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Benefits of combination therapy with immune checkpoint inhibitors and predictive role of tumour mutation burden in hepatocellular carcinoma: A systematic review and meta-analysis

Jiaxi Zheng [a,b], Minghai Shao [a,b], Weifang Yang [a,b], Justin Ren [c], Xiaofeng Chen [d,*], Haihua Yang [a,b,*]

[a] Key Laboratory of Minimally Invasive Techniques & Rapid Rehabilitation of Digestive System Tumour of Zhejiang Province, Taizhou, China
[b] Key Laboratory of Radiation Oncology of Taizhou, Radiation Oncology Institute of Enze Medical Health Academy, Department of Radiation Oncology, Taizhou Hospital Affiliated to Wenzhou Medical University, Taizhou, China
[c] Biological Sciences, Northwestern University, Evanston, Evanston, IL, USA
[d] Department of Radiation Oncology, Indiana University School of Medicine, Indianapolis, IU, USA

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ABSTRACT

Objectives: To investigate the clinical benefits of combination therapy with immune checkpoint inhibitors (ICIs) and best combination regimen for people with advanced hepatocellular carcinoma (HCC) and to explore the predictive performance of tumour mutation burden (TMB).
Methods: We conducted a systematic literature search to identify clinical trials. Meta-analysis and subgroup analyses were performed to estimate the benefits of combination regimens with PD-1/PD-L1 inhibitors for patients with advanced HCC and compare the effectiveness of PD-1/PD-L1 inhibitors and sorafenib as first-line therapy. Individualized analysis and Kaplan-Meier were used to assess the prognostic value of TMB.
Results: A total of 29 studies with 5396 patients were included. ICIs' combination therapy had higher ORR (26 % vs 15 %) and DCR (73 % vs 55 %), longer PFS (5.5 vs 3.1 months) and OS (15.9 vs 12.6 months) compared to monotherapy. Anti-PD-1/PD-L1 agents provided improved ORR, DCR, PFS and OS compared to sorafenib. The overall ORs of ORR and DCR in subgroup analysis were 3.49 (95 % CI 2.36–5.17, $p < 0.01$) and 1.60 (95 % CI 1.15–2.21, $p < 0.01$). The overall HRs of PFS and OS were 0.68 (95 % CI 0.48–0.96, $p = 0.03$) and 0.73 (95 % CI 0.62–0.85, $p < 0.01$). PD-1/PD-L1 inhibitors plus anti-VEGF agents had an advantage in DCR (0.80 vs 0.48, *meta*-regression = − 0.32, $P < 0.001$), but an equal ORR (0.29 vs 0.26) compared to dual immune checkpoint inhibitors. The total OS in Dua-ICIs were 16.5 months (95 % CI 14.2–18.7), yet not reached in the major studies of ICI plus anti-VEGF regimen. In individualized analysis, the 1-year OS was superior for patients who had high-TMB (>10, mutations/Mb) than moderate-TMB (1–10, mutations/Mb; 28 % vs 15 %, $P = 0.025$).
Conclusion: Immune checkpoint inhibitors' combination therapy improved clinical outcomes in the management of advanced hepatocellular carcinoma. However, the overall objective response rate still did not exceed 30%. PD-1/PD-L1 inhibitors plus anti-angiogenic agents and dual immunotherapy provided significantly increased survival over sorafenib, which also pose new challenges for future research, and more appropriate and guided control regimens are required. Also, TMB may be a promising prognostic biomarker for immunotherapy in HCC. However, the validation of prospective and large sample studies is needed.

1. Introduction

Hepatocellular carcinoma is the most lethal malignancy in patients with liver cirrhosis [1]. In the past, the standard first-line systemic treatments for hepatocellular carcinoma were only sorafenib and lenvatinib, and the second-line options were very few and ineffective [2,3]. As a result, the mortality rate of liver cancer has not decreased significantly. Recently, immunotherapy is changing treatment strategies for

* Corresponding authors at: Key Laboratory of Minimally Invasive Techniques & Rapid Rehabilitation of Digestive System Tumour of Zhejiang Province, Taizhou, China (H. Yang).
E-mail addresses: xiaof.chen@yahoo.com (X. Chen), yhh93181@hotmail.com (H. Yang).

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many malignancies, and there is growing evidence that patients with hepatocellular carcinoma (HCC) may benefit from these new treatments [4,5]. Immune checkpoint inhibitors (ICIs) including pembrolizumab, nivolumab, durvalumab, atezolizumab, etc. have been recently evaluated in HCC patients, and clinical trials assessing single-agent ICI have reported disappointing results. Conversely, immune-based combinations have been more striking [4].

To date, about 50 single-arm clinical trials and several randomized control trials (RCTs) have reported findings of investigations on the effectiveness of immunotherapy based on PD-1/PD-L1 inhibitors for advanced HCC [6]. In the last five years, pembrolizumab (KEYNOTE-240) or nivolumab monotherapy (CheckMate 459) have made progress in the treatment of HCC [7,8], but they have not replaced the traditional first-line drugs sorafenib or lenvatinib. In follow-up studies, atezolizumab plus bevacizumab (IMbrave 150), and Sintilimab plus bevacizumab (ORIENT-32) were found to significantly improve progression-free survival (PFS) and overall survival (OS) compared with sorafenib monotherapy [9,10]. Alessandro Rizzo reviewed immunotherapy-based studies and highlighted potential of lenvatinib plus pembrolizumab (KEYNOTE-524) in first-line treatment of HCC [11,12]. In addition, a few more combinations with antiangiogenic agents and dual- immunotherapy are under investigation (CheckMate040, ALTER-H003, VEGF Liver 100, [13–15]). More recently, based on positive results of HIMALAYA, durvalumab and tremelimumab combination therapy could become another choice in practice [16]. However, these clinical trials differed in drugs, patients, designs, terms of study phases, and inconsistent clinical outcomes were shown in several trials. Despite ICI seem to have finally found their role in HCC as part of combinatorial strategies, several questions remain unanswered. Among these, the lack of validated biomarkers of response represents an important issue since only a proportion of HCC patients benefit from immunotherapy [17]. Based on these premises, a greater understanding of the role of potential biomarkers including programmed death ligand 1 (PD-L1) expression, tumour mutational burden (TMB), microsatellite instability (MSI) status, gut microbiota and several others is fundamental [12,18]. In addition, clinical trials on HCC immunotherapy widely differed in terms of drugs, patients, designs, terms of study phases, and inconsistent clinical outcomes.

Considering the enormous number of immunotherapy studies and new combinations for HCC and to face the challenge of identifying specific predictors, we have chosen to overcome the limitations of individual research to better evaluate the clinical efficacy of PD-1 and PD-L1 inhibitors in this systematic review of the current treatment literature and have performed a retrospective analysis of all studies on TMB predicting response to immunotherapy.

2. Materials and Methods

2.1. Search strategy and study selection

We searched the following databases (Pubmed, Embase, Cochrane Library, Web of Science, and clinicaltrials.gov) and the meeting abstracts of conferences (ASCO, ESMO, AACR) from inception to 31st January 2022 for all PD-1/PD-L1 inhibitor-based monotherapies and combination therapies. The following terms were used to describe the cancer: HCC, hepatocellular carcinoma, liver cancer, and liver cell carcinoma. We searched for clinical trials using the specific terms: immunotherapy, immune checkpoint inhibitor, programmed death-ligand 1, programmed death receptor 1, tumour mutational burden, nivolumab, opdivo, pembrolizumab, keytruda, atezolizumab, durvalumab, avelumab, camrelizumab, cemiplimab, tislelizumab, toripalimab, sintilimab, penpulimab, and jemperli. In addition, we also checked all relevant articles to identify studies reporting HRs of PFS and OS based on TMB cut-off values. The detailed protocol is documented online in the INPLASY (https://doi.org/10.37766/inplasy2022.1.0008).

We included all clinical trials reporting on the effectiveness of immune checkpoint inhibitors for people with advanced HCC, with or without blinding. We applied no publication status restrictions, and when sufficient data was available, we included meeting abstracts and unpublished online data. The inclusion criteria were: (1) Clinical trials including monotherapy or combination therapy of PD-1/PD-L1 inhibitors for patients with advanced HCC (excluded monotherapy of cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) inhibitors or real-world studies); (2) Studies with published data based on RECIST 1.1 (Response Evaluation Criteria for Solid Tumours Version 1.1 guidelines) which evaluated overall response rate (ORR), disease control rate (DCR), PFS, and OS; (3) Published in English; (4) Sample size greater than 10; (5) Latest reported data were updated for past clinical trials.

2.2. Data extraction

Two investigators (JZ and HY) extracted the data and negotiate solutions to problems encountered. We gathered the following information: first author's name, country, published year, study design, National Clinical Trials (NCT) registry number, treatment regimen, trial phase, trial name, sample size, ORR, DCR, PFS, OS, and base-line characteristics, TMB and its detection method, threshold, and so on.

3. Quality assessment

The study quality assessment tools developed by NHLBI (National Heart, Lung, and Blood Institute, https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools, [19,20]) were used to determine the quality of included studies. Quality assessment tool of controlled intervention studies was performed in RCTs and quality assessment tool for observational cohort and cross-sectional studies was used in single arms.

3.1. Statistical analysis

We have summarized the characteristics of the included studies. For studies in which raw data were not reported, the investigators were contacted to request data. All *meta*-analyses were performed using a random-effects model (DerSimonian and Laird method). The heterogeneity among studies was evaluated by I^2 test and the Cochran Q test: $I^2 < 50$ % was considered as negligible heterogeneity, 50–75 % as moderate heterogeneity and ≥ 75 % as substantial heterogeneity, respectively [21,22], or $P < 0.05$ indicated the presence of significant heterogeneity. To identify probable sources of heterogeneity for the overall effects of combined therapies, subgroup analyses and *meta*-regression were conducted according to the predefined variables. Sensitivity analysis using leave-one-out *meta*-analysis was performed to detect the dependency of the overall effect size on a particular study. The visual inspection of funnel plot and Egger's test was performed to evaluate publication bias. The differences in treatment effect between subgroups were measured by P value for interaction. Individualized analysis and Kaplan-Meier were used to assess the prognostic value of TMB. Two-stage test [23,24] was performed to compare the overall survival of the high and moderate TMB groups by R package "TSHRC" [25]. R 4.1.0 and Stata (version 16.0) was used for all analysis and graphing. $p < 0.05$ was considered statistically significant.

