Journal of Cancer Research and Clinical Oncology (2022) 148:1195–1210
https://doi.org/10.1007/s00432-021-03716-1

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

The efficacy of immune checkpoint inhibitors in advanced hepatocellular carcinoma: a meta-analysis based on 40 cohorts incorporating 3697 individuals

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Received: 28 February 2021 / Accepted: 25 June 2021 / Published online: 23 July 2021

Abstract

Background This study was designed to investigate the efficacy and safety of immune checkpoint inhibitors (ICIs) in advanced hepatocellular carcinoma (HCC).

Methods Electronic databases were scanned to identify relevant trials. The primary endpoints were overall survival (OS), progression-free survival (PFS), and their prognostic factors. Stratified analyses were accomplished on ICIs agent and evaluation criteria.

Results Totally, 3697 individuals from 40 cohorts were recruited. For patients treated with ICIs, the pooled median time to progression (TTP) was 8.0 months, median PFS 4.9 months, and median OS 12.0 months; the pooled median PFS and OS of ICIs plus anti-vascular endothelial growth factor (VEGF) agents (PFS: 6.3 months, OS: 16.4 months) were longer than those of ICIs alone. Furthermore, Child–Pugh stage (HR = 1.37, $P = 0.0123$) and Eastern Cooperative Oncology Group (ECOG) (HR = 1.40, $P = 0.0016$) were prognostic factors for PFS. Hepatitis C virus (HCV) (HR = 0.71, $P = 0.0356$), Alpha-fetoprotein (AFP) (HR = 1.17, $P < 0.0001$), Child–Pugh stage (HR = 1.58, $P < 0.0001$), Barcelona Clinic Liver Cancer (BCLC) stage (HR = 1.23, $P = 0.0005$), ECOG (HR = 1.50, $P = 0.0012$), portal vein invasion (HR = 1.32, $P = 0.0053$), extrahepatic metastasis (HR = 0.84, $P = 0.0047$), best response (HR = 0.58, $P < 0.0001$), and neutrophil-to-lymphocyte ratio (NLR) (HR = 1.23, $P = 0.0451$) were the prognostic factors for OS. According to both RECIST 1.1 and mRECIST, the objective response rate (ORR) and disease control rate (DCR) rate of ICIs plus anti-VEGF agents were better than those of ICIs alone. The overall rate of any grade adverse events (AEs) was 0.76 (95% CI 0.61–0.89), grade 3 or higher AEs was 0.28 (95% CI 0.15–0.42), and the rate of AEs leading to treatment discontinuation was 0.09 (95% CI 0.06–0.12).

Conclusions The ICIs was promising in HCC with good efficacy and tolerated toxicity. Compared with ICIs monotherapy, the joint application of ICIs and anti-VEGF agents can contribute a lot more benefits to the survival of patients according to clinical practices.

Keywords Immune checkpoint inhibitors · Hepatocellular carcinoma · Efficacy · Safety

Introduction

Hepatocellular carcinoma (HCC) is the third most frequent cause of cancer-related death all over the world with the incidence rising rapidly recently (Bray et al. 2018). The prognosis for patients with early stage HCC has been greatly improved with the development of surgical resection and the extensive application of locoregional therapy composed by trans-arterial chemoembolization (TACE), radiofrequency ablation (RFA), and stereotactic body radiation therapy (SBRT) (Tella et al. 2019). However, the clinical outcome of advanced HCC remains frustrating for its insensitivity to chemotherapy and limited efficacy of molecular targeted drug such as sorafenib

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(Gomaa and Waked 2015). Consequently, it is crucial to seek a novel approach against advanced HCC.

Fortunately, in the last decade, immune checkpoint inhibitors (ICIs) have set off a revolutionary wave in several hematological and solid tumors, including Hodgkin lymphoma, melanoma, non-small cell lung cancer (NSCLC), and triple negative breast cancer (TNBC). Accumulating evidences have demonstrated remarkable improvements in survival outcomes with ICIs-based monotherapy or combination therapy in advanced malignancies (Schachter et al. 2017; Pasello et al. 2020; Simmons et al. 2020), which shed some light on advanced HCC.

Notably enough, ICIs have been tested in advanced HCC, where promising findings were observed in phase I and II clinical trials with the programmed cell death protein 1 (PD-1) inhibitors nivolumab and pembrolizumab assessed. Nonetheless, subsequent confirmatory phase III studies on these two agents were negative, failing to report an overall survival (OS) benefit in advanced HCC patients receiving ICIs monotherapy (Rizzo et al. 2021a). At the same time, notable responses were observed in selected HCC (Finn et al. 2020; Lee et al. 2020; Yau et al. 2020), further supporting the exploration of immunotherapy and the identification of potential predictive biomarkers. On the basis of preclinical and early phase clinical studies, ICIs-based combination therapies have been studied in advanced HCC. The combination of PD-L1 inhibitor atezolizumab plus the bevacizumab has been tested in the phase III IMbrave150 clinical trial. Interestingly, after more than a decade from the publication of the landmark SHARP phase III study establishing sorafenib as the reference front-line treatment, atezolizumab plus bevacizumab improved median OS compared to sorafenib (Rizzo et al. 2021b). These recently published results have witnessed a historical step forward, with the IMbrave150 establishing the novel first-line standard. In addition, atezolizumab is also being evaluated in the COSMIC-312 phase III trial testing the association of the PD-L1 inhibitor with cabozantinib, and thus, a bigger role of ICIs is supposed to play in treating patients with advanced HCC in the near future.

To overcome the limitations of individual studies and assess the overall benefit, here, we made a comprehensively survey based on a large sample size (40 cohorts incorporating 3697 individuals) and diverse dimensions (stratified by ICIs agent and evaluation criteria) to evaluate the efficacy and safety of ICIs in advanced HCC.

Materials and methods

Data sources and literature searches

Researches were screened by a systematic electronic literature retrieval for abstracts of relevant studies in the published literature. PubMed, Cochrane Library, and EMBASE were searched and the data were updated as of November 5th, 2020. The basic search terms were used as follows: "immunotherapy", "immune checkpoint inhibitors", "nivolumab", "atezolizumab", "pembrolizumab", "CTLA-4", "PD-1", "PD-L1", "ipilimumab", "programmed cell death ligand 1", "programmed cell death 1", "cytotoxic T lymphocyte-associated protein 4", "ICIs", "Camrelizumab", "Toripalimab", "Sintilimab", "HCC", "liver cancer", and "Hepatocellular carcinoma". Full-text articles were observed if abstracts did not provide enough information. Moreover, the references of related articles were reviewed for additional studies. Reviews, editorials comments, case reports, and letters to the editor were excluded. The retrieve was performed without language restriction.

Selection of studies

Initially, two investigators performed a screening of titles and abstracts, respectively, and then examined the full text of articles to acquire eligible studies. For the repetitive studies based on the same study patients, the latest or most comprehensive data were included.

Inclusion criteria

Inclusion criteria were: (1) prospective or retrospective studies to evaluate the efficacy and safety of ICIs in HCC; (2) patients pathologically or clinically confirmed as HCC; (3) the data [including any of the following outcomes: time to progression (TTP), progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and objective response rate (ORR)] to evaluate the efficacy of ICIs in HCC could be obtained or calculated from the original literature.

Data extraction

Data extraction was conducted conforming to the PRISMA guidance (S1 PRISMA Checklist). Two investigators independently evaluated the quality items and differences, and then collected data from recruited studies. All eligible studies involved information as follows: publication year and region, the first author's name, study type, number of patients, ICIs agent, and outcome measures.

Quality assessment

Quality of the included studies was assessed as reported in the literature, which consists of 20 items (Jonsson et al. 2006). The checklist examines the main domains including study design, population, intervention, outcome measures, statistical analysis, results/conclusions, competing interest, and sources of financial support.

