V2016 Shan QG2017 Wei Y 2019 Wei Y2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021	Mean 31.49 31.55 30 29 30 24.1 26.35 23	SD 17.6 66.28 13 13 13 11 12.1 6.24 8	Total 30 66 41 41 41 20 30 46	Mean 54.08 19.35 31 32 33 21 23.69 18	2.96 16.18 13 15 14 12.2 7.79 7	18 25 23 23 23 23 14 28 28	11.4% 13.7% 13.2% 13.2% 13.2% 13.2% 11.3% 11.3% 13.1%	IV, Random, 95% Cl -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]	IV, Random, 95% Cl
Granata V2016 Shan QG2017 Wei Y 2019 Wei Y2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021	Mean 31.49 31.55 30 29 30 24.1 26.35 23	SD 17.6 66.28 13 13 13 11 12.1 6.24 8	Total 30 66 41 41 41 20 30 46	Mean 54.08 19.35 31 32 33 21 23.69 18	2.96 16.18 13 15 14 12.2 7.79 7	18 25 23 23 23 23 14 28 9	11.4% 13.7% 13.2% 13.2% 13.2% 13.2% 11.3% 13.1% 10.9%	IV, Random, 95% Cl -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]	IV, Random, 95% Cl
Granata V2016 Shan QG2017 Wei Y 2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 <b>Total (95% CI)</b>	Mean 31.49 31.55 30 29 30 24.1 26.35 23	SD 17.6 66.28 13 13 13 11 12.1 6.24 8	<u>Total</u> 30 66 41 41 41 20 30 46 <b>315</b>	Mean 54.08 19.35 31 32 33 21 23.69 18	2.96 16.18 13 15 14 12.2 7.79 7	18 25 23 23 23 14 28 9 <b>163</b>	11.4% 13.7% 13.2% 13.2% 13.2% 13.2% 11.3% 13.1% 10.9% 100.0%	V, Random, 95% Cl -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]	IV, Random, 95% Cl
Granata V2016 Shan QG2017 Wei Y 2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 Total (95% CI) Heterogeneity: Tau <sup>2</sup> =	Mean 31.49 31.55 30 29 30 24.1 26.35 23 : 0.25; C	SD 17.6 66.28 13 13 11 12.1 6.24 8 hi <sup>2</sup> = 28	<u>Total</u> 30 66 41 41 20 30 46 <b>315</b> .74, df:	54.08 19.35 31 32 33 21 23.69 18 = 7 (P =	2.96 16.18 13 15 14 12.2 7.79 7 0.0002)	18 25 23 23 23 14 28 9 <b>163</b> ;   <sup>2</sup> = 7 (	11.4% 13.7% 13.2% 13.2% 13.2% 13.2% 11.3% 13.1% 10.9% 100.0%	IV, Random, 95% Cl -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]	N, Random, 95% Cl
Granata V2016 Shan QG2017 Wei Y 2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 <b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	<u>Mean</u> 31.49 31.55 30 29 30 24.1 26.35 23 : 0.25; Cl Z = 0.37	<b>SD</b> 17.6 66.28 13 13 11 12.1 6.24 8 hi <sup>2</sup> = 28 ' (P = 0.	<u>Total</u> 30 66 41 41 20 30 46 315 .74, df: 71)	54.08 19.35 31 32 33 21 23.69 18 = 7 (P =	2.96 16.18 13 15 14 12.2 7.79 7 0.0002)	18 25 23 23 23 14 28 9 <b>163</b> ;   <sup>2</sup> = 76	11.4% 13.7% 13.2% 13.2% 13.2% 13.2% 13.2% 13.1% 13.1% 10.9% 100.0%	IV, Random, 95% Cl -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]	-4 -2 0 2 4 Favours (experimental)
Granata V2016 Shan QG2017 Wei Y 2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 <b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	Mean 31.49 31.55 30 29 30 24.1 26.35 23 : 0.25; Cl Z = 0.37	SD         17.6         66.28         13         13         14         12.1         6.24         8         hi² = 28         ' (P = 0.)	<u>Total</u> 30 66 41 41 20 30 46 315 .74, df: 71)	54.08 19.35 31 32 33 21 23.69 18 = 7 (P =	2.96 16.18 13 15 14 12.2 7.79 7 0.0002)	18 25 23 23 23 14 28 9 <b>163</b> ;   <sup>2</sup> = 7(	11.4% 13.7% 13.2% 13.2% 13.2% 13.2% 13.2% 13.2% 13.1% 10.9%	IV, Random, 95% Cl -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]	-4 -2 0 2 4 Favours [experimental] Favours [control]