4. Results

A total of 29 studies met the inclusion criteria and were included in our overall analysis. Fig. 1 depicts the selection procedure. There were 5 RCTs and 23 single-arm trials among these studies. All studies used the latest and available clinical data. In 24 single-arm studies, there were 8 studies with PD-1/PD-L1 inhibitor monotherapy and 16 studies of combined immunotherapy. Treatment regimens in 5 RCTs were 2 monotherapy and 3 combinations.

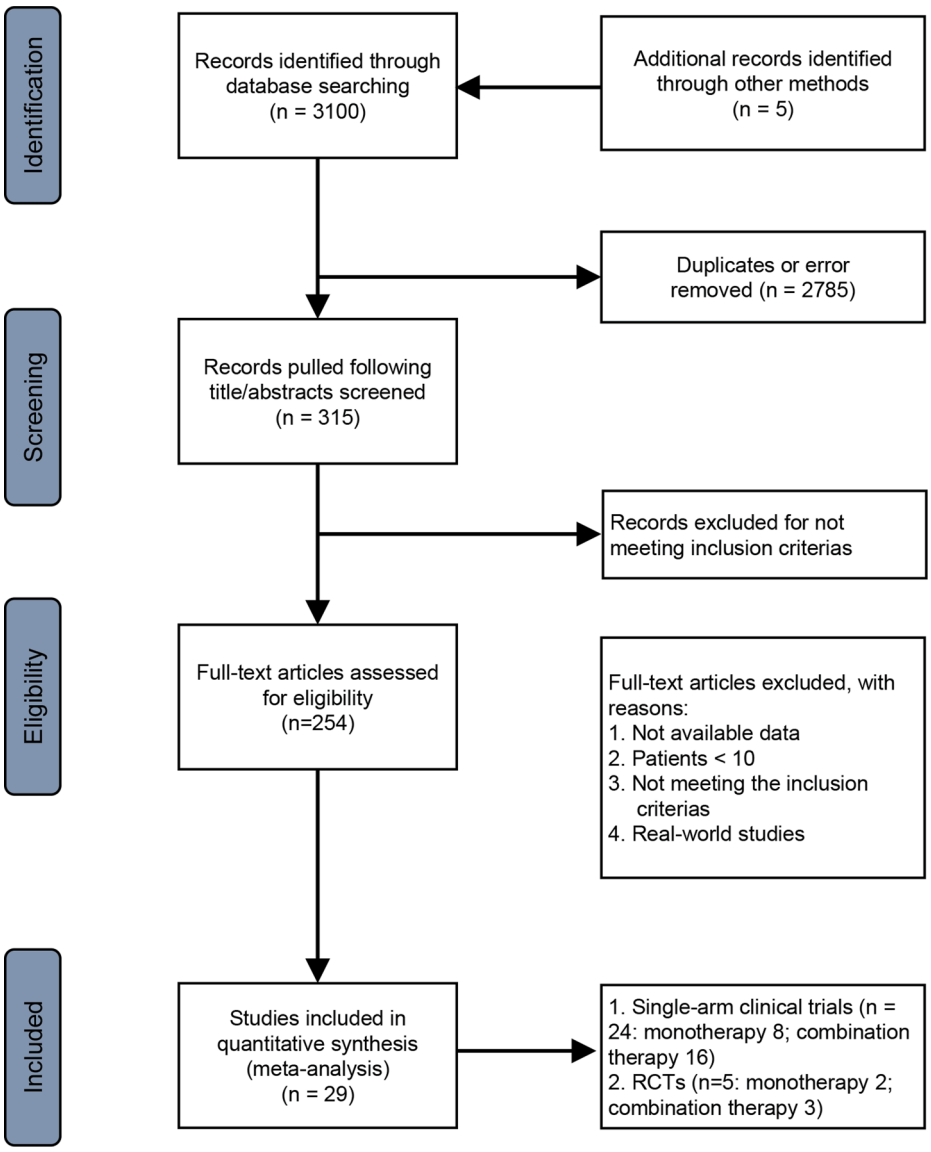

Fig. 1. PRISMA flowchart of study selection.

4.1. Characteristics

The summary of results of clinical trials with PD-1/PD-L1 inhibitors was shown in Table 1. A total of 5396 patients were included in this *meta*-analysis. More information about the baseline characteristics of the studies was shown in Table S4 in Supplementary Material.

4.2. Overall effects of ORR and DCR for people with advanced HCC undergoing immunotherapy with PD-1/PD-L1 inhibitors

As shown in 24 single-arm studies in Fig. 2 and Fig. 3, the overall ORR was 0.22 (95 % CI 0.19–0.25) and DCR was 0.67 (95 % CI 0.61–0.72). Combination therapy had higher ORR (0.26 vs 0.15, $p < 0.01$) and DCR (0.73 vs 0.55, $p < 0.01$) compared to monotherapy. For the ORR of combination therapy, the evidence demonstrated significant heterogeneity ($I^2 = 44.98$ %, $P < 0.01$). Results (Fig. S1) from sensitivity analysis using leave-one-out *meta*-analysis showed that exclusion of any single study did not influence the overall estimate for the ORR of combination therapy, however, the ORR in the combined treatment group decreased by 0.02 after the exclusion of the study 'Finn (2020, KEYNOTE-524)' which combination regimen of pembrolizumab plus lenvatinib demonstrated superior response rate. For the DCR in combination therapy, the evidence demonstrated significant heterogeneity ($I^2 = 65.53$ %, $P < 0.01$). Results (Fig. S2) from sensitivity analysis showed that the omission of study 'Yau1 (2020, CheckMate040, nivolumab plus ipilimumab)' or 'Finn (2020)' seems to have a relatively larger influence (when compared with other studies) on the estimation of the DCR. Considering the visual inspection of funnel plots, we found an asymmetry (Fig. 4).

4.3. Overall effects of PFS and OS for people with advanced HCC undergoing immunotherapy with PD-1/PD-L1 inhibitors

As shown in Fig. 5, The total PFS was 4.7 months (95 % CI 3.9–5.6), and the total OS was 13.7 months (95 % CI 11.8–15.7). Combination therapy had longer PFS (5.5 vs 3.1 months, $P < 0.01$) and OS (15.9 vs 12.6 months, $P = 0.05$) compared to monotherapy. For the PFS of combination therapy, the evidence demonstrated significant heterogeneity ($I 2 = 80.43$ %, $P < 0.01$). Results (Fig. S3) from sensitivity analysis using leave-one-out *meta*-analysis showed that exclusion of any single study did not influence the overall estimate for the PFS of combination therapy, however, the PFS in the combined treatment group decreased by 0.33 after the exclusion of the study 'Finn (2020, KEYNOTE-524, pembrolizumab plus lenvatinib)'. For the OS in combination therapy,

Table 1
Summary of results of clinical trials with PD-1/PD-L1 inhibitors.

Study name/Study registration	Study phase	Treatment	Number of patients	Median age (years)	RACE, White/ Asian	ORR by RECIST 1.1 criteria	DCR by RECIST 1.1 criteria	Median Progression-free survival(months)	Median Overall survival(months)	First author and date of publication
CheckMate040 (NCT01658878)	I/II	Nivolumab	49	67 (IQR 62–72)	NA	6 (12 %)	27 (55 %)	2.7 (1.6–4.0)	7.6 (4.4–10.5)	Kudo1 (2021)
	I/II	Nivolumab	48	62 (IQR 55–69)	28(58 %) /18(38 %)	7 (15 %)	28 (58 %)	3.4 (1.6–6.9)	15.0 (9.6–20.2)	El-Khoueiry1 (2017)
	I/II	Nivolumab	214	64 (IQR 56–70)	105 (49 %) /101(47 %)	42 (20 %)	138 (64 %)	4.0 (2.9–5.4)	9-m OS 74 %	El-Khoueiry2 (2017)
20151049 (NCT02658019)	II	Pembrolizumab	29	>=65 years (72.4 %)	27(93.1 %)/1 (3.4 %)	9 (32 %)	13 (46 %)	3.0 (2.0–7.0)	14.0 (3.0-NE)	Feun (2019)
KEYNOTE-224 (NCT02702414)	II	Pembrolizumab	104	68 (IQR 62–73)	84(81 %) /14(13 %)	18 (17 %)	64 (62 %)	4·9 (3·4–7·2)	12.9 (9.7–15.5)	Zhu (2018)
SHR-1210-II/III-HCC (NCT02989922)	II	Camrelizumab	217	49 (IQR 41–59)	Chinese (100 %)	32 (14.7 %)	96 (44.2 %)	2.1 (2.0–3.2)	14.2 (11.5–16.3)	Qin (2021)
H-1708-040-876 (NCT03389126)	II	Avelumab	30	62(range 36–81)	NA	3 (10 %)	22 (73.3 %)	3.5 (2.0–5.1)	14.2 (9.5–18.9)	Lee (2021)
RATIONALE-208 (NCT03419897)	II	Tslelizumab	249	62 (IQR NA)	NA	30 (11.2 %)	NA	2.7 (1.5–2.8)	12.4 (10.8-NE)	M.Ducreux (2021)
R2810-ONC-1423 (NCT02383212)	I	Cemiplimab	26	65 (range 40–78)	NA	5 (19 %)	19 (73 %)	3.7 (2.3–9.1)	NA	Pishvaian (2018)
CD-ON-MEDI4736-1108 (NCT01693562)	I/II	Durvalumab	40	NA	19(47.5 %)/9 (22.5 %)	4 (10.3 %)	13 (33.3 %)	NA	13.2 (6.3–21.1)	Wainberg (2017)
KEYNOTE-240 (NCT02702401)	III	Pembrolizumab vs Placebo	413(278 vs 135)	67 (range 18–91)	NA /157(38 %)	18.3 % vs 4.4 %	62.2 % vs 53.3 %	3.0 (2.8–4.1) vs 2.8 (1.6–3.0)	13.9(11.6–16.0) vs 10.6 (8.3–13.5)	Finn2 (2020)
CheckMate 459 (NCT02576509)	III	Nivolumab vs Sorafenib	743(371 vs 372)	65 (IQR 57–71)	395(54 %) /332(44 %)	15.4 % vs 7.0 %	55 % vs 58 %	3.7 (3.1–3.9) Vs 3.8 (3.7–4.5)	16.4 (13.9–18.4) vs 14.7 (11.9–17.2)	Yau (2019)
KEYNOTE-524 (NCT03006926)	Ib	Pembrolizumab + Lenvatinib	104	66.5 (range 47–86)	NA /18(18 %)	41 (41 %)	86 (86 %)	8.2 (7.4–9.7)	22.0 (20.4–NE)	Finn (2020)
GO30140 (NCT03434379)	Ib	Atezolizumab +bevacizumab	104	62(range 23–82)	20(19 %) /75(72 %)	37 (36 %)	74(71 %)	7.3 (5.4–9.9)	17.1 (13.8-NE)	Lee (2020)
CIBI338B101 (NCT04072679)	Ib	Sintilimab +bevacizumab	50	NA	Chinese (100 %)	13 (28 %)	47 (79 %)	6-m PFS 60.5 %	NA	Zhang (2020)
ALTER-H003 (ChiCTR1900028295)	II	Toripalimab +anlotinib	18	NA	Chinese (100 %)	3 (21.4 %)	13 (92.9 %)	NA	NA	Lin (2021)
KEEP-G 04 (NCT04052152)	II	Sintilimab +anlotinib	20	56 (range 41–70)	Chinese (100 %)	8 (40 %)	19 (95 %)	6-m PFS 66.4 %	NA	Chen (2021)
AK105-203 (NCT04172571)	Ib/II	Penpulimab +anlotinib	31	56 (range 23–74)	Chinese (100 %)	9 (31.0 %)	24 (82.8 %)	8.8 (4.0–12.3)	12-m OS 69.0 %	Han (2021)
RESCUE (NCT03463876)	II	Camrelizumab +apatinib	70	53 (IQR 44–60)	Chinese (100 %)	24 (34.3 %)	54 (77.1 %)	5.7 (CI 5.4–7.4)	12-m OS 74.7 %	Xu1 (2021)

