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Efficacy of immune checkpoint inhibitors differs in various status of carcinoma: a study based on 29 cohorts with 3255 participants

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Abstract

Background Pre-clinical data have revealed that viral infection, such as Hepatitis B virus (HBV), Hepatitis C virus (HCV), and Human Papilloma virus (HPV), may lead to the development of "hot" or "immune-sensitive" tumors, which may impact the efficacy of immune checkpoint inhibitor (ICIs). Therefore, This study aimed to investigate the impact of viral status on the efficacy of ICIs.

Methods Electronic databases were searched to identify relevant trials. The primary endpoints were overall survival (OS) and progression-free survival (PFS) measured by hazard ratio (HR). Stratified analyses were accomplished based on viral types, treatment regimens, and patient locations.

Results A total of 3255 participants were recruited, including 252 cases of gastric cancer, 156 cases of nasopharyngeal carcinoma, 1603 cases of hepatocellular carcinoma, and 1244 cases of head and neck squamous cell carcinoma. Pooled results demonstrated a significant association between viral infection and favorable outcomes in patients receiving ICIs, including improved OS [HR = 0.67, 95%CI (0.57–0.79), P < 0.0001], increased ORR [OR = 1.43, 95%CI (1.14–1.80), P = 0.0018], and a trend toward enhanced PFS [HR = 0.75, 95%CI (0.56–1.00), P = 0.05]. In subgroup analyses, patients treated with ICIs who were exposed to HBV/HCV or HPV infection exhibited an evidently superior OS without heterogeneity, compared to those without infection.

Conclusions This study indicated that the presence of viral infection was evidently associated with improved outcomes in cancer patients undergoing ICIs, particularly in cases of HBV/HCV and HPV infections.

Keywords Immune checkpoint inhibitors (ICIs) · Viral infection · Malignancy · efficacy · Hot tumor microenvironment

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Introduction

Immune checkpoint inhibitors (ICIs) have revolutionized the field of cancer treatment [1–4]. This groundbreaking approach has shifted the focus from indiscriminate targeting of cancer cells by traditional chemotherapy to enhancing the immune system's ability to selectively attack tumor cells. However, the efficacy of ICIs is still far from satisfactory due to resistance [5, 6], and the distinction of biomarkers of response is an intense area of research [7]. This could potentially be linked to the variability observed in the tumor microenvironment (TME) across different types of tumors [8, 9]. Thus, it is crucial to identify the populations that benefit from ICIs treatment.

Based on the infiltration of T cells, Chen and Mellman have classified the tumor immune microenvironment into three different phenotypes: immune-desert, immune-excluded, and immune-inflamed. Among them, the immune-desert and immune-excluded phenotypes, also known as "cold tumors", were non-inflamed tumors that were typically insensitive to ICIs. In contrast, the immune-inflamed phenotype, referred to as "hot tumors", exhibited a significantly stronger response to ICIs [8, 10]. Studies demonstrated that tumors associated viral infection often exhibit an "hot tumor" [11, 12]. However, the impact of viral infection in tumors on the efficacy of ICIs remains a topic of debate in clinical practice, with no established consensus. While some researchers supported a positive impact [13, 14], others advocated for non-inferior survival outcome [15, 16]. Additionally, the types of tumors, viruses and ICIs were various. Therefore, it remains to be fully illuminated that the impact of viral status on the efficacy of ICIs in cancer patients.

Previous studies had preliminarily explored the effect of human papilloma virus (HPV) on ICIs through meta-analysis [17], but they focused on single type of tumor and lack of subgroup analyses. Here, we conducted a comprehensive survey based on a large sample size (29 cohorts incorporating 3,255 individuals), multiple types of viruses and tumors to evaluate the impact of viral status on ICIs efficacy for malignancies.