Statistical methods

The primary endpoints were OS and/or PFS. The association between prognostic factors and efficacy of ICIs was measured by HR with the corresponding 95% CI. Stratified analyses were accomplished on ICIs agent. The secondary endpoints were best responses evaluated by RECIST 1.1 and m RECIST 1.1. Funnel plots and Egger's test were performed to evaluate publication bias. Statistical analysis was performed with R 4.0 statistical software. Survival data were obtained based on the Kaplan–Meier curves. Heterogeneity was assessed by *I*-square tests and Chi-square. If $P < 0.1$ or $I^2 > 40\%$, remarkable heterogeneity existed. A random-effect model was adopted to calculate the pooled data when heterogeneity existed, or else, a fixed effect model was employed.

Results

Selection of study

Initially, 8058 relevant articles were scrutinized intensively. Of them, 386 were filtered for duplication, and 7574 were excluded for digression after screening the titles and abstracts. Then, the full text of 98 articles was thoroughly reviewed, and 58 were filtered for reasons as follows: they were not human research, and not solid cancer, repeated study cohort, reviews or meta-analysis, and the data to evaluate the efficacy of ICIs in HCC were unavailable.

Finally, a total of 40 cohorts (detailed supplementary file in Table S1) incorporating 3697 individuals were recruited in this research. The elaborate procedure is displayed in Fig. 1.

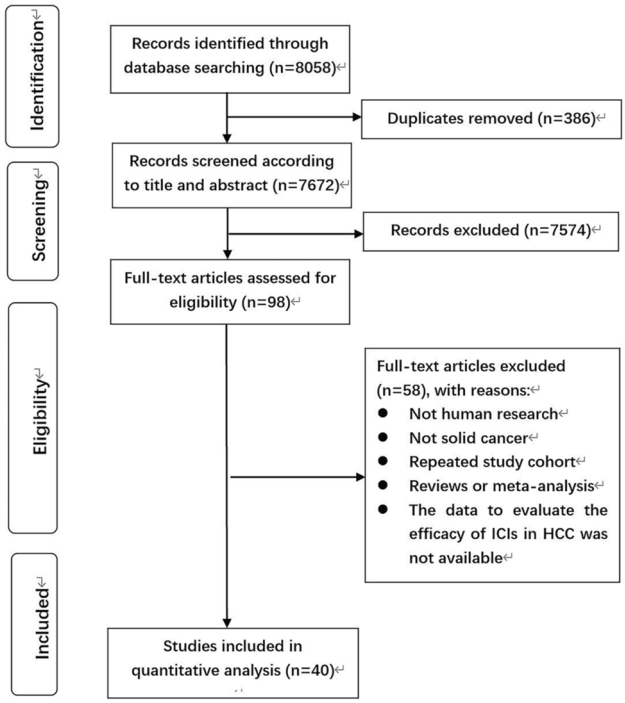

Fig. 1 Flowchart on selection including trials in the meta-analysis

Study characteristics

Totally, 3697 individuals in the 40 cohorts published as of November 5th, 2020 were recruited. The sample size ranged from 11 to 341. Of these studies, 22 were retrospective and 18 prospective. Meanwhile, all of these studies involved ICIs: anti-PD-(L)1 and anti-CTLA-4. HR for PFS and/or OS were used to assess the impact of probable prognostic factors on the efficacy of ICIs. Of all the adopted studies, 34 cohorts contained data for OS and 31 for PFS. The principal traits are presented in Table 1.

Data analyses

Pooled survival outcomes of ICIs in HCC

In this study, for HCC treated with ICIs, the pooled median TTP was 8.0 months (Fig. 2a), median PFS 4.9 months (Fig. 2b), and median OS 12.0 months (Fig. 2c).

Regarding ICIs-based combination therapy, seven different combination drugs were reported in recruited studies: bevacizumab, codrituzumab, apatinib, sorafenib, regorafenib, lenvatinib, and chemotherapy, of which five were anti-VEGF agents, thus constituting ICIs plus anti-VEGF agent subgroup. Stratified analyses were performed according to ICIs agent and combination therapy: the pooled median PFS of PD-(L)1 (4.7 months) was shorter than that of CTLA-4 or ICIs plus anti-VEGF agents (6.3 months) (Fig. 3a); additionally, concerning PD-(L)1, the pooled median PFS of Nivolumab (Nivo) (2.7 months) was shorter than that of Pembrolizumab (Pembro) (5.3 months) or Camrelizumab (5.4 months) (Fig. 3b); the pooled median OS of PD-(L)1 (11.4 months) was shorter than that of ICIs plus anti-VEGF agents (16.4 months) (Fig. 3c); furthermore, with regard to PD-(L)1, the pooled median OS of Nivo (9.4 months) was shorter than that of Pembro (14.7 months) (Fig. 3d). The pooled estimates for rates of PFS and OS are summarized by single-arm analysis in Table S2 and Table S3.

Pooled analyses of prognostic factors for PFS and OS

The pooled analyses of the relationship between PFS and/or OS and probable prognostic factors are summarized in Table 2. Child–Pugh stage (HR = 1.37, 95% CI 1.07–1.74, $P = 0.0123$) and ECOG (HR = 1.40, 95% CI 1.14–1.72, $P = 0.0016$) were the probable prognostic factors for

Table 1 The principal characteristics and further details of eligible articles

Author	Year	Region	Study phase	Trial identifier	ICI agent	Dose	Study type	Number	Male (%)	Combination drug
El-Khoueiry[1]	2017	Global	Phase 1/2	NCT01658878	Nivo	3 mg/kg, q2w	Prospective	214	171 (80)	NA
Fessas[2]	2020	Global	NA	NA	Nivo	3 mg/kg, q2w	Prospective	233	184 (79)	NA
Yau[3]	2020	Global	Phase 1/2	NCT01658878	Nivo	1 mg/kg, q3w (4 doses), followed by 240 mg q2w	Prospective	50	43 (86)	IPI
			Phase 1/2			3 mg/kg, q3w (4 doses), followed by 240 mg q2w		49	37 (76)	IPI
			Phase 1/2			3 mg/kg, q2w		49	40 (82)	IPI
Yu[4]	2019	Asia	NA	NA	Nivo	3 mg/kg, q2w	Retrospective	54	46 (85)	RT
			NA					22	19 (86)	NA
Finkelmeier[5]	2019	Europe	NA	NA	Nivo	NA	Retrospective	34	26 (76)	NA
Kambhampati[6]	2019	USA	NA	NA	Nivo	3 mg/kg, q2w	Retrospective	18	13 (72)	NA
Lee[7]	2020	Asia	NA	NA	Nivo	3 mg/kg, q2w	Retrospective	48	39 (81)	NA
Feng[8]	2017	Asia	NA	NA	Nivo	3 mg/kg, q2w	Retrospective	11	8 (73)	Sorafenib
Kim[9]	2020	Asia	NA	NA	Nivo	NA	Retrospective	189	159 (84)	NA
Choi[10]	2020	Asia	NA	NA	Nivo	3 mg/kg, q2w	Retrospective	150	125 (83)	NA
Dharmapuri[11]	2020	Global	NA	NA	Nivo	NA	Retrospective	103	86 (83)	NA
Marinelli[12]	2020	USA	NA	NA	Nivo	240 mg, q2w	Retrospective	12	26 (90)	Locoregional
			NA			240 mg, q2w		17		NA
Chen[13]	2020	Asia	NA	NA	Nivo	3 mg/kg, q3w	Retrospective	22	19 (86)	TKI/chemotherapy
Sung[14]	2020	Asia	NA	NA	Nivo	3 mg/kg, q2w	Retrospective	33	25 (76)	NA
Smith[15]	2020	USA	NA	NA	Nivo	NA	Retrospective	35	29 (83)	RT
Finn[16]	2019	Global	Phase 3	NCT02702401	Pembro	200 mg, q3w	Prospective	278	226 (81)	NA
Feun[17]	2019	USA	Phase 2	NCT02658019	Pembro	200 mg, q3w	Prospective	29	25 (86)	NA
Zhu[18]	2018	Global	Phase 2	NCT02702414	Pembro	200 mg, q3w	Prospective	104	86 (83)	NA
Finn[19]	2020	Global	Phase 1b	NCT03006926	Pembro	200 mg, q3w	Prospective	100	81 (81)	Lenvatinib
Kuo[20]	2020	Asia	NA	NA	Nivo/Pembro	3 mg/kg, q2w/ 200 mg, q3w	Retrospective	42	33 (79)	TKI
Lee[21]	2020	Asia	NA	NA	Nivo/Pembro	NA	Retrospective	95	73 (77)	NA
Saeed[22]	2020	USA	NA	NA	Nivo/Pembro	NA	Retrospective	41	30 (73)	NA
Mahn[23]	2020	Europe	NA	NA	Nivo/Pembro	NA	Retrospective	14	10 (71)	NA
Xu[24]	2019	Asia	Phase 1	NCT02942329	Camrelizumab	200 mg, q2w	Prospective	18	17 (94)	Apatinib
Qin[25]	2020	Asia	Phase 2	NCT02989922	Camrelizumab	3 mg/kg, q2w or q3w	Prospective	217	196 (90)	NA
Yen[26]	2017	NA	Phase 1	NCT02407990	Tislelizumab	5 mg/kg, q3w	Prospective	11	NA	NA
Cui[27]	2020	Asia	NA	NA	PD-1	NA	Retrospective	55	46 (84)	NA
He[28]	2018	USA	Phase 1	NCT02383212	Cemiplimab	3 mg/kg, q2w	Prospective	26	25 (96)	NA
Finn[29]	2020	Global	Phase 3	NCT03434379	Atezo	1200 mg, q3w	Prospective	336	277 (82)	Bev
Lee[30]	2020	Global	Phase 1b	NCT02715531	Atezo	1200 mg, q3w	Prospective	104	84 (81)	Bev
			Phase 1b			1200 mg, q3w		60	54 (90)	Bev
			Phase 1b			1200 mg, q3w		59	49 (83)	NA
Cheng[31]	2018	Asia	Phase 1	NA	Atezo	NA	Prospective	20	16 (80)	Codrituzumab