(*continued on next page*)

Table 1 (*continued*)

Study name/Study registration	Study phase	Treatment	Number of patients	Median age (years)	RACE, White/ Asian	ORR by RECIST 1.1 criteria	DCR by RECIST 1.1 criteria	Median Progression-free survival(months)	Median Overall survival(months)	First author and date of publication
	II	Camrelizumab +apatinib	120	51 (IQR 43–58)	Chinese (100 %)	27 (22.5 %)	91 (75.8 %)	5.5 (CI 3.7–5.6)	12-m OS 68.2 %	Xu2 (2021)
NCT03289533 (NCT03289533)	Ib	Avelumab +axitinib	22	68.5 (range 20–84)	Japanese (100 %)	3 (13.6 %)	15 (68.2 %)	5.5 (1.9–7.4)	14.1(8.0–NE)	Kudo2 (2021)
JVDJ (NCT02572687)	Ib	Durvalumab +ramucirumab	28	63 (range 27–87)	11(39 %) /7(25 %)	3 (11 %)	17 (61 %)	4.4 (1.6–5.7)	10.7 (5.1–18.4)	Bang (2020)
D4190C00022 (NCT02519348)	I/II	Durvalumab +tremelimumab	332/75	66 (range 26–86)	27(36.0 %) /44(58.7 %)	18 (24.0 %)	34 (45.3 %)	2.2 (1.9–5.5)	18.7 (10.8–27.3)	Kelley (2020)
16-C-0135 (NCT02821754)	II	Durvalumab +tremelimumab	22/10	62.5 (range 19–80)	NA	2 (20 %)	60 (60 %)	7.8 (2.6–10.6)	15.9 (7.1–16.3)	Floudas (2019)
CheckMate040 (NCT01658878)	I/II	Nivolumab +ipilimumab	148	60 (IQR 52.5–66.5)	47(32 %) /94(64 %)	46 (31 %)	72 (49 %)	NA	NA	Yau1 (2020)
	I/II	Nivolumab +cabozantinib	36	NA	NA	6 (17 %)	29 (81 %)	5.5 (NA)	NA	Yau2 (2020)
	I/II	Nivolumab +ipilimumab +cabozantinib	35	NA	NA	9 (26 %)	29 (83 %)	6.8 (NA)	NA	Yau3 (2020)
B2018-151-01 (NCT03939975)	II	Nivolumab/ Pembrolizumab + ablation	50	51 (range 19–74)	Chinese (100 %)	12 (24 %)	30 (60 %)	5 (2.9–7.1)	16.9 (7.7–26.1)	Lyu (2020)
RT + PD-1-HCC (NCT04193696)	II	Camrelizumab +radiotherapy	17	54 (range 32–69)	Chinese (100 %)	8 (47 %)	NA	NA	NA	Li (2021)
CA 209-678 (NCT03033446)	II	Nivolumab + radioembolization	36	64 (IQR 59.7–70.9)	Asian (100 %)	11 (31 %)	22 (58 %)	4.6 (2.3–8.4)	15.1 (7.8-NE)	Meng (2020)
SHR-1210-APTN-II-203-PLC (NCT03092895)	II	Camrelizumab +chemotherapy	34	NA	Chinese (100 %)	9 (26.5 %)	27 (79.4 %)	5.5 (NA)	NA	Qin (2019)
IMbrave 150 (NCT03434379)	III	Atezolizumab +bevacizumab vs Sorafenib	501(336 vs 165)	64 (IQR 56–71)	175(35 %)/194(39 %)	29.8 % vs 11.3 %	73.6 % vs 53.3 %	6.8(5.7–8.3) vs 4.3(4.0–5.5)	19.2 (17.0–23.7) vs 13.4 (11.4–16.0)	Finn1 (2020)
ORIENT-32 (NCT03794440)	II/III	Sintilimab +bevacizumab vs Sorafenib	571(380 vs 191)	53 (range 21–82)	Chinese (100 %)	21.0 % vs 4.0 %	73 % vs 63 %	4.6(4.1–5.7) vs 2.8(2.7–3.2)	not reached vs 10.4 (8.5-not reached)	Ren (2021)
HIMALAYA (NCT03298451)	III	Durvalumab +tremelimumab vs Sorafenib	782(393 vs 389)	NA	NA	20.1 % vs 5.1 %	NA	NA	16.4 (14.2–19.6) vs 13.8 (12.3–16.1)	Ghassan (2022)

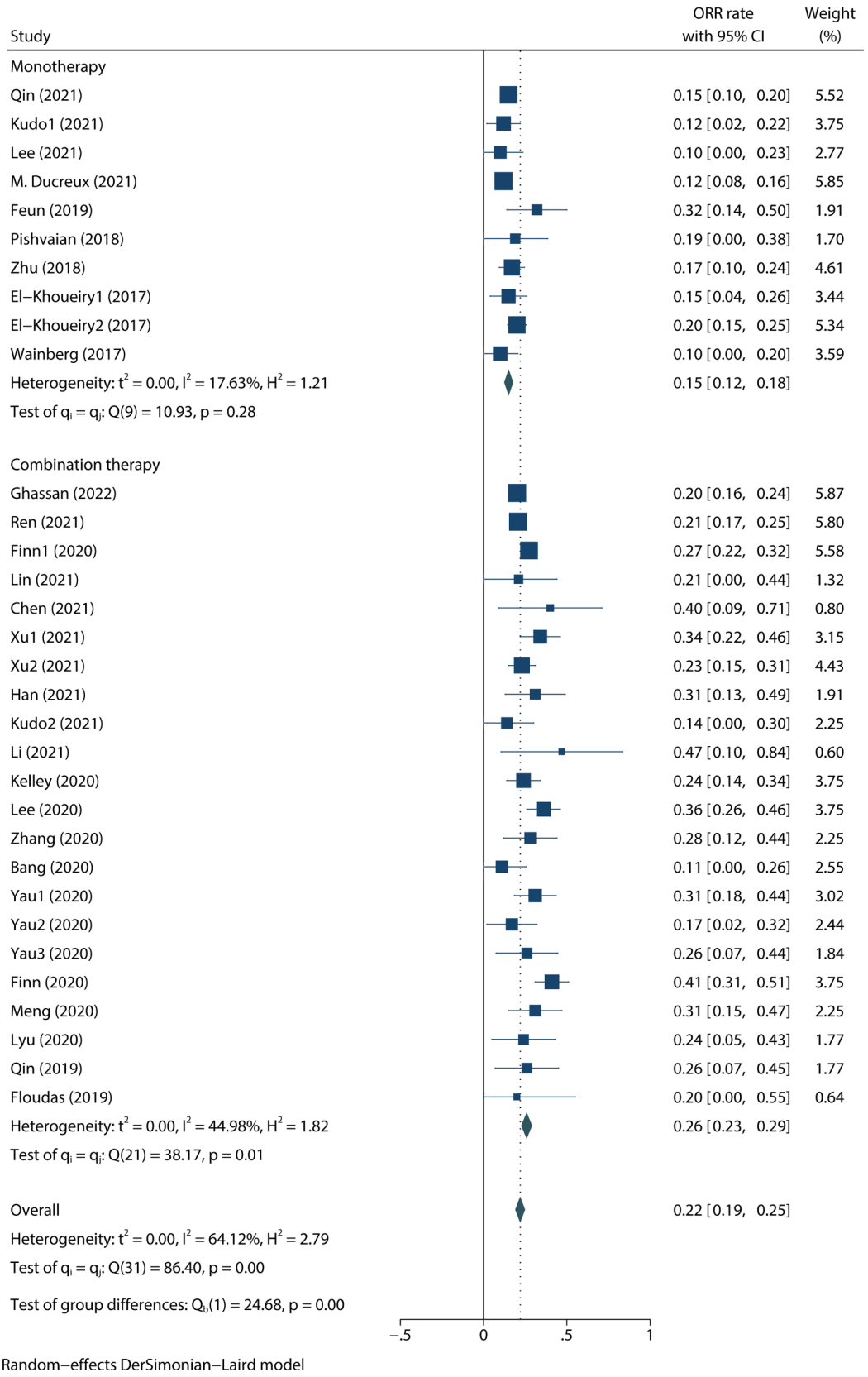

Fig. 2. Forest plot of overall effects of ORR for people with advanced HCC undergoing immunotherapy with PD-1/PD-L1 inhibitors.