Granata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 <b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = Test for overall effect: <b>D</b>	Mean 31.49 31.55 30 24.1 26.35 23 0.25; Cl Z = 0.37	SD 17.6 66.28 13 13 11 12.1 6.24 8 hi <sup>2</sup> = 28 ' (P = 0.	<u>Total</u> 30 66 41 41 20 30 46 315 .74, df: 71)	<u>mean</u> 54.08 19.35 31 32 33 21 23.69 18 = 7 (P =	2.96 16.18 13 15 14 12.2 7.79 7 0.0002)	18 25 23 23 23 14 28 9 <b>163</b> ;   <sup>2</sup> = 76	11.4% 13.7% 13.2% 13.2% 13.2% 13.2% 13.2% 13.2% 13.1% 10.9%	IV, Random, 95% Cl -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]	-4 -2 0 2 4 Favours [experimental] Favours [control]
Granata V2016 Shan QG2017 Wei Y 2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 <b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = Test for overall effect: <b>D</b>	Mean 31.49 31.55 30 29 30 24.1 26.35 23 = 0.25; Cl Z = 0.37	SD 17.6 66.28 13 13 11 12.1 6.24 8 hi² = 28 ' (P = 0.	<u>Total</u> 30 66 41 41 20 30 46 315 .74, df: 71)	<u>mean</u> 54.08 19.35 31 32 33 21 23.69 18 = 7 (P =	2.96 16.18 13 15 14 12.2 7.79 7 0.0002)	18 25 23 23 23 14 28 9 <b>163</b> ;   <sup>2</sup> = 78	11.4% 13.7% 13.2% 13.2% 13.2% 13.2% 13.2% 13.2% 13.1% 10.9%	IV, Random, 95% Cl -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	N, Random, 95% Cl
Granata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 <b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = Test for overall effect: <b>D</b>	Mean 31.49 31.55 30 29 30 24.1 26.35 23 0.25; Cl Z = 0.37	SD 17.6 66.28 13 13 11 12.1 6.24 8 hi² = 28 (P = 0. √IVI(-) SD	Total 30 66 41 41 20 30 46 315 .74, df: 71) Total	<u>mean</u> 54.08 19.35 31 32 33 21 23.69 18 = 7 (P = <u>Mean</u>	2.96 16.18 13 15 14 12.2 7.79 7 0.0002)	18 25 23 23 14 28 9 <b>163</b> ;   <sup>2</sup> = 7(	11.4% 13.7% 13.2% 13.2% 13.2% 13.2% 13.2% 13.2% 13.1% 10.9% 100.0%	IV, Random, 95% Cl -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	TV, Random, 95% Cl
Granata V2016 Shan QG2017 Wei Y 2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: D <u>Study or Subgroup</u> Li H2018	<u>Mean</u> 31.49 31.55 30 29 30 24.1 26.35 23 ○ 0.25; Cl Z = 0.37 Mean 20.4	<u>SD</u> 17.6 66.28 13 13 11 12.1 6.24 8 hi² = 28 (P = 0. ₩V/(-) <u>SD</u> 9.7	<u>Total</u> 30 66 41 41 20 30 46 <b>315</b> .74, df: 71) <u>Total</u> 20	<u>mean</u> 54.08 19.35 31 32 33 21 23.69 18 = 7 (P = <b>M</b> <u>Mean</u> 19.3	2.96 16.18 13 15 14 12.2 7.79 7 0.0002) ₩(+) <u>SD</u> 7.9	18 25 23 23 14 28 9 <b>163</b> ;   <sup>2</sup> = 78 <u>Total</u> 21	11.4% 13.7% 13.2% 13.2% 13.2% 13.2% 13.2% 13.2% 13.1% 10.9% 100.0% 3%	IV, Random, 95% Cl -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 0.12 [-0.49, 0.74]	N, Random, 95% Cl