Materials and methods

Literature searches

PubMed, Cochrane Library, and EMBASE were systematically searched to identify relevant studies up until December 15th, 2023 by entering the following keywords: "immune checkpoint inhibitors", "ICI", "immunotherapy", "PD-1", "PD-L1", "CTLA-4", "programmed cell death protein 1", "programmed cell death protein ligand 1", "cytotoxic T lymphocyteassociated protein 4", "pembrolizumab", "nivolumab", "atezolizumab", "ipilimumab", "tremelimumab", "avelumab", "durvalumab", "carelizumab", "tislelizumab", "cemiplimab", "toripalimab", "penpulimab", "cemiplimab", "adebrelimab", "sugemalimab", "Epstein Barr virus", "EBV", "Hepatitis B virus", "HBV", "Human Papilloma virus", "HPV", "hepatitis C virus", "HCV", "gastric cancer", "GC", "stomach Cancer", "hepatic cancer", "liver cancer", "HCC", "nasopharyngeal carcinoma", "NPC", "head and neck cancer", "HNSCC", "lymphoma", "cancer", "neoplasm", "tumor", "carcinoma", and "malignancy". Moreover, the reference lists of related articles were scrutinized for additional studies.

Selection of studies

Two investigators respectively performed an initial screening of titles and abstracts, and then scrutinized the full texts to identify eligible studies.

Inclusion criteria

Inclusion criteria were included: (1) individuals were pathologically confirmed as malignancies; (2) therapeutic outcomes were analyzed on the efficacy of ICIs according to viral status (including Epstein Barr virus (EBV), hepatitis B virus (HBV), hepatitis C virus (HCV), and HPV; (3) A hazard ratio (HR) accompanied by a 95% confidence interval (CI) for progression-free survival (PFS) and/or overall survival (OS) and/or odds ratios (OR) with 95% CI for objective response rate (ORR) could be obtained or calculated from the original literature.

Data extraction

Data from all enrolled studies were independently collected by two investigators. The data was collected from each publication as follow: publication year, first author, number of patients, primary tumor, immunotherapy agents, viral types, HR for OS and/or PFS, and OR for ORR between the viral infection group and viral uninfection group.

Quality assessment

The quality of studies was assessed using the Newcastle–Ottawa quality assessment scale (NOS), with scores of more than six indicating medium to high quality [18]. Discrepancies were settled through a consensus reached among all investigators.

Statistical methods

The primary endpoints of the study were OS and PFS. The association between viral status (infection vs uninfection) and the efficacy ICIs was measured applying HR with the corresponding 95% CI. Subgroup analyses were accomplished based on the viral types, treatment regimen, patient locations, and ICI agents. Statistical analysis was performed by R 4.2.2 statistical software. Heterogeneity was evaluated through the *I*-square tests and Cochran's Q test. if P < 0.05 or $I^2 > 50\%$, it indicated remarkable heterogeneity, and a random effect model was employed. Otherwise, a fixed effect model was adopted. Publication bias was assessed using funnel plot, Egger's test, and trimand-fill method [19].

Results

Study selection and characteristics of trials

A total of 18,347 potentially relevant articles were intensively scrutinized. Among them, 1,658 were removed for duplication, while 16,689 were filtered out for digressing from the subject after screening the titles and abstracts. Subsequently, the full texts of 163 articles were thoroughly reviewed, of which 134 were excluded for the following reasons: repeated study cohort (n = 23), unavailable data to evaluate the efficacy of ICIs (n = 47), non-human research (n = 22), reviews or meta-analysis (n = 42). Finally, a total of 29 studies incorporating 3,255 participants were identified (The links of original article and details were shown in Supplementary 1). The elaborate procedure is displayed in Fig. 1.

A total of 3255 individuals in 13 retrospective studies and 16 prospective studies were recruited. All 29 adopted studies were rated as moderate or high quality. Furthermore, the sample size ranged from 12 to 421. Of these studies, 3 focused on gastric cancer (GC), 1 on nasopharyngeal carcinoma (NPC), 14 on hepatocellular carcinoma (HCC), 11 on headneck squamous cell carcinoma (HNSCC). Principal traits and details were presented in Table 1.