Table 1 (continued)

Author	Year	Region	Study phase	Trial identifier	ICI agent	Dose	Study type	Number	Male (%)	Combination drug
Bang[32]	2020	Global	Phase 1a/b	NCT02572687	Durvalumab	1125 mg, q3w or 750 mg, q2w	Prospective	28	24 (86)	NA
Duffy[33]	2017	USA	NA	NCT01853618	Tremelimumab	3.5 or 10 mg/kg, q4w	Prospective	32	28 (88)	NA
Sangro[34]	2013	Europe	Phase 2	NCT01008358	Tremelimumab	15 mg/kg q3m	Prospective	21	15 (71)	NA
Pinato[35]	2020	Global	NA	NA	ICIs	NA	Prospective	341	262 (77)	NA
Zhan[36]	2019	USA	NA	NA	ICIs	Nivo: 3 mg/kg, q2w; IPI: 1 mg/kg, q6w	Retrospective	26	18 (69)	Radioembolization
Shao[37]	2019	Asia	NA	NA	ICIs	NA	Retrospective	43	35 (81)	NA
Ng[38]	2020	Asia	NA	NA	ICIs	NA	Retrospective	114	101 (89)	NA
Chen[39]	2020	Asia	NA	NA	Toripalimab	3 mg/kg or 240 mg, q2w	Retrospective	26	25 (96)	NA
			NA		Camrelizumab	200 mg, q2-3w		33	28 (85)	NA
			NA		Sintilimab	200 mg, q3w		16	15 (94)	NA
Scheiner[40]	2019	Europe	NA	NA	Nivo	1-3 mg/kg, q2w	Retrospective	34	24 (71)	NA
			NA		Pembro	200 mg, q3w		31	25 (81)	NA

Author	Child–Pugh (%)			BCLC (%)				ALBI grade (%)			Median age	HBV	HCV	NAFLD	Alcoholic
	A	B	C	A	B	C	D	1	2	3					
El-Khoueiry[1]	210 (98)	4 (2)	0 (0)	NA	NA	NA	NA	NA	NA	NA	64 (56–70)	51	50	NA	NA
Fessas[2]	158 (68)	75 (32)	0 (0)	4 (2)	23 (10)	204 (88)	2 (1)	NA	NA	NA	64 (56–69)	83	95	24	29
Yau[3]	50 (100)	0 (0)	0 (0)	2 (4)	4 (8)	43 (86)	0 (0)	NA	NA	NA	61 (54–67)	28	7	NA	NA
	47 (96)	NA	NA	0 (0)	4 (8)	45 (92)	0 (0)	NA	NA	NA	65 (56–67)	21	14	NA	NA
	47 (96)	NA	NA	0 (0)	3 (6)	46 (94)	0 (0)	NA	NA	NA	58 (47–65)	26	12	NA	NA
Yu[4]	45 (83)	NA	NA	0 (0)	1 (2)	50 (93)	3 (6)	NA	NA	NA	62 (37–81)	43	4	NA	2
	14 (64)	NA	NA	0 (0)	3 (14)	19 (86)	0 (0)	NA	NA	NA	64 (40–82)	13	2	NA	4
Finkelmeier[5]	19 (56)	14 (41)	1 (3)	4 (12)	13 (38)	17 (50)	0 (0)	1 (3)	14 (41)	19 (56)	65 (40–77)	2	10	7	7
Kambhampati[6]	0 (0)	18 (100)	0 (0)	0 (0)	4 (22)	14 (78)	0 (0)	0 (0)	8 (44)	10 (56)	66.5 (26–86)	6	5	3	2
Lee[7]	39 (81)	9 (19)	0 (0)	0 (0)	1 (2)	47 (98)	0 (0)	NA	NA	NA	61 (54–67)	38	NA	NA	NA
Feng[8]	NA	NA	NA	0 (0)	4 (36)	7 (64)	0 (0)	NA	NA	NA	54.8 (42–70)	11	NA	NA	NA
Kim[9]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	139	NA	NA	NA
Choi[10]	94 (63)	56 (37)	0 (0)	0 (0)	6 (4)	144 (96)	0 (0)	NA	NA	NA	56.9	125	4	NA	NA
Dharmapuri[11]	64 (62)	32 (31)	7 (7)	0 (0)	20 (19)	83 (81)	0 (0)	NA	NA	NA	66 (29–89)	33	50	10	8
Marinelli[12]	22 (76)	5 (17)	2 (7)	0 (0)	12 (100)	0 (0)	0 (0)	8 (28)	18 (62)	3 (10)	58.7 (28–72)	10	9	NA	3
				0 (0)	0 (0)	17 (100)	0 (0)								
Chen[13]	13 (59)	9 (41)	0 (0)	NA	NA	NA	NA	NA	NA	NA	53 (36–71)	22	NA	NA	NA
Sung[14]	26 (79)	7 (21)	0 (0)	0 (0)	4 (12)	49 (148)	0 (0)	15 (45)	18 (55)	0 (0)	57 (37–79)	29	1	NA	NA
Smith[15]	NA	NA	NA	NA	NA	32 (91)	0 (0)	NA	NA	NA	NA	NA	NA	NA	NA
Finn[16]	277 (100)	1 (0)	0 (0)	0 (0)	56 (20)	222 (80)	0 (0)	NA	NA	NA	67 (18–91)	72	43	NA	NA
Feun[17]	28 (97)	1 (3)	0 (0)	NA	NA	NA	NA	NA	NA	NA	67 (28–89)	5	9	NA	NA

Table 1 (continued)