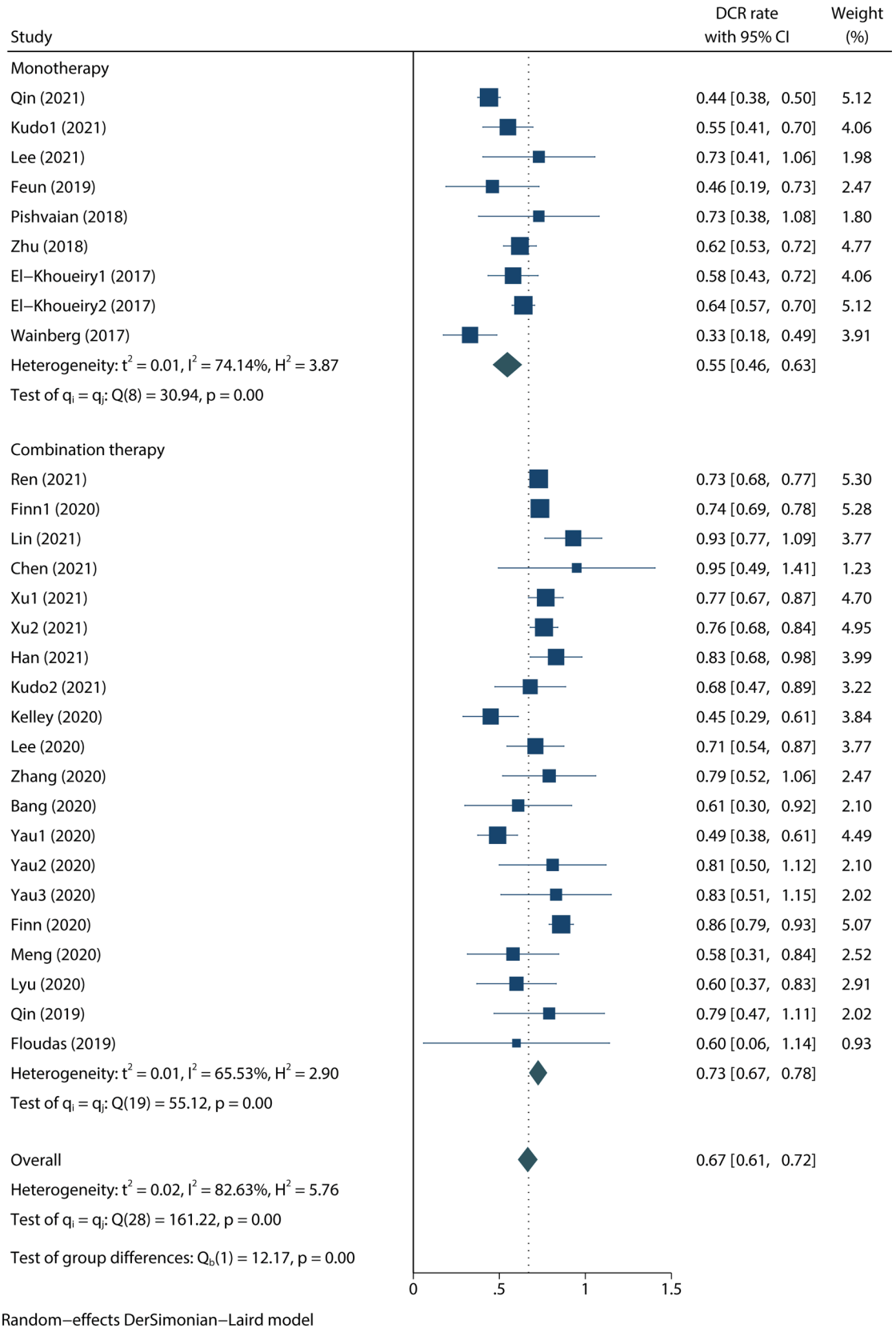

Fig. 3. Forest plot of overall effects of DCR for people with advanced HCC undergoing immunotherapy with PD-1/PD-L1 inhibitors.

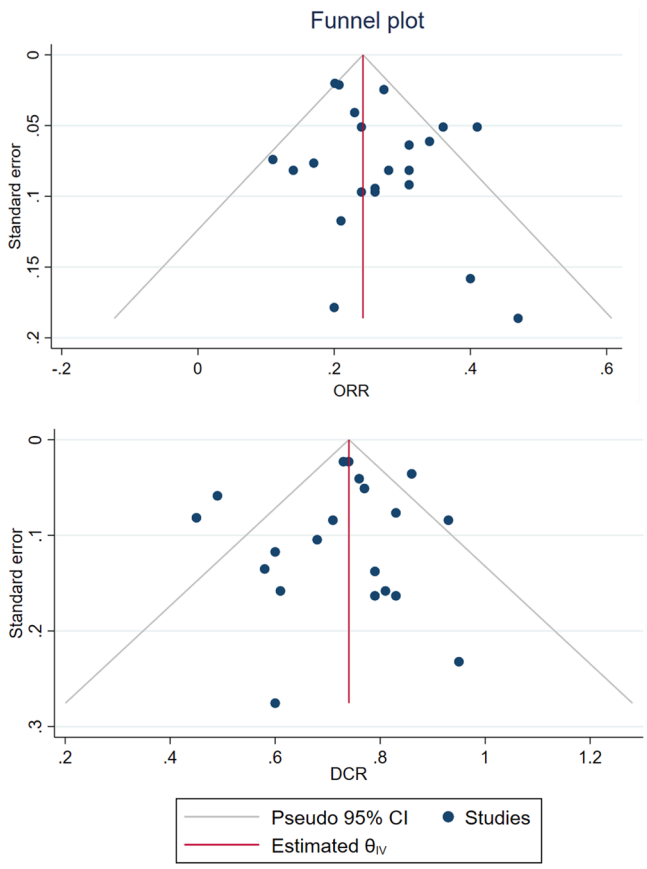

Fig. 4. Funnel plot of overall effects of ORR and DCR for people with advanced HCC undergoing immunotherapy with PD-1/PD-L1 inhibitors.

the evidence demonstrated no heterogeneity (I^2 = 0.00 %, P = 0.56). Results (Fig. S3) from sensitivity analysis showed that the omission of study 'Ghassan (2022, HIMALAYA, durvalumab plus tremelimumab)' seems to have a relatively larger influence (decreased by 0.68, when compared with other studies) on the estimation of the OS. Considering the visual inspection of funnel plots, we found an asymmetry (Fig. 6).

5. Subgroup analysis

5.1. PD-1/PD-Ll inhibitors compared to sorafenib for people with advanced HCC

In this group, a total of 5 RCTs were included to compare the clinical benefits between PD-1/PD-Ll inhibitors with or without targeted drugs and sorafenib for advanced HCC. The data of ORs (ORR and DCR) and HRs (PFS and OS) from treatment and control group were analyzed. As shown in Fig. 7, the corresponding OR of ORR and DCR were 3.49 (95 % CI 2.36–5.17, p < 0.01) and 1.60 (95 % CI 1.15–2.21, p < 0.01), and the corresponding HRs of PFS and OS were 0.68 (95 % CI 0.48–0.96, p = 0.03) and 0.73 (95 % CI 0.62–0.85, p < 0.01). There was no evidence of heterogeneity between studies for ORR (I^2 = 48.02 %, p = 0.12), DCR (I^2 = 54.38 %, p = 0.11), and OS (I^2 = 57.79 %, 0.07). However, substantial heterogeneity was observed in PFS (I^2 = 89.27 %, p < 0.01) and heterogeneity was derived from Yau (2019, CheckMate 459). Considering the visual inspection L'Abbe plots and funnel plots, we found no asymmetry for ORR, DCR, and OS, but PFS showed an asymmetry (Fig. 8).

5.2. PD-1/PD-Ll inhibitors as first-line combination therapy versus second or subsequent-line therapy for people with advanced HCC

In combination therapies except RCTs, we analyzed the clinical benefits of anti-PD-1/PD-Ll drugs as first-line vs second or subsequent-line therapy. In this subgroup, as shown in Table 2, the results showed first-line combination therapy had advantages of ORR (0.30 vs 0.26), DCR (0.77 vs 0.65), PFS (6.9 vs 5.3 months) and OS (18.7 months vs 14.6 months) than second or subsequent-line therapy. A considerable number of first-line immunotherapy studies with OS outcomes not reached were not included in OS analysis. Reduced heterogeneity for clinical outcomes was observed. meta-regression showed an association between treatment lines and clinical outcomes (Fig. 9). However, this association was not statistically significant (ORR: regression = − 0.67, P = 0.113; DCR: regression = − 0.11, P = 0.143; PFS: regression = − 1.67, P = 0.079; OS: insufficient studies).

5.3. Combined single immune checkpoint inhibitor with anti-VEGF agents compared to dual-immune checkpoint inhibitors for people with advanced HCC

In this group, we compared the regimen of single-ICI plus anti-VEGF drugs and dual-ICIs. As shown in Table 3, PD-1/PD-L1 inhibitors plus anti-VEGF drugs had an advantage in ORR (0.29 vs 0.26), DCR (0.80 vs 0.48) compared to dual immune checkpoint inhibitors. Reduced heterogeneity for clinical outcomes was observed. meta-regression showed a statistically significant association between different DCR and anti-PD-1 or PD-L1 drugs combinations (regression = − 0.32, P < 0.001, Fig. 10). In addition, *meta*-regression showed no statistically association between different drug combinations and ORR (regression = − 0.01, P = 0.992) and PFS (ORR: regression = 1.45, P = 0.561). However, OS outcomes were not reached for a considerable number of single-ICI plus anti-VEGF drugs.