Main results

The impact of viral status on malignancy patients treated with ICIs

Pooled results showed that tumor patients with viral infection who received ICI agents had a significantly favorable OS [HR = 0.67, 95%CI (0.57–0.79), P < 0.0001] by a random-effect model ($I^2 = 42\%$, P = 0.02) (Fig. 2a), and a trend towards improved PFS [HR = 0.75, 95%CI (0.56–1.00), P = 0.05] based on a random-effect model (I2 = 58%, P < 0.01)(Fig. 2b). Furthermore, There was



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

Table 1 The principal characteristics and further details of eligible articles

Author		Year	Patier	nts location	Stı	udy type	Cancer	type	Viral type	e	ICI agent	S	Numbe	r of p	atients	Male (%)
													Uninfec	ction	Infection	
Chang [S1]		2022	China	l	R ^c		GC ^e		EBV ^k		Nivo ^r or sintilim tislelizu	ab or 1mab	107		19	74 (58)
Kim [S2]		2020	Korea	ı	R		GC		EBV		Pembro ^s	or Nivo	56		4	37 (59)
Bai [S3]		2022	China	ı	R		GC		EBV		ICIs ^t		44		22	49 (74)
Yang [S4]		2021	China	ı	\mathbf{P}^{d}		NPC ^f		EBV		Camreliz	umab	39		117	124 (80)
Liu [S5]		2022	China	ı	R		$\mathrm{HCC}^{\mathrm{g}}$		HBV^m		Camreliz	umab	26		28	43 (77)
Wu [S6]		2022	China	ı	Р		HCC		HBV or H	HCV ⁿ	Pembro		18		53	62 (87)
Yau [S7]		2019	Multi		Р		HCC		HBV or H	HCV	Nivo		89		93	65 (76)
Wu [S8]		2022	China	ı	R		HCC		HBV or H	HCV	Nivo		5		35	29 (73)
Yao [S9]		2021	China	ı	R		HCC		HBV		ICIs		12		124	115 (85)
Sun [S10]		2022	China	ı	R		HCC		HBV		ICIs		13		71	69 (82)
Kim [S11]		2021	Korea	ı	R		HCC		HBV or H	HCV	Nivo		17		85	87 (85)
El-Khoueiry [S1	2]	2017	Multi	a	Р		HCC		HBV or H	HCV	Nivo		57		101	171 (80)
Ju [S13]		2022	China	ı	Р		HCC		HBV		Camreliz	umab	15		65	66 (83)
Xin [S14]		2022	China	ı	R		HCC		HBV		Atezo ^u		5		47	46 (89)
Zhu [S15]		2018	Multi		Р		HCC		HBV or H	HCV	Pembro		81		22	86 (83)
Verset [S16]		2020	Multi		Р		HCC		HBV or H	ICV	Pembro		29		20	44 (86)
Tomonari [S17]		2022	Japan		R		HCC		HBV or H	ICV	Atezo		33		38	58 (82)
Tada [S18]		2022	Japan		R		HCC		HBV or H	HCV	Atezo		208		213	340 (81)
Ferris [S19]		2021	USA	and Europe ^b	Р		HNSC	C ^h	HPV^q		Nivo		26		26	38 (73)
Powell [S20]		2020	USA		Р		HNSC	С	HPV		Pembro		25		34	50 (85)
Bauml [S21]		2017	Multi		Р		HNSC	С	HPV		Pembro		131		37	138 (81)
Chow [S22]		2016	Multi		Р		HNSC	С	HPV		Pembro		104		28	110 (83)
Black-Mono [S2	3]	2023	USA		R		HNSC	С	HPV		Pembro		165		163	330 (77)
Black-combinati [S23]	on	2023	USA		R		HNSC	С	HPV		Pembro		93		70	170 (79)
Zandberg [S24]		2019	USA	and Europe	Р		HNSC	С	HPV		Durva		65		34	NA ^v
Kim [S25]		2020	Korea	ı	R		HNSC	С	HPV		Pembro o	or Nivo	5		7	25 (71)
Leddon [S26]		2022	USA		Р		HNSC	С	HPV		Nivo		16		10	27 (69)
Seiwert [S27]		2018	USA	and Israel	Р		HNSC	С	HPV		Pembro		37		23	49 (82)
Colevas [S28]		2018	USA		Р		HNSC	С	HPV		Atezo		12		13	27 (84)
Ferris [S29]		2018	Multi		Р		HNSC	С	HPV		Nivo		56		64	NA
Author	Mee	dian ag	e	Combination		Line of	therapy	PFS	@(months))		OS# (m	onths)			Quality
				urug				Unin	fection	Infec	tion	Uninfec	ction	Infe	ction	tion
Chang [S1]	57 ((37–78))	Mono ^{&}		2nd-line		3.5 (3.3–3.7)	3.8 (3	3.3–4.2)	NA		NA		7
Kim [S2]	54 (29-82))	Mono		2nd-line	or late	NA*		NA		NA		NA		8
Bai [S3]	NA			CTLA-4i ^{\$} or Mono		1st-line	or later	NA		NA		NA		NA		8
Yang [S4]	NA			Mono		3rd-line	or late	6.0 (2.9–11.1)	2.7 (1.9–3.9)	22.7 (1 NR ^β)	5.2-	16.5 19	(13.5– .5)	9
Liu [S5]	Infe 55.9 U 59.5	ection: 0 ± 11.5 ninfection 5 ± 10.9	5 ion:)	Mono		1st-line	or later	6.7 (5.0-8.4)	9.2 (7.4–11.0)	11.1 (9	.7–12.5)	13.3 15	.(11.4– .2)	8
Wu [S6]	63 ((28-89))	Lenvatinib		1st-line	or later	NA		NA		NA		NA		8