Author	Child–Pugh (%)			BCLC (%)				ALBI grade (%)			Median age	HBV	HCV	NAFLD	Alcoholic
	A	B	C	A	B	C	D	1	2	3					
Zhu[18]	98 (94)	6 (6)	0 (0)	0 (0)	25 (24)	79 (76)	0 (0)	NA	NA	NA	68 (62–73)	22	26	NA	NA
Finn[19]	71 (71)	27 (27)	2 (2)	0 (0)	29 (29)	71 (71)	0 (0)	NA	NA	NA	66.5 (47–86)	19	36	NA	28
Kuo[20]	31 (74)	10 (24)	1 (2)	0 (0)	0 (0)	42 (100)	0 (0)	NA	NA	NA	58 (51–65)	29	6	NA	2
Lee[21]	69 (73)	23 (24)	3 (3)	0 (0)	20 (21)	75 (79)	0 (0)	27 (28)	58 (61)	10 (11)	65.5 (57.2–72.9)	62	21	NA	NA
Saeed[22]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	62.3	22	3	NA	9
Mahn[23]	9 (64)	4 (29)	1 (7)	0 (0)	3 (21)	11 (79)	0 (0)	2 (14)	6 (43)	6 (43)	62.5 (47–76)	2	4	6	3
Xu[24]	13 (72)	5 (28)	0 (0)	0 (0)	1 (6)	17 (94)	0 (0)	NA	NA	NA	49 (29–64)	18	0	NA	0
Qin[25]	2 (1)	13 (6)	4 (2)	0 (0)	11 (5)	206 (95)	0 (0)	NA	NA	NA	49 (41–59)	181	NA	NA	NA
Yen[26]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cui[27]	35 (64)	18 (33)	2 (4)	NA	NA	NA	NA	NA	NA	NA	56	43	2	NA	NA
He[28]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	65 (40–78)	NA	NA	NA	NA
Finn[29]	333 (99)	NA	NA	8 (2)	52 (15)	276 (82)	0 (0)	NA	NA	NA	64 (56–71)	164	72	NA	NA
Lee[30]	98 (94)	6 (6)	0 (0)	NA	NA	NA	NA	0 (0)	10 (10)	94 (90)	62 (23–82)	51	31	NA	NA
	60 (100)	0	0 (0)	NA	NA	NA	NA	0 (0)	6 (10)	54 (90)	60 (22–82)	34	11	NA	NA
	59 (100)	0	0 (0)	NA	NA	NA	NA	2 (3)	4 (7)	53 (90)	63 (23–85)	32	10	NA	NA
Cheng[31]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	58	11	4	NA	NA
Bang[32]	NA	NA	NA	0 (0)	6 (21)	22 (79)	0 (0)	NA	NA	NA	63 (27–87)	4	10	NA	8
Duffy[33]	19 (59)	3 (9)	10 (31)	0 (0)	7 (22)	21 (66)	0 (0)	NA	NA	NA	61 (36–76)	5	19	NA	NA
Sangro[34]	12 (57)	9 (43)	0 (0)	3 (14)	6 (29)	12 (57)	0 (0)	NA	NA	NA	65.2 (48–79)	0	21	NA	0
Pinato[35]	250 (73)	81 (24)	9 (3)	5 (1)	72 (21)	254 (74)	10 (3)	104 (30)	187 (55)	39 (11)	64 (15–89)	95	135	34	57
Zhan[36]	20 (77)	6 (23)	0 (0)	0 (0)	5 (19)	21 (81)	0 (0)	6 (23)	20 (77)	0 (0)	66	8	10	4	1
Shao[37]	43 (100)	0	0 (0)	0 (0)	3 (7)	40 (93)	0 (0)	29 (67)	14 (33)	0 (0)	54	29	8	NA	NA
Ng[38]	93 (82)	21 (18)	0 (0)	0 (0)	6 (5)	107 (94)	1 (1)	25 (22)	79 (69)	9 (8)	66 (23–85)	62	13	16	13
Chen[39]	18 (69)	8 (31)	0 (0)	0 (0)	4 (15)	22 (85)	0 (0)	NA	NA	NA	42.5	NA	NA	NA	NA
	26 (79)	7 (21)	0 (0)	0 (0)	7 (21)	26 (79)	0 (0)	NA	NA	NA	56.6	NA	NA	NA	NA
	14 (88)	2 (13)	0 (0)	0 (0)	3 (19)	13 (81)	0 (0)	NA	NA	NA	45.9	NA	NA	NA	NA
Scheiner[40]	17 (50)	14 (41)	3 (9)	0 (0)	2 (6)	28 (82)	4 (12)	NA	NA	NA	64	5	8	8	5
	15 (48)	14 (45)	2 (6)	0 (0)	6 (19)	23 (74)	2 (6)	NA	NA	NA	66.5	3	2	3	14

References	Macro-vascular invasion	Extra-hepatic disease	ECOG		AFP	Previous systematic treatment	Treatment lines of ICIs	Median follow-up (month)
			0	1				
El-Khoueiry[1]	63	144	NA	77 (36)	≥400: 79	Sorafenib (145)	1, 2	NA
Fessas[2]	59	66	44 (19)	99 (42)	>400: 132	NA	1, 2, 3, 4	8 (3.8–15)

Table 1 (continued)

References	Macro-vascular invasion	Extra-hepatic disease	ECOG		AFP	Previous systematic treatment	Treatment lines of ICIs	Median follow-up (month)
			0	1				
Yau[3]	18	40	NA	NA	≥400: 25	sorafenib	1 to ≥3	30.7
	13	40	NA	NA	≥400: 18	Sorafenib	1 to ≥3	30.7
	19	42	NA	NA	≥400: 22	Sorafenib	1 to ≥3	30.7
Yu[4]	15	45	4 (7)	48 (89)	272 (1.3–193,801)	Sorafenib (53)	1, 2	5.7
	7	14	2 (9)	19 (86)	871 (1.3–200,000)	Sorafenib (17)	1, 2	5.7
Finkelmeier[5]	19	19	7 (21)	24 (71)	NA	Sorafenib (25)	1, 2	NA
Kambhampati[6]	9	14	NA	NA	≥400: 13	Sorafenib (13)	1–7	NA
Lee[7]	24	41	NA	NA	760 (18.4–4665)	Sorafenib	2	5
Feng[8]	NA	NA	9 (82)	2 (18)	>20: 5	NA	NA	NA
Kim[9]	72	NA	NA	NA	NA	Sorafenib (113)	1, 2, 3, 4, 5	NA
Choi[10]	65	136	80 (53)	66 (44)	NA	Sorafenib	2	NA
Dharmapuri[11]	NA	NA	NA	NA	NA	Sorafenib (28)	1, 2	17
Marinelli[12]	9	NA	23 (79)	6 (21)	>400: 10	NA	NA	11.5 (1.8–35.1)
Chen[13]	NA	NA	NA	NA	≥40: 12	NA	NA	8.8(1–25)
Sung[14]	10	26	NA	NA	≥1000: 16	Sorafenib (31); lenvatinib (2); Regorafenib (13)	NA	12.5
Smith[15]	16	25	NA	NA	NA	NA	NA	12.9
Finn[16]	36	195	162 (58)	116 (42)	≥200: 129	Sorafenib	2	13.8
Feun[17]	9	21	15 (52)	14 (48)	>400: 9	Sorafenib (10)	1, 2	17
Zhu[18]	18	67	63 (61)	41 (39)	>200: 43	Sorafenib	2	12.3
Finn[19]	20	52	62 (62)	38 (38)	≥400: 30	NA	1	10.6
Kuo[20]	24	26	28 (67)	11 (26)	≥400: 16	Sorafenib (30)	1, 2, 3	4.6
Lee[21]	51	48	NA	NA	≥400: 53	Sorafenib (56)	1, 2	5.2
Saeed[22]	NA	12	NA	NA	NA	Sorafenib/lenvatinib	2	NA
Mahn[23]	8	10	0 (0)	10 (71)	NA	Sorafenib/regorafenib	2, 3	6.6
Xu[24]	6	16	10 (56)	8 (44)	NA	Sorafenib (15)	1, 2	7.9
Qin[25]	27	177	46 (21)	171 (79)	≥400: 111	NA	1 to ≥3	12.5 (0.7–23.5)
Yen[26]	NA	NA	NA	NA	NA	NA	NA	4.1 (0.7–13.6)
Cui[27]	22	34	37 (67)	16 (29)	>400: 18	Sorafenib (14)		13
HE[28]	NA	NA	6 (23)	19 (73)	NA	Sorafenib (24)	1, 2	7.2 (1.8–15.5)
Finn[29]	129	212	209 (62)	127 (38)	≥400: 126	NA	1	8.9
Lee[30]	55	74	52 (50)	52 (50)	≥400: 37	NA	1	12.4
	20	40	27 (45)	33 (55)	≥400: 18	NA	1	6.6
	25	39	25 (42)	34 (58)	≥400: 19	NA	1	6.7

Table 1 (continued)