5.4. PD-1 inhibitors combination therapy compared to PD-L1 inhibitors for people with advanced HCC

In this subgroup, as shown in Table 4, PD-1 inhibitors combinations had an advantage in ORR (0.29 vs 0.22), DCR (0.76 vs 0.61), PFS (6.2 vs 5.9 months) and OS (16.9 vs 14.9 months) compared to PD-L1 inhibitors. Reduced heterogeneity for clinical outcomes was observed. meta-regression showed a weak association between PD1/PD-L1 inhibitors and clinical outcomes (Fig. 11). However, this association was not statistically significant (ORR: regression = − 0.06, P = 0.224; DCR: regression = − 0.15, P = 0.087; PFS: regression = − 1.93, P = 0.761; OS: insufficient studies). However, OS outcomes were not reached for a considerable number of PD-1 inhibitors combinations.

5.5. Subgroup analysis of clinical outcomes stratified by Age, Country, AFP, HBV/HCV, and Child-Pugh score

In Table S1, we conducted subgroup analysis to further analyze the sources of heterogeneity, based on the baseline characteristics of the studies including age, country/ region, alpha-fetoprotein (AFP), extrahepatic metastases and HBV etiology. The results of *meta*-regression plots of the association between baseline characteristics and clinical outcomes were presented in Fig. S4.

Association between tumour mutation burden and PFS/OS for people with advanced HCC receiving immune checkpoint inhibitors.

In the absence of prospective studies, we searched for retrospective studies that explored predictive value of TMB for advanced HCC with immunotherapy in Table S2 and five studies were included. Data on 155 patients were included in the analysis, and all studies were retrospective. As shown in Fig. S5, the corresponding HRs of PFS and OS were 0.71 (95 % CI 0.33–1.09) and 0.61 (95 % CI 0.08–1.14). Sustained heterogeneity was observed for the effect of OS between groups. To

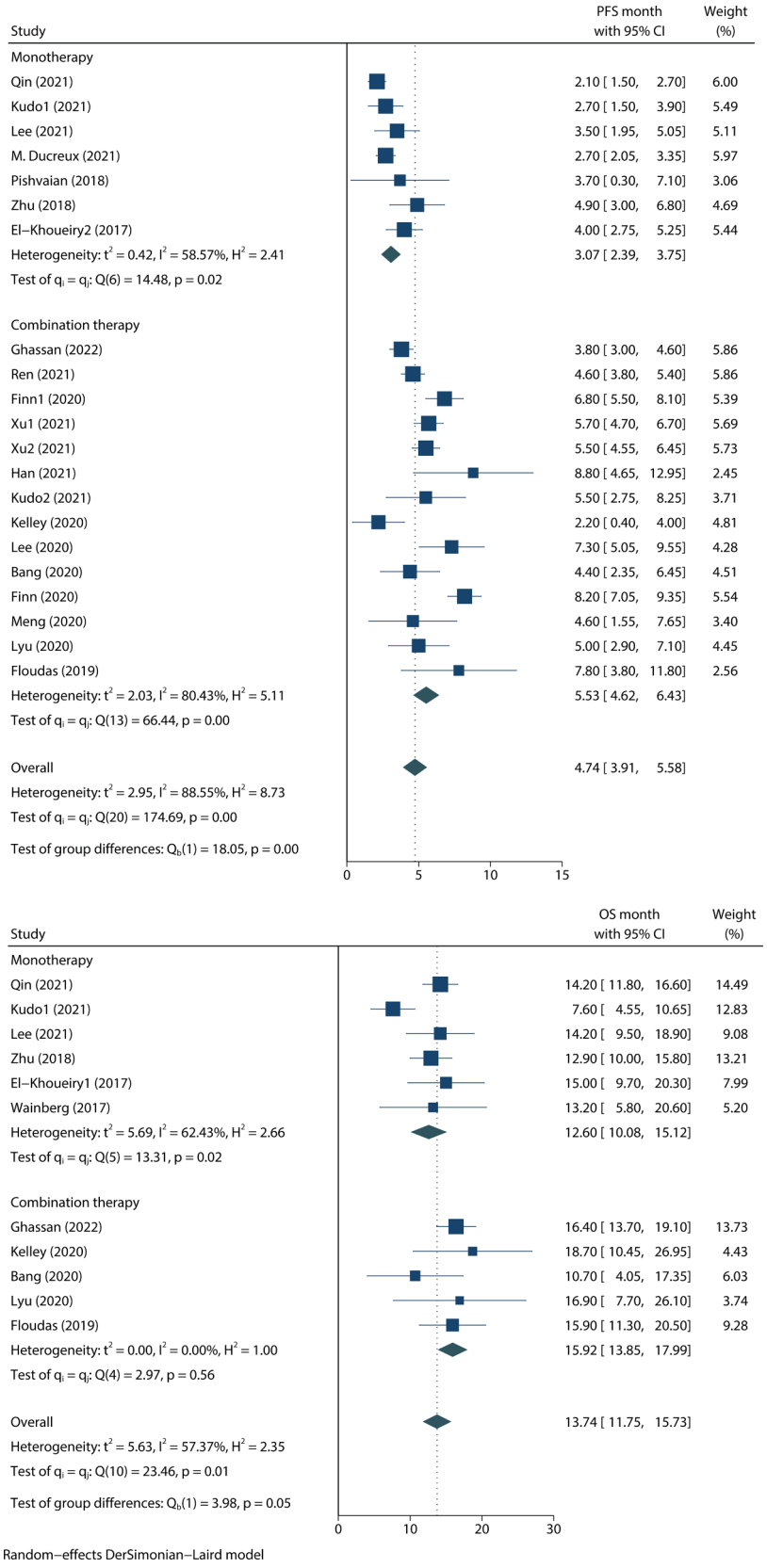

Fig. 5. Forest plots of overall effects of PFS and OS for people with advanced HCC undergoing immunotherapy with PD-1/PD-L1 inhibitors.

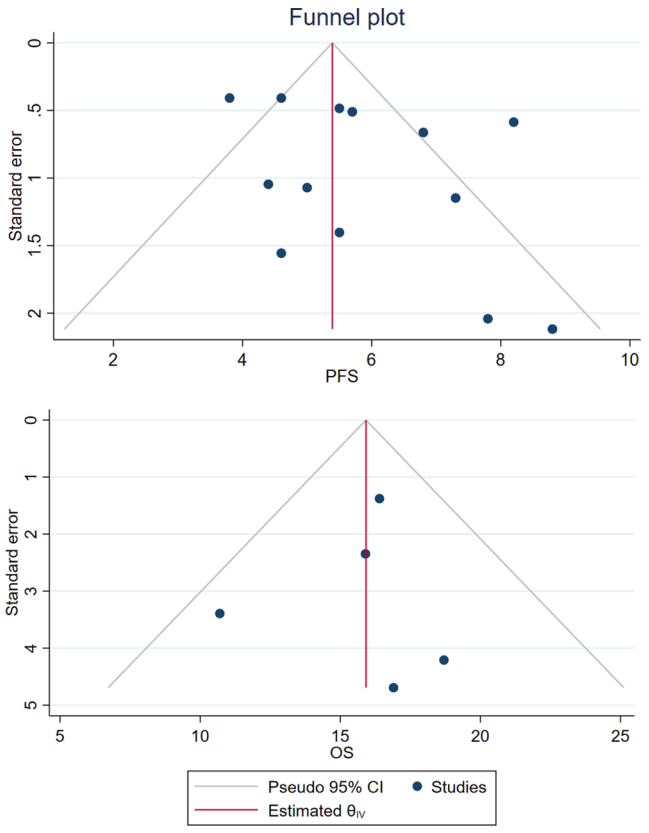

Fig. 6. Funnel plot of overall effects of PFS and OS for people with advanced HCC undergoing immunotherapy with PD-1/PD-L1 inhibitors.

overcome the effect of different TMB cut-off values on the results, we grouped all patients according to the new TMB cut-off values, >10 mutations/Mb (top 10 % of all cases) was defined high-TMB, 1–10 mutations/Mb was defined moderate-TMB, and < 1 mutations/Mb (min 11 % of all cases) was defined low-TMB. TMB = 1–10 cases account for about 80 %, while TMB = 1–5 cases account for about 60 %. As shown in Fig. 12 and Fig. 13, high-TMB group had a significantly longer 1-year OS than moderate-group (28 % vs 15 %, p = 0.025). However, there were no differences in PFS, 18-months and 2-years OS between TMB-H and TMB-M groups.

5.6. Evaluation of study quality and publication bias

Fig. S6 and Table S4 provide separate summaries of the quality assessment of RCTs and single arms. Evidence of publication bias by egger's test was shown in Table S3.

6. Discussion

Immunotherapy offers promising results for cancer therapy. PD-1/PD-L1 pathway is an essential approach to reactivate the anti-tumour immune effect of T cells, which plays a crucial role in suppressing immune responses and promoting self-tolerance by regulating T cell activity, activating apoptosis of antigen-specific T cells and inhibiting apoptosis of regulatory T cells [26]. The binding of PD-1 to PD-L1 reverses immune escape of tumour cells and activates the anti-tumour response of infiltrating T cells. This antitumour immunity may be dependent on tumour antigens and infiltrating CD8 T cells in the tumour microenvironment; therefore, only some patients have benefit from targeting PD-1/PD-L1 [27,28].