Granata V2016 Shan QG2017 Wei Y 2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: D <u>Study or Subgroup</u> Li H2018 Wei Y2019	<u>Mean</u> 31.49 31.55 30 29 30 24.1 26.35 23 ○ 0.25; Cl Z = 0.37 Mean 20.4 36	SD 17.6 66.28 13 13 11 12.1 6.24 8 hi² = 28 (P = 0. VIVI(-) SD 9.7 14	<u>Total</u> 30 66 41 41 20 300 46 <b>315</b> .74, df: 71) <u>Total</u> 20 80	<u>mean</u> 54.08 19.35 32 33 21 23.69 18 = 7 (P = <u>Mean</u> 19.3 36	2.96 16.18 13 15 14 12.2 7.79 7 0.0002) ₩(+) <u>SD</u> 7.9 16	18 25 23 23 23 14 28 9 <b>163</b> ;   <sup>2</sup> = 7( <b>Total</b> 21 55	11.4% 13.7% 13.2% 13.2% 13.2% 13.2% 13.2% 13.2% 13.3% 10.9% 100.0%	IV, Random, 95% Cl -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 0.12 [-0.49, 0.74] 0.00 [-0.34, 0.34]	N, Random, 95% Cl
Granata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 <b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = Test for overall effect: <b>D</b> <u>Study or Subgroup</u> Li H2018 Wei Y2019 Zhao W2018	Mean           31.49           31.55           30           29           30           24.1           26.35           23           0.25; Cl           Z = 0.37           Mean           20           30           24.1           26.35           23	SD 17.6 66.28 13 13 11 12.1 6.24 8 hi² = 28 (P = 0. VIVI(-) SD 9.7 14 18.9	<u>Total</u> 30 66 41 41 20 30 46 <b>315</b> .74, df: 71) <u>Total</u> 20 80 33	<u>mean</u> 54.08 19.35 32 33 21 23.69 18 = 7 (P = <u>Mean</u> 19.3 36 24.17	2.96 16.18 13 15 14 12.2 7.79 7 0.0002) ₩(+) <u>SD</u> 7.9 16 13.32	18 25 23 23 23 23 14 28 9 <b>163</b> <b>163</b> <b>5</b> 18	11.4% 13.7% 13.2% 13.2% 13.2% 13.2% 13.2% 13.1% 10.9% 100.0% 100.0% 18.8% 60.0% 21.2%	IV, Random, 95% Cl -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 0.12 [-0.49, 0.74] 0.00 [-0.34, 0.34] 0.32 [-0.26, 0.89]	N, Random, 95% Cl
Granata V2016 Shan QG2017 Wei Y 2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: D <u>Study or Subgroup</u> Li H2018 Wei Y2019 Zhao W2018	Mean           31.49           31.55           30           29           30           24.1           26.35           23           0.25; Cl           Z = 0.37           Mean           20.4           36           29.67	SD 17.6 66.28 13 13 11 12.1 6.24 8 hi² = 28 (P = 0. VIVI(-) SD 9.7 14 18.9	<u>Total</u> 30 66 41 41 20 30 46 <b>315</b> .74, df: 71) <u>Total</u> 20 80 33 	<u>mean</u> 54.08 19.35 32 33 21 23.69 18 = 7 (P = <u>Mean</u> 19.3 36 24.17	2.96 16.18 13 15 14 12.2 7.79 7 0.0002) ₩(+) 5D 7.9 16 13.32	18 18 25 23 23 23 23 14 28 9 163 (I <sup>2</sup> = 7( 10 163 18 18 18 18 18 18 18 18 18 18	11.4% 13.7% 13.2% 13.2% 13.2% 13.2% 13.3% 13.1% 10.9% 100.0% 3%	IV, Random, 95% Cl -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 0.12 [-0.49, 0.74] 0.00 [-0.34, 0.34] 0.32 [-0.26, 0.89]	The second secon