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Author Yau [S7] Wu [S8] Yao [S9] Sun [S10] Kim [S11S1] El-Khoueiry [S12] Ju [S13] Xin [S14] Zhu [S15] Verset [S16] Tomonari[S17] Tada [S18] Ferris [S19]	Median age	Combination	Line of therapy	PFS @(months	3)	OS [#] (months)	Quality		
		drug		Uninfection	Infection	Uninfection	Infection	evalua- tion	
Yau [S7]	63 (19–81)	Mono	2nd-line	NA	NA	15.1 (11.7– 18.9)	HBV ^K group 14.8 (9.1– 20.2); HCV ^α group 18.8 (11.2– 30.8)	9	
Wu [S8]	58.5±13.8	Lenvatinib	1st-line or later	NA	NA	12.4	HBV group: NR HCV group: 23.2 (NR)	7	
Yao [S9]	58 (14-84)	Antiangiogenic therapy	1st-line or later	NA	NA	NA	NA	7	
Sun [S10]	53 (25–78)	Lenvatinib	1st-line or later	NA	NA	NA	NA	7	
Kim [S11S1]	61 (54–69)	Mono	1st-line or later	NA	NA	NA	NA	7	
El-Khoueiry [S12]	64 (56–70)	Mono	1st-line or later	4.0 (2.6–6.7)	4.0 (1.3–4.1)	13.2 (8.6-NE ^w)	NR ^y	8	
Ju [S13]	52 (46-62)	Apatinib	1st-line or later	NA	NA	NA	NA	8	
Xin [S14]		Beva^{Φ}	NA	NA	NA	NA	NA	7	
Zhu [S15]	68 (62–73)	Mono	2nd-line	NA	NA	NA	NA	8	
Verset [S16]	68 (41–91)	Mono	1st-line	NA	NA	NA	NA	9	
Tomonari[S17]	71 (66–79)	Beva	2nd-line or late	NA	NA	NA	NA	7	
Tada [S18]	NA	Beva	2nd-line or late	NA	NA	NA	NA	7	
Ferris [S19]	Infection: 63 (34–82) Uninfection: 60 (42–85)	Mono	1st-line	NA	NA	49.8 (12.4-NE)	NR	9	
Powell [S20]	60 (36-81)	Cisplatin	1st-line	NA	NA	NA	NA	9	
Bauml [S21]	61 (33–90)	Mono	2nd-line or late	NA	NA	NA	NA	9	
Chow [S22]	60 (25-84)	Mono	1st-line or later	NA	NA	NA	NA	9	
Black-Mono [S23]	69 (68–70)	Mono	1st-line	NA	NA	NA	NA	7	
Black- Combination [S23]	64 (63–65)	Chemotherapy	1st-line	NA	NA	NA	NA	7	
Zandberg [S24]	NA	Mono	2nd-line	NA	NA	5 (3.4–8.4)	10.2 (7.2–16.3)	9	
Kim [S25]	58 (39–73)	Mono	1st-line or later	1.8 (1.3–2.3)	4.5 (0.0–11.0)	6.8 (1.1–12.6)	NR	8	
Leddon [S26]	68 (49–85)	Mono	1st-line	NA	NA	NA	NA	9	
Seiwert [S27]	63 (20-83)	Mono	1st-line or later	2 (2-4)	4 (2–10)	8 (4-NR)	NR (8-NR)	9	
Colevas [S28]	62 (32–78)	Mono	1st-line or later	NA	NA	NA	NA	9	
Ferris [S29]	59 (29-83)	Mono	2nd-line or late	NA	NA	7.7 (4.8–13.0)	9.1 (6.5– 11.8)	9	