References	Macro-vascular invasion	Extra-hepatic disease	ECOG		AFP	Previous systematic treatment	Treatment lines of ICIs	Median follow-up (month)
			0	1				
Cheng[31]	NA	NA	15 (75)	5 (25)	NA	NA	2	NA
Bang[32]	NA	NA	9 (32)	19 (68)	≥400: 15	NA	2, 3	20
Duffy[33]	NA	14	8 (25)	24 (75)	NA	Sorafenib (21)	1, 2	18.8
Sangro[34]	6	2	15 (71)	6 (29)	≥400:6	Sorafenib (5)	1, 2	NA
Pinato[35]	NA	175	NA	NA	NA	Sorafenib (207)	1 to ≥2	11(1–34)
Zhan[36]	15	6	NA	NA	NA	Sorafenib (4)	1, 2	7.8 (5.6–11.8)
Shao[37]	17	38	NA	NA	>400: 23	NA	1, 2, 3	NA
Ng[38]	58	86	70 (61)	40 (35)	≥400: 53	Sorafenib (33)	1 to ≥2	13.8
Chen[39]	18	11	1 (4)	17 (65)	≥400: 16	Sorafenib (5), apatinib (5), lenvatinib (15)	1 to ≥3	31.3
	22	11	3 (9)	23 (70)	≥400: 11	Sorafenib (2), apatinib (10), lenvatinib (11)	1 to ≥3	15.1
	10	9	0 (0)	11 (69)	≥400: 5	Sorafenib (8), apatinib (2), Lenvatinib (2)	1 to ≥3	23.3
Scheiner[40]	13	21	16 (47)	NA	≥400: 13	Sorafenib (28), regorafenib (10)	1, 2, 3, 4	NA
	11	14	16 (52)	NA	≥400: 15	Sorafenib (28), regorafenib (15)	1, 2, 3, 4	NA

The details of superscript numbers in the top right corner of authors can be found in the Table S1

ICIs immune checkpoint inhibitors, *BCLC* Barcelona Clinic Liver Cancer, *ALBI* Albumin-Bilirubin, *Atezo* Atezolizumab, *Bev* bevacizumab, *NA* not available, *Pembro* Pembrolizumab, *Nivo* Nivolumab, *RT* radiotherapy, *PD-1* Programmed cell death 1, *TKI* Tyrosine kinase inhibitors, *IPI* Ipilimumab, *HBV* Hepatitis B Virus, *HCV* Hepatitis C Virus, *NAFLD* nonalcoholic fatty liver disease, *ECOG* Eastern Cooperative Oncology Group

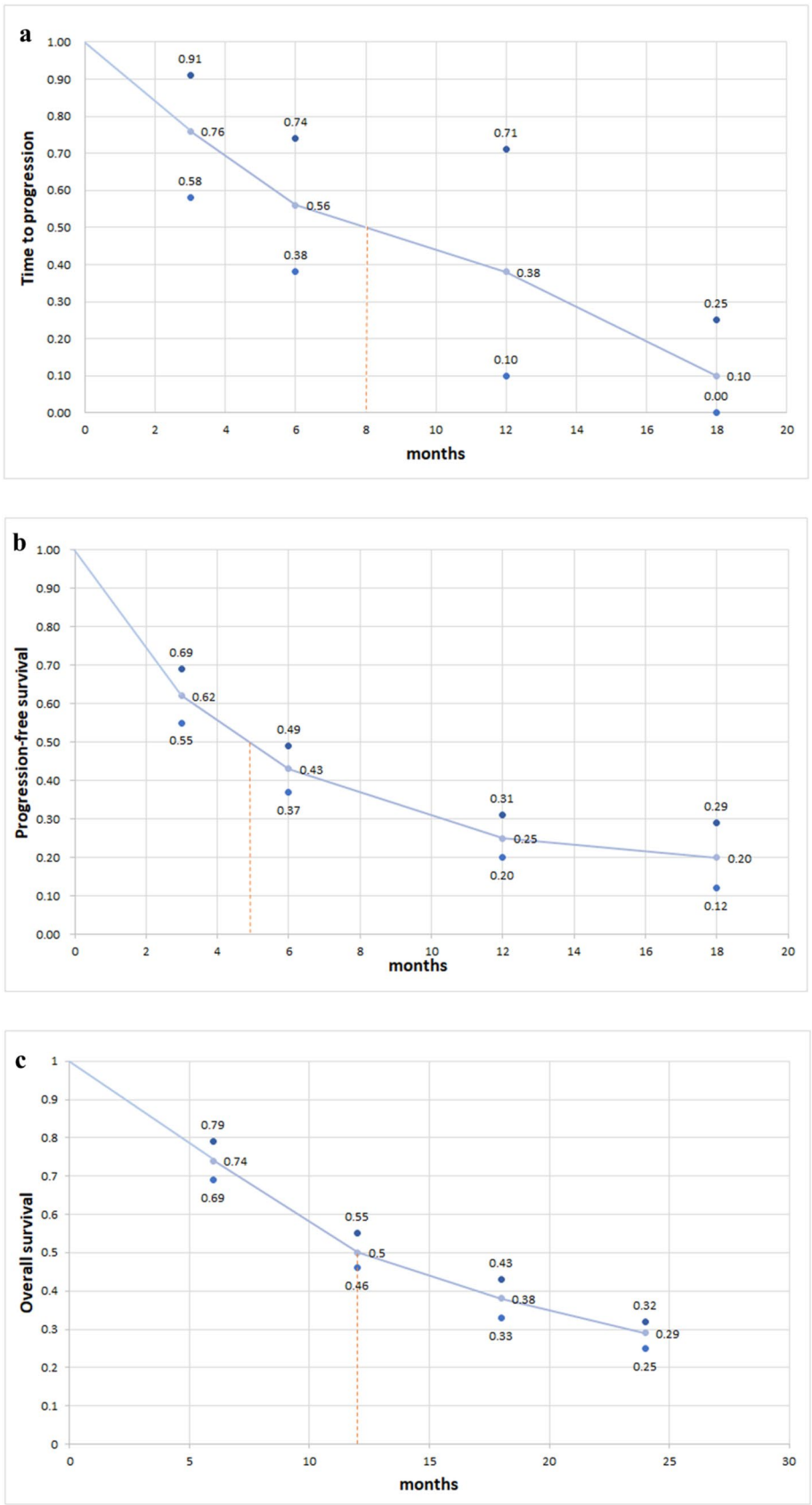

Fig. 2 The efficacy of immune checkpoint inhibitors (ICIs) in advanced hepatocellular carcinoma (HCC). **a** Pooled time to progression (TTP); **b** pooled progression-free survival (PFS); **c** pooled overall survival (OS)