Our analysis revealed that immunotherapy based on PD-1/PD-L1 inhibitors was associated with improved overall survival and progression-free survival for patients with advanced HCC. Compared to monotherapy, combination immunotherapy based on PD-1/PD-L1 inhibitors demonstrated superior clinical efficacy in ORR (26 % vs15%), DCR (73 % vs 55 %), PFS (5.5 vs 3.1 months), and OS (15.9 vs 12.6 months), respectively. Our findings suggested that first-line immunotherapy based on PD-1/PD-L1 antibodies showed a longer duration of effect than sorafenib on PFS (HR: 0.68, 95 % CI 0.48–0.96, p = 0.03) and OS (HR: 0.73, 95 % CI 0.62–0.85, p < 0.01) for advanced HCC. Moreover, combinations of PD-1/PD-L1 inhibitors and VEGF (vascular endothelial growth factor) antibodies elicited the strongest anti-tumour efficacy. Among them, the first- line atezolizumab plus bevacizumab and sintilimab plus bevacizumab were seemingly superior to other treatments. Second- or third-line immunotherapy still benefited HCC patients after failure of first-line targeted therapy. Additionally, high TMB was discovered to be an encouraging biomarker for survival in HCC with immunotherapy based on our results. However, TMB alone may be unstable as a perfect predictive biomarker for immunotherapy in HCC and the further combination model are needed.

Compared with dual immune checkpoint inhibitors such as durvalumab plus tremelimumab, or nivolumab plus ipilimumab, PD-1/PD-L1 inhibitors plus anti-VEGF drugs had an advantage in DCR (0.80 vs 0.48) but an equal ORR (0.27 vs 0.26), even though there isn't any randomized controlled trial comparing the two. The results of a 2020 phase III

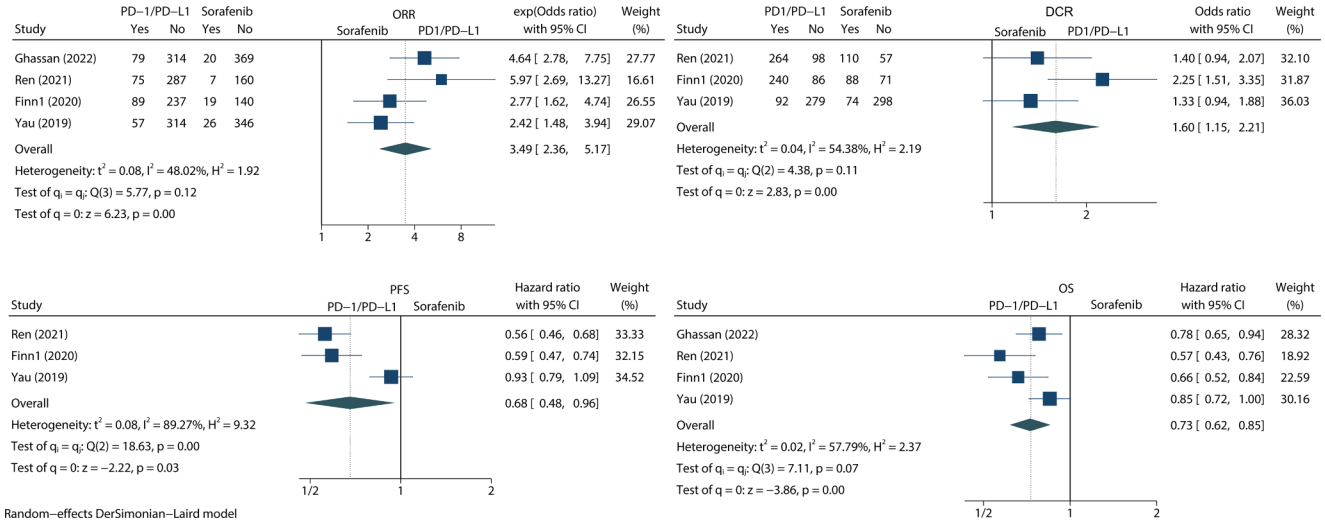

Fig. 7. Forest plots of comparison of ORR, DCR, PFS, and OS regarding immune checkpoint inhibitors versus sorafenib.

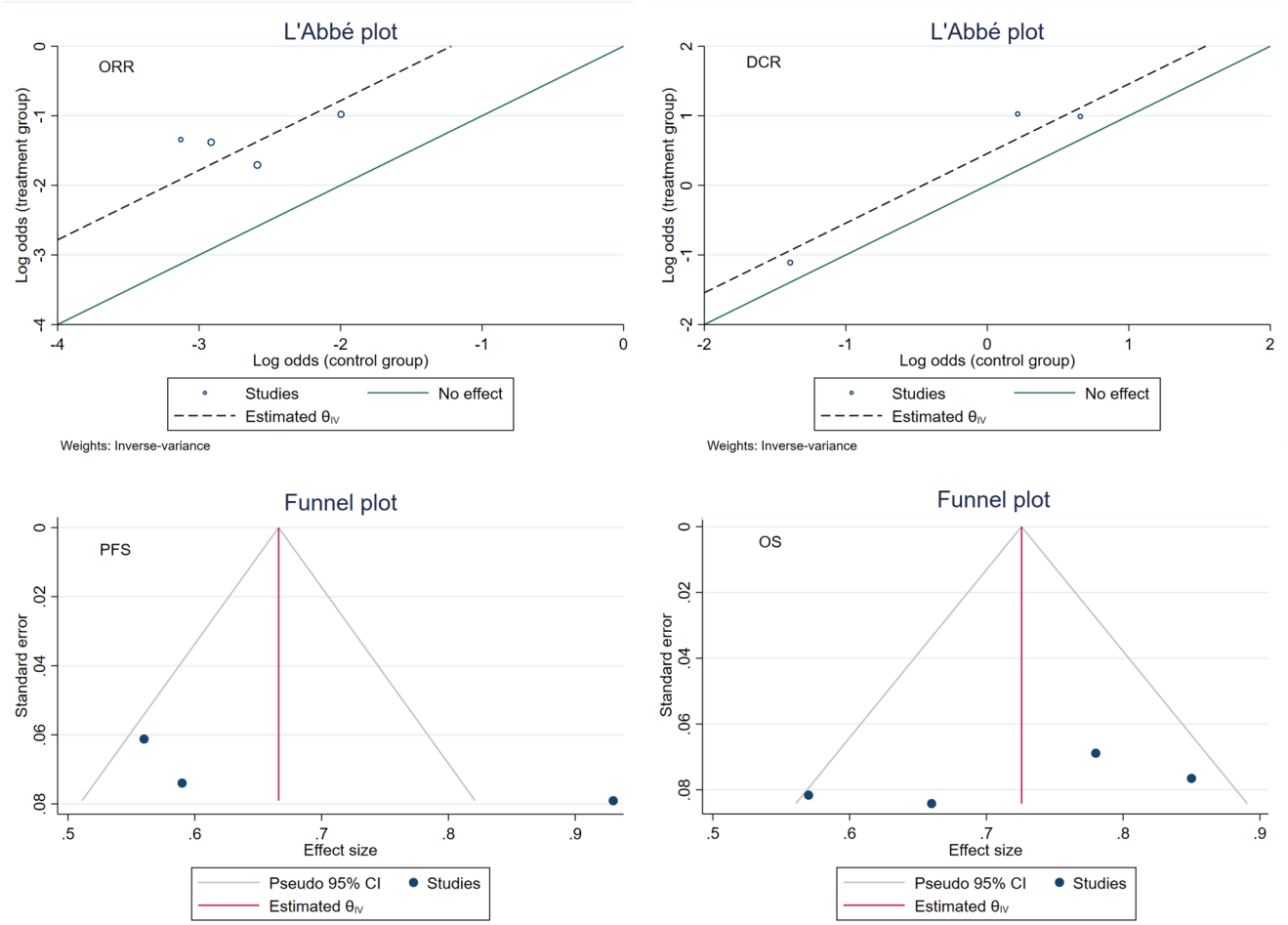

Fig. 8. L'Abbe plots of overall effects of ORR and DCR and funnel plots of overall effects of PFS and DCR for people with advanced HCC undergoing immunotherapy with PD-1/PD-L1 inhibitors.

Table 2
Subgroup analysis of clinical outcomes of first-line treatment and subsequent-line treatment for combination immunotherapy.

Outcome	First-line treatment					Second or subsequent-line treatment			
	No. of studies	Rate (95 %CI)	I^2(%)	p		No. of studies	Rate (95 %CI)	I^2(%)	p
ORR	10	0.30(0.18–0.41)	0.00	0.99		8	0.26(0.14–0.39)	0.00	1.00
DCR	10	0.77(0.68–0.86)	66.49	0.00		8	0.65(0.54–0.77)	58.88	0.02
	No.	Month (95 %CI)				No.	Month (95 %CI)		
PFS	5	6.9(5.5–8.4)	67.43	0.02		5	5.3(4.6–6.1)	0.00	0.61
OS	1	18.7(10.4–26.9)	–		–	3	14.6(11.1–18.1)	0.00	0.39

RCT with 501 patients (IMbrave 150) with advanced HCC showed that atezolizumab plus bevacizumab as a first-line treatment achieved a long-term survival (19.2 months) [9]. More recently, a randomized phase III trial (HIMALAYA), durvalumab plus tremelimumab combination achieved a median survival of 16.4 months [16]. Although OS did not exceed atezolizumab plus bevacizumab, durvalumab plus tremelimumab showed considerable benefit for patients with liver cancer and may be another first-line treatment choice. Additionally, the side effects of toxicity of combined immunotherapy were tolerable according to these results, although we do not yet know which patients will have fatal complications. Since PD-1/PD-L1 inhibitors induce long-term anti-tumour effects in T cells, OS of combination therapy needs to be more emphasized in clinical practice.