Granata V2016 Shan QG2017 Wei Y2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 <b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = Test for overall effect: <b>D</b> <u>Study or Subgroup</u> Li H2018 Wei Y2019 Zhao W2018 <b>Total (95% CI)</b>	<u>Mean</u> 31.49 31.55 30 29 30 24.1 26.35 23 ○ 25; Cl Z = 0.37 Mean 20.4 36 29.67	<u>SD</u> 17.6 66.28 13 11 12.1 6.24 8 hi <sup>2</sup> = 28 (P = 0. <u>VIVI(-)</u> <u>SD</u> 9.7 14 18.9	<u>Total</u> 30 66 41 41 20 30 46 <b>315</b> .74, df: 71) <u>Total</u> 20 80 33 133	<u>mean</u> 54.08 19.35 32 33 21 23.69 18 = 7 (P = M <u>Mean</u> 19.3 36 24.17	SD           2.96           16.18           13           15           14           12.2           7.79           7           0.00002)           M(+)           SD           7.9           16           13.32	18 18 25 23 23 23 23 14 28 9 <b>163</b> 55 18 <b>94</b>	11.4% 13.7% 13.2% 13.2% 13.2% 13.2% 13.2% 13.1% 10.9% 100.0%	IV, Random, 95% Cl -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 0.12 [-0.49, 0.74] 0.00 [-0.34, 0.34] 0.32 [-0.26, 0.89] 0.09 [-0.18, 0.36]	N, Random, 95% Cl
Granata V2016 Shan QG2017 Wei Y 2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 <b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = Test for overall effect: <b>D</b> <u>Study or Subgroup</u> Li H2018 Wei Y2019 Zhao W2018 <b>Total (95% CI)</b> Heterogeneity: Chi <sup>2</sup> =	<u>Mean</u> 31.49 31.55 30 29 30 24.1 26.35 23 ○ 25; Cl Z = 0.37 Mean 20.4 36 29.67 ○ ○.86, df	SD 17.6 66.28 13 11 12.1 6.24 8 hi <sup>2</sup> = 28 (P = 0. MVI(-) <u>SD</u> 9.7 14 18.9 	<u>Total</u> 30 66 41 41 20 30 46 <b>315</b> .74, df: 71) <u>Total</u> 20 80 33 <b>133</b> = 0.65);	<u>mean</u> 54.08 19.35 32 33 21 23.69 18 = 7 (P = <u>Mean</u> 19.3 36 24.17	2.96 16.18 13 15 14 12.2 7.79 7 0.0002) <b>M(+)</b> 5D 7.9 16 13.32	18 25 23 23 23 14 28 9 <b>163</b> 3;   <sup>2</sup> = 7{ <b>163</b> 21 55 18 94	11.4% 13.7% 13.2% 13.2% 13.2% 13.2% 13.1% 10.9% 100.0% 100.0%	IV, Random, 95% Cl -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 0.12 [-0.49, 0.74] 0.00 [-0.34, 0.34] 0.32 [-0.26, 0.89] 0.09 [-0.18, 0.36]	Favours [experimental] Favours [control]
Granata V2016 Shan QG2017 Wei Y 2019 Wei Y2019 Woo S2014 Wu B2020 Zhou Y2021 <b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = Test for overall effect: <b>D</b> <u>Study or Subgroup</u> Li H2018 Wei Y2019 Zhao W2018 <b>Total (95% CI)</b> Heterogeneity: Chi <sup>2</sup> = Test for overall effect	Mean           31.49           31.55           30           29           30           24.1           26.35           23           0.25; Cl           Z = 0.37           Mean           20.4           36           29.67           0.86, df           Z = 0.66	SD           17.6           66.28           13           11           12.1           6.24           8           hi² = 28           '(P = 0.           VIVI(-)           9.7           14           18.9           '= 2 (P = 0.	<u>Total</u> 30 66 41 41 20 30 46 <b>315</b> .74, df: 71) <u>Total</u> 20 80 33 <b>133</b> = 0.65); .51)	<u>mean</u> 54.08 19.35 31 32 33 21 23.69 18 = 7 (P = <u>Mean</u> 19.3 36 24.17	2.96 16.18 13 15 14 12.2 7.79 7 0.00002) ₩(+) <u>SD</u> 7.9 16 13.32	18 25 23 23 23 14 28 9 <b>163</b> ; I <sup>P</sup> = 7€ <b>163</b> 21 55 18 94	11.4% 13.7% 13.2% 13.2% 13.2% 13.2% 13.1% 10.9% 100.0% 3% Weight 18.8% 60.0% 21.2% 100.0%	IV, Random, 95% Cl -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 0.12 [-0.49, 0.74] 0.00 [-0.34, 0.34] 0.32 [-0.26, 