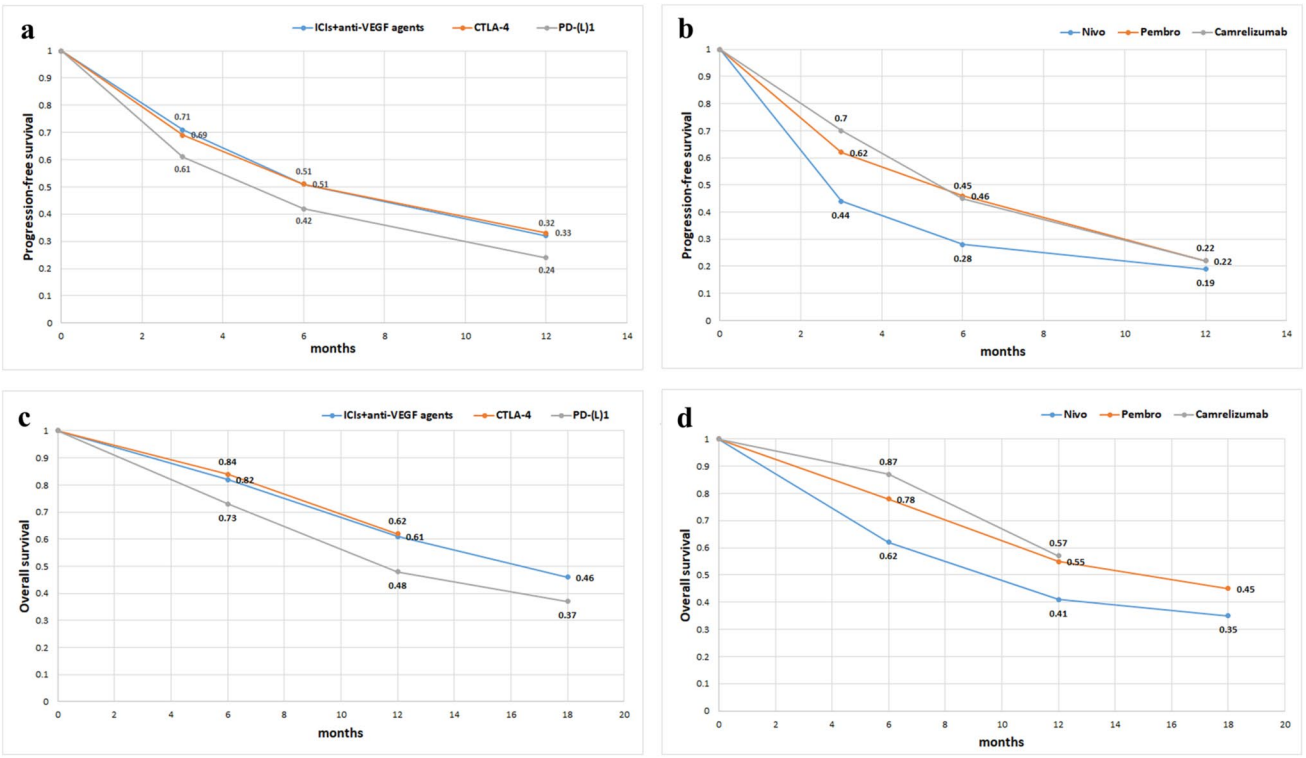

Fig. 3 Subgroup analyses for PFS and OS. **a** Pooled PFS of ICIs plus anti-vascular endothelial growth factor (VEGF) agents, cytotoxic T lymphocyte-associated protein 4 (CTLA-4), and Programmed cell death ligand 1 (PD-(L)1); **b** pooled PFS of Nivolumab (Nivo), Pembrolizumab (Pembro), and Camrelizumab; **c** pooled OS of ICIs plus anti-VEGF agents, CTLA-4, and PD-(L)1; **d** pooled OS of Nivo, Pembro, and Camrelizumab

PFS (Fig. S1). With regard to OS, the following prognostic factors possessed significance: HCV (HR = 0.71, 95% CI 0.52–0.98, $P = 0.0356$), AFP (HR = 1.17, 95% CI 1.10–1.25, $P < 0.0001$), Child–Pugh stage (HR = 1.58, 95% CI 1.33–1.87, $P < 0.0001$), BCLC stage (HR = 1.23, 95% CI 1.09–1.38, $P = 0.0005$), ECOG (HR = 1.50, 95% CI 1.17–1.93, $P = 0.0012$), portal vein invasion (HR = 1.32, 95% CI 1.09–1.60, $P = 0.0053$), extrahepatic metastasis (HR = 0.84, 95% CI 0.74–0.95, $P = 0.0047$), best response (HR = 0.58, 95% CI 0.52–0.64, $P < 0.0001$), and NLR (HR = 1.23, 95% CI 1.00–1.50, $P = 0.0451$) (Fig. S2).

Analyses of best response stratified by ICIs agent and evaluation criteria

Subgroup analyses were implemented according to different RECIST criteria (RECIST vs. mRECIST) and ICIs agent (ICIs vs. CTLA-4 vs. PD-(L)1), which are summarized in Table 3. With regard to ICIs alone, the ORR and DCR were 0.23 (95% CI 0.20–0.27) and 0.62 (95% CI 0.57–0.66) according to RECIST 1.1, 0.23 (95% CI 0.17–0.29) and 0.59 (95% CI 0.49–0.69) judged by mRECIST 1.1; concerning ICIs plus anti-VEGF agents, the ORR and DCR of were 0.29 (95% CI 0.22–0.37) and 0.72 (95% CI 0.61–0.82) according to RECIST 1.1, and 0.33 (95% CI 0.25–0.41) and 0.69 (95% CI 0.57–0.81) judged by mRECIST 1.1. Furthermore, the ORR and DCR of CTLA-4/PD-(L)1 plus anti-VEGF agents were also better than those of CTLA-4/PD-(L)1 alone.

Adverse events (AEs) of ICIs in HCC

The overall rate of any grade AEs was 0.76 (95% CI 0.61–0.89) (Fig. 4a), grade 3 or higher AEs was 0.28 (95% CI 0.15–0.42) (Fig. 4b), and AEs leading to treatment discontinuation was 0.09 (95% CI 0.06–0.12) (Fig. 4c). Stratified analyses of AEs were performed according to ICIs agent: the rate of any grade AEs was 0.73 (95% CI 0.43–0.95) (Fig. 4d) in Nivo and 0.74 (95% CI 0.42–0.96) (Fig. 4g) in Pembro; the rate of grade 3 or higher AEs was 0.24 (95% CI 0.03–0.56) (Fig. 4e) in Nivo and 0.39 (95% CI 0.19–0.60) (Fig. 4h) in Pembro; the rate of AEs leading to treatment discontinuation was 0.08 (95% CI 0.02–0.16) (Fig. 4f) in Nivo, 0.11 (95% CI 0.05–0.19) (Fig. 4i) in Pembro, and 0.07 (95% CI 0.05–0.10) (Fig. 4j) in Atezolizumab (Atezo).

Table 2 Pooled analyses of probable prognostic factors for PFS and OS

Factors	PFS				OS			
	No. of studies	HR (95% CI)	*P*	I^2	No. of studies	HR (95% CI)	*P*	I^2 (%)
Age (old vs. young)	5	0.99 (0.98–1.00)	0.0549	39%	9	0.98 (0.94–1.02)	0.3861	58
Gender (male vs. female)	5	1.08 (0.93–1.25)	0.3033	0%	9	1.07 (0.92–1.23)	0.3872	3
HBV (positive vs. negative)	4	1.07 (0.77–1.49)	0.6856	70%	6	1.13 (0.89–1.44)	0.3207	59
HCV (positive vs. negative)	NA	NA	NA	NA	3	0.71 (0.52–0.98)	0.0356	0
AFP (high vs. low)	5	1.09 (0.97–1.22)	0.1334	0%	11	1.17 (1.10–1.25)	< 0.0001	0
Child–Pugh stage (B/C vs. A)	4	1.37 (1.07–1.74)	0.0123	50%	10	1.58 (1.33–1.87)	< 0.0001	73
ALBI score (2/3 vs. 1)	NA	NA	NA	NA	5	1.22 (0.96–1.54)	0.0983	65
BCLC stage (C vs. B)	NA	NA	NA	NA	7	1.23 (1.09–1.38)	0.0005	0
ECOG (high vs. low)	3	1.40 (1.14–1.72)	0.0016	0%	6	1.50 (1.17–1.93)	0.0012	56
Portal vein invasion (yes vs. no)	4	1.09 (0.96–1.23)	0.1900	1%	7	1.32 (1.09–1.60)	0.0053	64
Extrahepatic metastasis (yes vs. no)	4	0.94 (0.81–1.08)	0.3628	0%	6	0.84 (0.74–0.95)	0.0047	0
Best response (CR/PR vs. SD/CR/PD)	NA	NA	NA	NA	3	0.58 (0.52–0.64)	< 0.0001	0
NLR (high vs. low)	NA	NA	NA	NA	3	1.23 (1.00–1.50)	0.0451	0

PFS progression-free survival, *OS* overall survival, *HBV* Hepatitis B Virus, *HCV* Hepatitis C Virus, *ALBI* Albumin-Bilirubin, *BCLC* Barcelona Clinic Liver Cancer, *ECOG* Eastern Cooperative Oncology Group, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* disease progression, *NLR* Neutrophil-to-lymphocyte ratio, *NA* not available

Assessment of study quality and publication bias

Quality assessment of 40 recruited studies is summarized in Table S4. No evidence of publication bias was observed via egger's tests in the pooled analysis of ORR, DCR, CR, PR, SD, and PD (Table S5), so were the pooled analysis of OS and PFS via funnel plots (Fig. S3) and Egger's tests (Table S6).