In addition to existing combinations such as specific PD-1/PD-L1 inhibitors with anti-angiogenic drug or PD-1/PD-L1 inhibitors with CTLA-4 inhibitor, other combination treatments such as PD-1/PD-L1 inhibitors with other anti-angiogenic or TKI (tyrosine kinase inhibitor), radiotherapy, TACE, ablation, or other immune checkpoint agents will likely be promising treatment options. Anlotinib, a novel multi-target RTK inhibitor, displays substantial anti-tumour effectiveness for VEGF signaling and is mainly used in the treatment of lung cancer and is surprisingly effective against HCC [29]. The efficacy of anti-PD-1/PD-L1 inhibitors with anlotinib as first-line therapy is being evaluated in randomized phase Ib/II trial [30] and randomized phase II trial [31] and preliminary results showed that DCR were 93 % and 95 %, respectively. Anlotinib plus immunotherapy may show therapeutic potential in patients with previous anti-VEGF drug resistance and EGFR mutation-positive patients for intratumoural immune microenvironments with heterogeneous features for HCC. In addition, because of the limited number of clinical trials with available data, the clinical benefit of immunotherapy combined with radiotherapy is not clear. ISABR (Immuno Stereotactic Ablative Body Radiotherapy), which combines immunotherapy and SBRT, has been developed and is currently being tested in several clinical trials for NSCLC and the relationship between

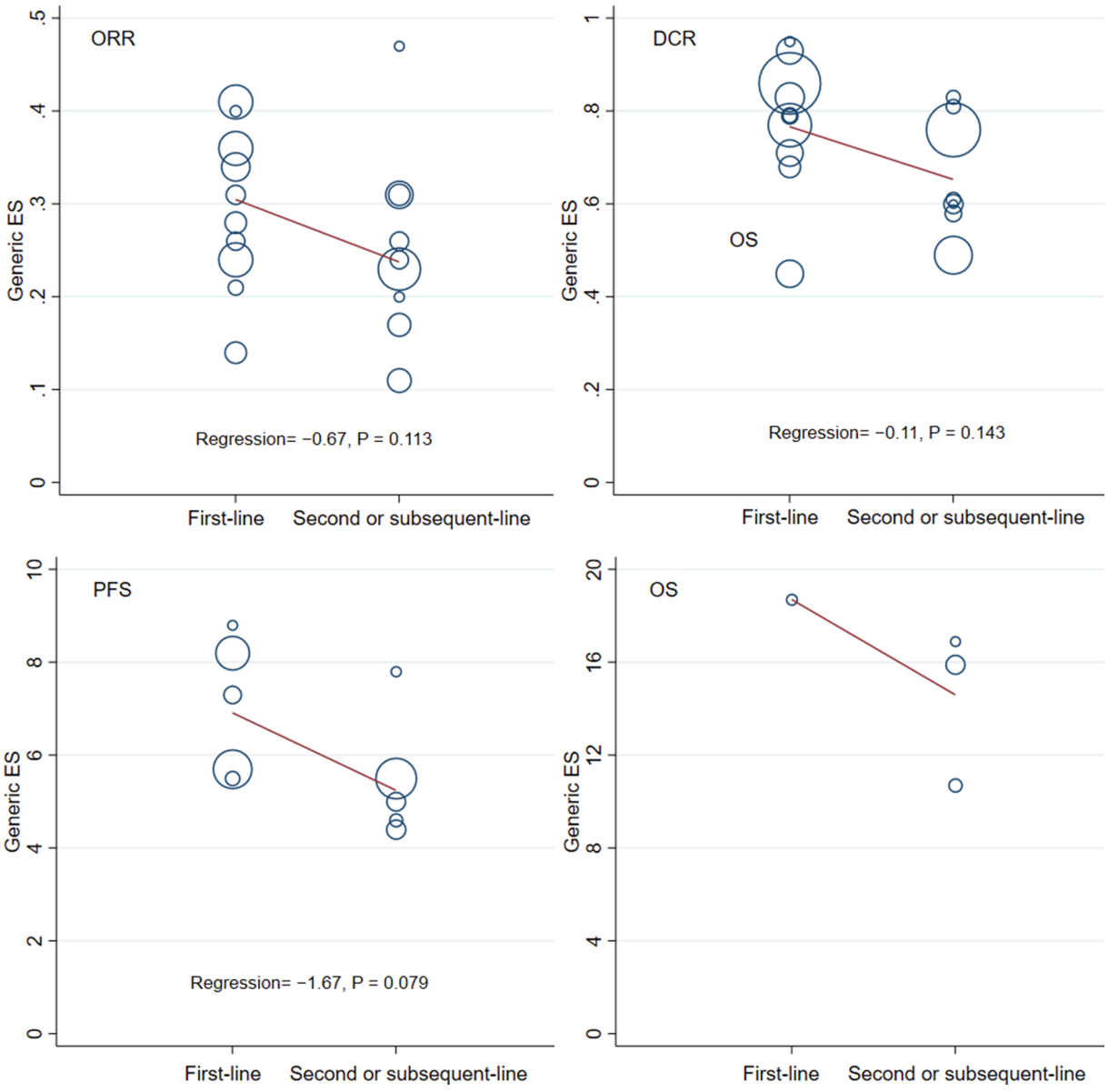

Fig. 9. Random-effects *meta*-regression plots of the association between First-/subsequent-line treatment and clinical outcomes.

Table 3
Subgroup analysis of clinical outcomes of single immune checkpoint inhibitor plus anti-VEGF agents and dual-immune checkpoint inhibitors for combination immunotherapy.

Outcome	Single-ICI + anti-VEGF				Dual-ICIs			
	No. of studies	Rate (95 %CI)	I^2(%)	p	No. of studies	Rate (95 %CI)	I^2(%)	p
ORR	11	0.29(0.17–0.41)	0.00	0.99	3	0.26(0.19–0.34)	0.00	0.87
DCR	11	0.80(0.76–0.84)	8.92	0.36	3	0.48(0.39–0.56)	0.00	0.84
	No.	Month (95 %CI)			No.	Month (95 %CI)		
PFS	7	6.3(5.2–7.4)	70.43	0.00	1	7.8(3.8–11.8)	–	–
OS	–	–	–	–	2	16.6(12.5–20.6)	0.00	0.56

immunotherapy and radiotherapy for HCC has been seldom reported [32]. However, based on effective evidence from basic experiments and some high-quality retrospective studies [33–35], we believe that ISABR, which can rebuild the tumour immune microenvironment, recruit infiltrating T cells, and enhance anti-tumour immunity, has promising application prospects for HCC patients in the era of immunotherapy. In addition, several other studies of transcatheter arterial chemoembolization (TACE) in combination with immunotherapy are underway. TACE has a pivotal role in the treatment of unresectable liver cancer. What role will it play in the era of immunotherapy? Overall, the management for advanced HCC will enter the era of the joint use of immunotherapy and targeted therapy combined with local treatment in the future.

Screening oncogenic driver mutations is emerging as a unique method to identify patients who will benefit from immunotherapy, and to explore predictors for advanced HCC. Our study found that

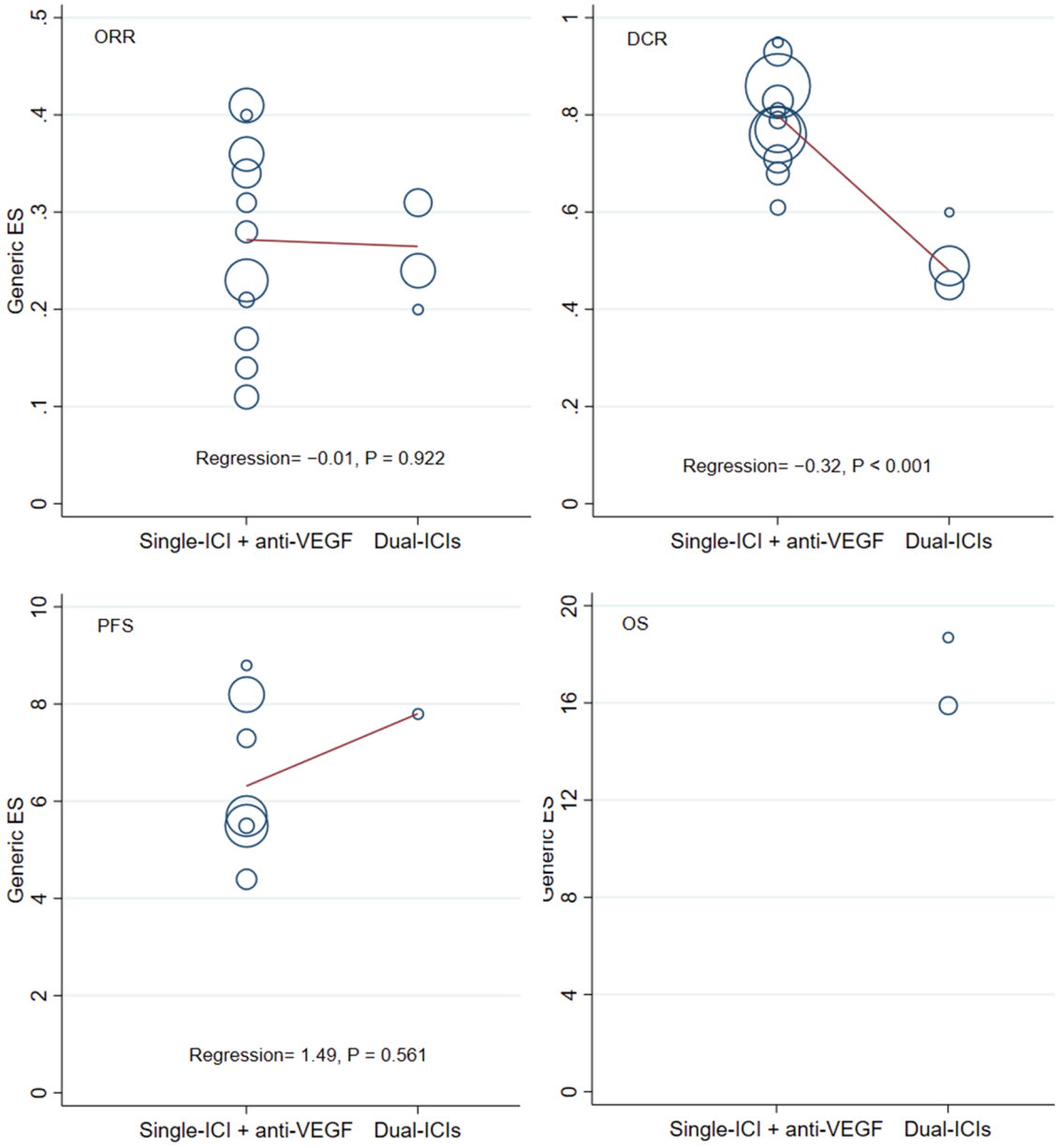

Fig. 10. Random-effects *meta*-regression plots of the association between First-/subsequent-line treatment and clinical outcomes.