0.89] 0.09 [-0.18, 0.36] -	N, Random, 95% Cl       -4       -2       -4       Favours [experimental]       Favours [control]   Std. Mean Difference       N, Fixed, 95% Cl         -2         -1         -2         -2         -2         -2         -2         -2         -2         -1         -2         -1         -2         -1         -2         -1         -2         -1         -2         -1         -2         -1         -2         -1         -2         -1         -2         -1         -2

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).

Α	n	onpd-H	ICC		pd-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		
Cao L2019	1.54	0.22	45	1.34	0.18	29	17.4%	0.96 [0.47, 1.46]	-		
Wang GZ 2020	0.95	0.24	59	0.81	0.22	69	33.5%	0.61 [0.25, 0.96]			
Wang 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]			
Total (95% CI)			193			195	100.0%	0.63 [0.43, 0.84]	•		
Heterogeneity: Chi <sup>2</sup> =	2.46, df	= 3 (P =	= 0.48);								
Test for overall effect	: Z = 6.04	(P < 0.	00001)						-4 -2 U Z 4		
									Favours (experimental) Favours (control)		
В											
	1	MVI(-)			/IVI(+)			Std. Mean Difference	Std. Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl		
Cao L2019	1.51	0.22	36	1.41	0.22	38	29.0%	0.45 [-0.01, 0.91]			
Wang WT 2020	1.59	0.398	52	1.46	0.219	40	35.7%	0.39 [-0.03, 0.80]	+		
Wang WT2020	1.7	0.504	52	1.48	0.322	40	35.3%	0.50 [0.08, 0.92]			
Total (95% CI)			140			118	100.0%	0.45 [0.20, 0.69]	◆		
Heterogeneity: Chi <sup>2</sup> =	0.14, df	= 2 (P =	= 0.93);	l² = 0%					+ $+$ $+$ $+$ $+$ $+$		
Test for overall effect	Z = 3.51	(P = 0.	0004)						-4 -2 U 2 4 Favours [experimental] Favours [control]		

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 parameter
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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

Indicators/Sub- Groups group (Studies)	Groups (Studies)	AUC (95%CI)	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% Cl)	DOR (95% CI)		2
	(otdaloo)					0.,		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)	0.28 (0.15, 0.50)	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)	2.8 (2.2, 3.7)	0.32 (0.25, 0.42)	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)	4.5 (2.2, 9.1)	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)	3.1 (2.1, 4.6)	0.36 (0.27, 0.48)	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)	2.0 (1.4, 2.9)	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<sup>\*</sup> 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<sup>\*</sup> or f values in predicting HCC pathological grades. The reason may be that the D<sup>\*</sup> value is mainly related to microcirculation blood flow velocity; thus, this can lead to inaccurate measurements under subjective dynamics. In addition, the D<sup>\*</sup> value could not truthfully reflect the real value of cancer focus because the D<sup>\*</sup> 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.

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# 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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