Discussion

HCC is the sixth most common malignancy and the fourth leading cause of cancer-related death worldwide (Llovet et al. 2018). For patients with advanced HCC, the effective therapeutic strategies are limited. Most patients are not able to benefit from chemotherapy due to the low effectiveness and serious AEs of chemotherapeutics. With the prolonged overall survival and improved quality of life, sorafenib was approved as first- line drug for advanced HCC by United States Food and Drug Administration (FDA) and China FDA (Furuse 2008; Llovet et al. 2008; Salhab and Canelo 2011). Until now, the optional drugs have expanded to regorafenib, lenvatinib, and other targeted drugs (Bruix et al. 2017; Kudo et al. 2018). Nevertheless, the expectant survival remains shorter than 1 year (El-Serag et al. 2008). In last decade, ICIs has initiated a new era for immunotherapy in oncology by monoclonal antibodies to release the anti-tumor activity of preexisting tumor-specific T-cell immunity, which inspired researchers to focus on the application of ICIs in advanced HCC.

Based on the existing studies, the pooled results of our study revealed that ICIs-based therapy is promising in advanced HCC. Additionally, compared with ICIs monotherapy, the joint application of ICIs and anti-VEGF agents has witnessed better outcomes in DCR, ORR, PFS, and OS. ICIs can effectively alleviate immune escape and enhance the anti-tumor effect mediated by T cells (Reul et al. 2019). However, there are a lot of neovascularization with special structure in tumor tissue, which makes it difficult for anti-tumor drugs and immune cells to reach the tumor site. It was documented that there were no more than 20% of patients with advanced HCC robustly responding to ICIs' monotherapy (El-Khoueiry et al. 2017; Zhu et al. 2018). The combination of ICIs and anti-VEGF agents has a consistent vessel fortification effect in HCC and can overcome treatment resistance, as compared to monotherapies with either of the two agents (Shigeta et al. 2019). The FDA has granted the combined therapy between pembrolizumab and lenvatinib for first-line treatment of patients with HCC based on the latest interim results of the Phase 1b trial, KEYNOTE-524. Furthermore, based on the results of the phase 3 IMbrave150 study, the US FDA approved atezolizumab combined with bevacizumab (A + T) for the treatment of unresectable or metastatic HCC patients who have not received systemic treatment before (Bomze et al. 2020). Therefore, the effectiveness of a single drug is relatively limited. Combined therapy is the future development direction (Wang et al. 2020).

Currently, unlike other solid tumors, there are no recognized or validated biomarkers for HCC immunotherapy (Xu et al. 2019; Vitale et al. 2020). The pooled analysis of our

Table 3 Analyses of response rates stratified by ICIs agent and evaluation criteria

	ICIs						ICIs + anti-VEGF agents					
	RECIST 1.1			mRECIST 1.1			RECIST 1.1			mRECIST 1.1		
	No. of studies	Rate (95% CI)	I^2 (%)	No. of studies	Rate (95% CI)	I^2 (%)	No. of studies	Rate (95% CI)	I^2 (%)	No. of studies	Rate (95% CI)	I^2 (%)
CR	34	0.03 (0.02–0.05)	73	14	0.04 (0.02–0.07)	78	8	0.04 (0.02–0.08)	60	5	0.10 (0.08–0.13)	13
PR	34	0.18 (0.16–0.21)	65	14	0.18 (0.14–0.22)	61	8	0.23 (0.15–0.31)	76	5	0.22 (0.14–0.30)	78
SD	34	0.35 (0.31–0.40)	81	14	0.33 (0.27–0.40)	79	8	0.40 (0.32–0.48)	67	5	0.36 (0.30–0.42)	50
PD	34	0.35 (0.30–0.40)	86	14	0.36 (0.25–0.47)	92	8	0.24 (0.14–0.37)	89	5	0.26 (0.13–0.40)	92
DCR	34	0.62 (0.57–0.66)	84	15	0.59 (0.49–0.69)	90	8	0.72 (0.61–0.82)	86	5	0.69 (0.57–0.81)	89
ORR	34	0.23 (0.20–0.27)	71	15	0.23 (0.17–0.29)	78	8	0.29 (0.22–0.37)	69	5	0.33 (0.25–0.41)	74
	CTLA-4						CTLA-4 + anti-VEGF agents					
	RECIST 1.1			mRECIST 1.1			RECIST 1.1			mRECIST 1.1		
	No. of studies	Rate (95% CI)	I^2 (%)	No. of studies	Rate (95% CI)	I^2 (%)	No. of studies	Rate (95% CI)	I^2 (%)	No. of studies	Rate (95% CI)	I^2 (%)
CR	5	0.05 (0.02–0.09)	50	4	0.09 (0.06–0.14)	51	3	0.06 (0.02–0.11)	70	3	0.10 (0.06–0.15)	55
PR	5	0.19 (0.14–0.24)	41	4	0.22 (0.18–0.25)	32	3	0.22 (0.18–0.26)	0	3	0.23 (0.19–0.27)	0
SD	5	0.42 (0.35–0.49)	50	4	0.37 (0.33–0.41)	0	3	0.44 (0.40–0.48)	49	3	0.38 (0.33–0.42)	11
PD	5	0.28 (0.20–0.38)	74	4	0.27 (0.19–0.36)	75	3	0.21 (0.18–0.25)	27	3	0.22 (0.18–0.26)	0
DCR	5	0.66 (0.57–0.75)	71	5	0.68 (0.59–0.75)	67	3	0.72 (0.68–0.76)	0	3	0.72 (0.68–0.76)	0
ORR	5	0.23 (0.16–0.31)	70	5	0.28 (0.21–0.36)	66	3	0.28 (0.21–0.35)	58	3	0.34 (0.29–0.38)	29
	PD-(L)1						PD-(L)1 + anti-VEGF agents					
	RECIST 1.1			mRECIST 1.1			RECIST 1.1			mRECIST 1.1		
	No. of studies	Rate (95% CI)	I^2 (%)	No. of studies	Rate (95% CI)	I^2 (%)	No. of studies	Rate (95% CI)	I^2 (%)	No. of studies	Rate (95% CI)	I^2 (%)
CR	25	0.02 (0.01–0.04)	65	10	0.02 (0.00–0.06)	72	5	0.04 (0.00–0.11)	58	2	0.11 (0.06–0.17)	0
PR	25	0.18 (0.15–0.21)	60	10	0.16 (0.11–0.23)	66	5	0.25 (0.09–0.46)	86	2	0.18 (0.00–0.54)	95
SD	25	0.35 (0.29–0.41)	83	10	0.31 (0.22–0.42)	84	5	0.36 (0.21–0.54)	76	2	0.32 (0.14–0.53)	82
PD	25	0.36 (0.30–0.42)	84	10	0.39 (0.24–0.56)	93	5	0.25 (0.03–0.56)	93	2	0.30 (0.00–0.88)	98
DCR	25	0.60 (0.54–0.66)	83	10	0.54 (0.38–0.69)	92	5	0.73 (0.46–0.94)	92	2	0.66 (0.15–1.00)	97
ORR	25	0.22 (0.19–0.25)	53	10	0.20 (0.13–0.28)	77	5	0.32 (0.17–0.49)	77	2	0.31 (0.07–0.62)	92

ICIs immune checkpoint inhibitors, *PD-(L)1* Programmed cell death (ligand) 1, *CTLA-4* Cytotoxic T lymphocyte antigen 4, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* disease progression, *DCR* Disease Control Rate, *ORR* Objective Response Rate