Table 4
Subgroup analysis of clinical outcomes of PD1 and PD-L1 inhibitors for combination immunotherapy.

Outcome	PD-1				PD-L1			
	No. of studies	Rate (95 %CI)	I^2(%)	p	No. of studies	Rate (95 %CI)	I^2(%)	p
ORR	14	0.29(0.25–0.33)	2.83	0.42	5	0.22(0.12–0.32)	60.54	0.04
DCR	13	0.76(0.68–0.84)	68.68	0.00	5	0.61(0.49–0.72)	29.47	0.23
	No.	Month (95 %CI)			No.	Month (95 %CI)		
PFS	6	6.2(4.9–7.4)	72.94	0.00	4	5.9(4.4–7.6)	33.19	0.21
OS	1	16.9(7.7–26.1)	–	–	3	14.9(10.9–18.9)	20.82	0.28

hepatocellular carcinoma patients with high TMB had better outcomes in 1-year OS than the moderate TMB group for immunotherapy. However, survival analysis performed by any cut-off value that separated the population into two groups was not statistically significant. This is probably due to a significant proportion of HCC patients with low TMB also responding to the immunotherapy, reflecting the complexity of the

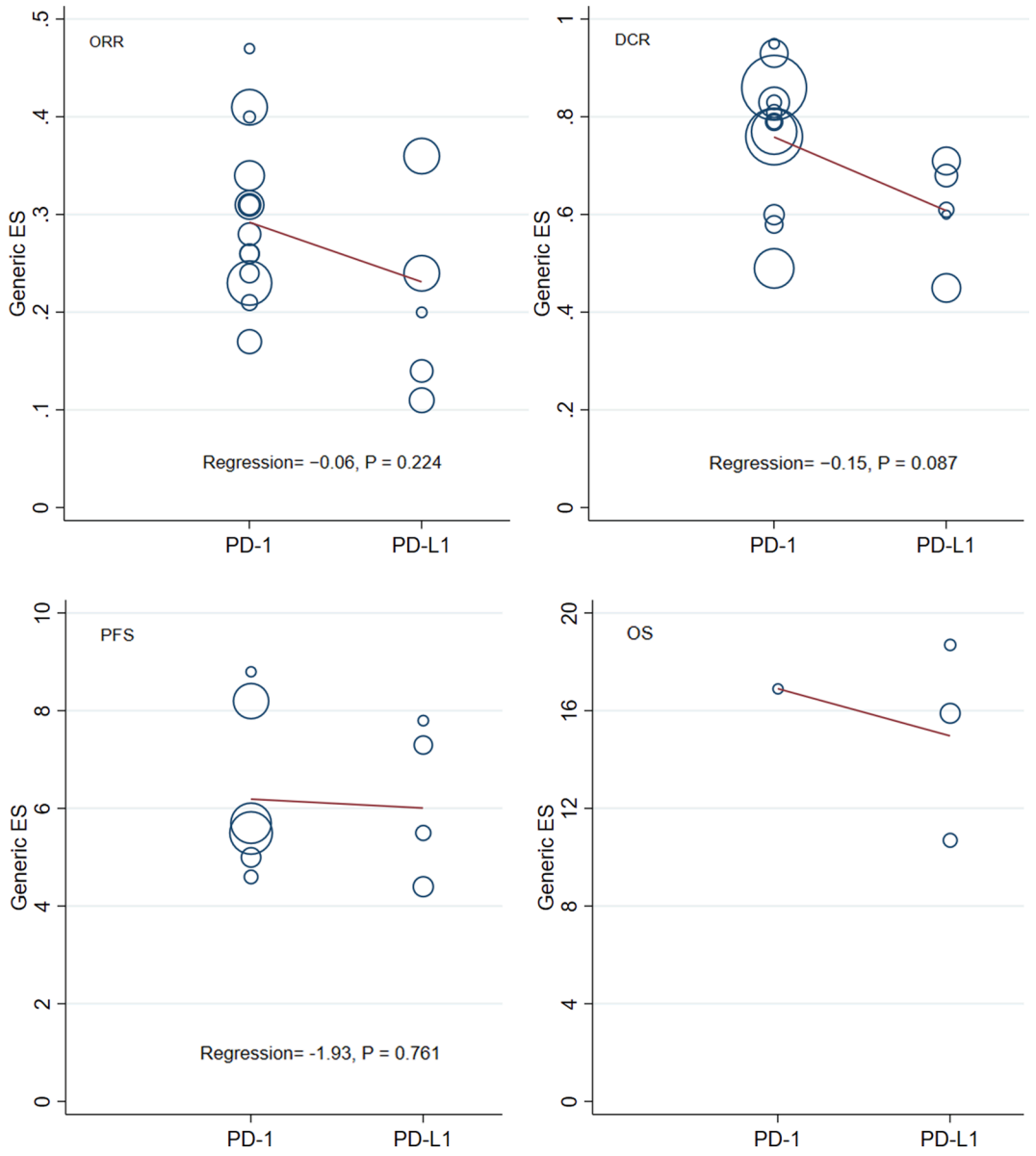

Fig. 11. Random-effects *meta*-regression plots of the association between PD-1/PD-L1 inhibitors combination therapy and clinical outcomes.

Survival rates	TMB–H	TMB–M	TMB–L	Favors TMB–H	Favors TMB–M	P value Two– stage test
PFS						
3 months	0.50 [0.22, 0.79]	0.43 [0.32, 0.53]	0.69 [0.42, 0.87]			0.786
6 months	0.43 [0.16, 0.75]	0.24 [0.16, 0.34]	0.46 [0.23, 0.71]			0.844
9 months	0.43 [0.16, 0.75]	0.15 [0.09, 0.27]	0.15 [0.03, 0.42]			0.922
OS						
12 months	0.63 [0.31, 0.86]	0.30 [0.21, 0.42]	0.71 [0.36, 0.95]			0.025
18 months	0.50 [0.22, 0.79]	0.19 [0.11, 0.30]	0.29 [0.05, 0.64]			0.863
24 months	0.25 [0.05, 0.60]	0.12 [0.06, 0.21]	0.14 [0.01, 0.51]			0.961

Fig. 12. Results of survival rates and comparison of PFS and OS regarding TMB-H versus TMB-M groups.

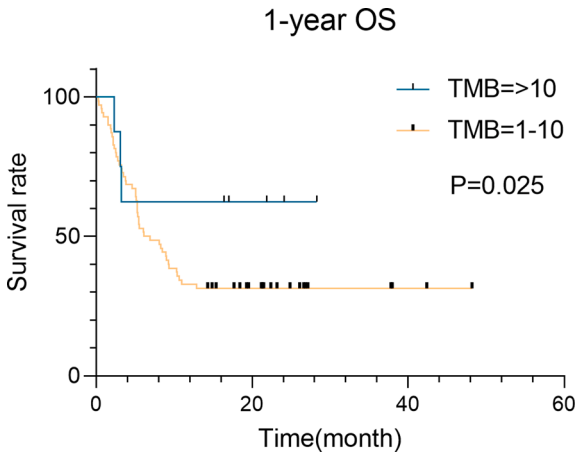

Fig. 13. Kaplan-Meier of 1-year overall survival according to TMB groups.

immune system in the immune microenvironment of hepatocellular carcinoma [36]. Regarding intratumoural immune microenvironments with heterogeneous features in liver cancer, TMB as an independent biomarker is presumably insufficiently predictive [[37–39]. The development of an integrated multi parameter evaluation model is needed to overcome tumour heterogeneity and identify those most likely to benefit from immunotherapy. For instance, Valero [40] found that by combining NLR (neutrophil-to-lymphocyte ratio) with tumour mutational burden (TMB), the probability of benefit from ICIs is significantly higher in the NLR low/TMB high group compared to the NLR high/TMB low group in a retrospective cohort study of 1714 patients. In another retrospective study (NCT01658878), Sangro introduced an inflammatory gene signature consisting of 4 genes which was associated with improved objective response rate and OS for HCC [41]]. In addition, F. Stephen Hodi and his colleagues highlighted the potential predictive value of TMB and suggested that combining TMB and inflammatory signature to evaluate response to immunotherapy in individuals with advanced melanoma [42]. These findings are in line with what we found in our investigation and demonstrated that the combination use of TMB, clinical predictors and gene features reveal more effective predictive value survival and response for people with advanced HCC receiving immune checkpoint inhibitors than TMB or other biomarkers alone. Future more stable and efficient model to overcome tumour heterogeneity from among the available choices will be widely used with the advent of the era of comprehensive sequential immunotherapy.

Our study has some limitations. First, there is a lack of analysis for the safety of immunotherapy. Second, several ongoing studies published with a lack of reporting OS are included. Third, different study designs, PD-1/PD-L1 inhibitors and patient populations were a significant source of heterogeneity. In addition, analysis of TMB was performed with individual data and high-TMB patients are relatively not enough, which would limit the power of our analysis. Despite these constraints, we believe our study provides the most comprehensive and up-to-date analysis of immunotherapy strategies in HCC.

7. Conclusions

Immune checkpoint inhibitors' combination therapy improved clinical outcomes in the management of advanced hepatocellular carcinoma. However, the overall objective response rate still did not exceed 30 %. PD-1/PD-L1 inhibitors plus anti-angiogenic agents and dual immunotherapy provided significantly increased survival over sorafenib, which also pose new challenges for future research, and more appropriate and guided control regimens are required. Also, TMB may be a promising prognostic biomarker for immunotherapy in HCC. However, the validation of prospective and large sample studies is needed.

8. Data Availability

The data used to support the findings of this study are available from the corresponding authors upon request.

9. Funding Statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2022.109244.

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