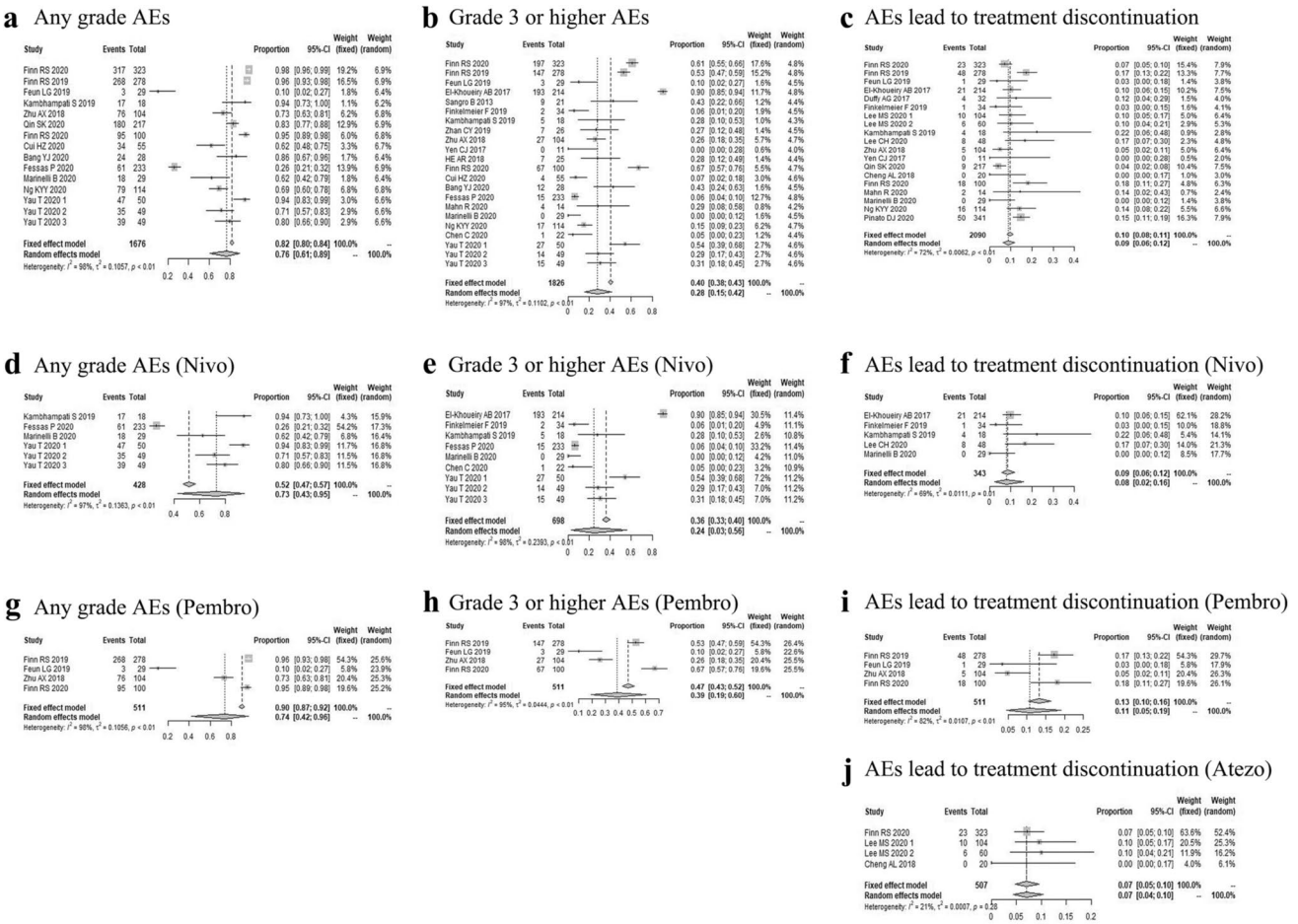

Fig. 4 Adverse events (AEs) of ICIs in advanced HCC. **a** Any grade AEs; **b** grade 3 or higher AEs; **c** AEs lead to treatment discontinuation; **d** any grade AEs for Nivo; **e** grade 3 or higher AEs for Nivo; **f** AEs lead to treatment discontinuation for Nivo; **g** any grade AEs for Pembro; **h** grade 3 or higher AEs for Pembro; **i** AEs lead to treatment discontinuation for Pembro; **j** AEs lead to treatment discontinuation for Atezolizumab (Atezo)

study revealed that AFP, Child–Pugh stage, BCLC stage, ECOG, portal vein invasion, and neutrophil-to-lymphocyte ratio (NLR) were the independent poor prognostic factors, which implied that high AFP (Shao et al. 2019), weak physical condition (Kuo et al. 2020), poor liver functional reserve, macroscopic vascular invasion, and high inflammatory reaction have negative influences on the efficacy of ICIs.

Concerning NLR, studies have shown consistently that inflammation is associated with prognosis in solid tumors due to its effect on the immune response to the disease (Bagley et al. 2017; Cheng et al. 2016; Fouad and Aanei 2017). NLR is a marker for the general immune response to various stress stimuli (Gibney et al. 2016). It was documented that the peripheral neutrophil count measured by the NLR has been found to be directly correlated with the levels of intratumor neutrophil population (Moses and Brandau 2016) and granulocyte myeloid-derived suppressor cells (gMDSCs) (Gonda et al. 2013), which is directly associated with the anti-tumor effect of immune checkpoint inhibitors (Sacdalan et al. 2018).

On the other hand, infection with HCV, extrahepatic metastasis, and best response with CR or PR were good prognosis factors of ICIs used in advanced HCC.

Concerning ICIs used in HCC patients infected with HCV, there is a lack of data based on large clinical trials. It was documented that the HCV-specific cytotoxic T lymphocytes (CTLs) can be activated by ICIs without liver damage (Fukuda et al. 2020). However, the immunopathogenesis of HCV after the administration of ICIs has not been clarified. Due to the small number of included studies, the results need to be further confirmed by large sample research.

Extrahepatic metastases, with a diverse antigen load, may serve as a source of antigen-specific T-cell immunity, increase the immunogenicity of HCC, and enhance the anti-tumor effect of ICIs. Additionally, the tumor response to ICIs in HCC varies among different organs.

This diversity of organ-specific response indicates that the immune microenvironments of different organs often differ. Different from other organs, liver sustains an immunosuppressive milieu because of a series of regulatory mechanisms including inherent tolerance, chronic HBV-mediated immunosuppression, and HCC immune escape (Pardee and Butterfield 2012). With the change of the extrahepatic immune microenvironment, the immunosuppression decreased and the immune response increased.

There were not any new specific AEs related specifically HCC and the incidence rate of grade 3 or higher AEs (leading to treatment discontinuation) was not high for patients treated with ICIs-based therapy. On the whole, the toxicity of ICIs-based therapy was tolerable for advanced HCC.

In conclusion, the ICIs-based therapeutic strategies (especially combination of ICIs and anti-VEGF agents) were promising in advanced HCC. The best strategy and time of ICIs for HCC remain a challenge to be addressed. On one hand, in the exploration of the best strategy of ICIs for HCC, we need to optimize the order of the existing drugs, to design and promote clinical research based on biomarkers, and to explore the development of other ICIs drugs and cell-based treatment schemes (such as Car-T-cell therapy); on the other hand, in choosing the best time of ICIs for HCC, we need to compare the curative effect of first-line and second-line setting on the basis of the existing outcomes, and consider perioperative immunotherapy; at the same time, the existing ICIs-based schemes need to be combined with local treatment (including TACE, HAIC, SIRT, and radiotherapy). The top priority for future research of ICIs in HCC is to find appropriate biomarkers [such as tumor mutational burden (TMB), PD-L1 expression, tumor infiltrating lymphocytes (TILs), and mismatch repair deficiency (MMR)] to screen beneficiaries (Zeng et al. 2020; Cheng et al. 2020), to explore the feasibility of ICIs combined with local therapeutics (such as radiotherapy, RFA, and TACE) (Choi et al. 2019), and to expand the application of ICIs in perioperative period for HCC and realize the transformation therapy (Tovoli et al. 2020).

Limitations

This study had some drawbacks: first, the majority of the included cohorts were single-arm trials, and multicenter randomized-controlled trials are recommended in the future; second, the recruited studies showed a high level of heterogeneity and a certain level of publication bias; finally, the ICIs served at different treatment line among included studies, which may be a possible source of bias.

Conclusions

The ICIs was promising in HCC with good efficacy and tolerated toxicity. Compared with ICIs monotherapy, the joint application of ICIs and anti-VEGF agents can contribute a lot more benefits to the survival of patients according to clinical practices.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00432-021-03716-1.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by QW, NL, BM, and RW. The first draft of the manuscript was written by QW, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding None.

Availability of data and materials The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

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