^a: Multi countries; ^b:Europe; ^c: Retrospectively; ^d: Prospectively; ^e: Gastric cancer; ^f: Nasopharyngeal carcinoma; ^g: Hepatocellular carcinoma; ^h: Head and neck squamous cell carcinoma; ^k: Epstein Barr virus; ^m: Hepatitis B virus; ⁿ: Hepatitis C virus; ^q: Human Papilloma virus; ^r: Nivolumab; ^s: Pembrolizumab; ^t: Immune checkpoint inhibitors; ^u: Atezolizumab; ^v: No answer; [S1-S29]: The links of original article and details were shown in Supplementary 1

[@]:Progression-free survival; [#]: Overall survival; ^{*}: No answer; [&]: Monotherapy; ^{\$}: Cytotoxic T lymphocyte-associated protein 4 inhibitor; ^{β}: No rearch; ^K: Hepatitis B virus; ^{α}: Hepatitis C virus; ^{Φ}: Bevacizumab; ^w: Not estimable; [S1-S29]: The links of original article and details were shown in Supplementary 1

a

Study	logHR	SE(logHR)	Hazard Ratio	HR	95%-CI	Weight (common)	Weight (random)
2022 Chang	-0.0305	0.2395	!!	0.9700	[0.6100; 1.5600]	6.8%	6.9%
2022 Bai	-1.0788	0.2976	- <u></u> }	0.3400	[0.1900; 0.6100]	4.4%	5.2%
2022 Liu	-0.7133	0.2683		0.4900	[0.2900; 0.8300]	5.4%	6.0%
2022 Wu	-0.5108	0.4315	——————————————————————————————————————	0.6000	[0.2580; 1.4000]	2.1%	3.0%
2019 Yau-HBV	0.0100	0.2018	+	1.0100	[0.6800; 1.5000]	9.6%	8.3%
2019 Yau-HCV	-0.1508	0.2375		0.8600	[0.5400; 1.3700]	6.9%	6.9%
2022 Wu-HBV	-1.6094	0.9654		0.2000	[0.0300; 1.3200]	0.4%	0.7%
2021 Yao	-0.3567	0.4709	<u>_</u>	0.7000	[0.3000; 1.9000]	1.8%	2.6%
2022 Sun	0.0953	0.4364		1.1000	[0.4700; 2.6000]	2.1%	2.9%
2021 Kim	-0.2549	1.5070		0.7750	[0.0040; 1.4710]	0.2%	0.3%
2022 Ju	-0.5763	0.5022		0.5620	[0.2100; 1.5040]	1.5%	2.3%
2022 Tada	-0.1370	0.1967		0.8720	[0.5930; 1.2820]	10.1%	8.5%
2021 Ferris	-1.9661	0.6686	j	0.1400	[0.0400; 0.5500]	0.9%	1.4%
2020 Powell	-2.4079	0.7511		0.0900	[0.0200; 0.3800]	0.7%	1.1%
2017 Bauml	-0.4308	0.2264		0.6500	[0.4200; 1.0200]	7.6%	7.3%
2023 Black-Mono	-0.4700	0.1794		0.6250	[0.4420; 0.8930]	12.1%	9.2%
2023 Black-Combination	-0.4894	0.2251		0.6130	[0.3940; 0.9520]	7.7%	7.4%
2019 Zandberg	-0.4463	0.2413		0.6400	[0.4000; 1.0300]	6.7%	6.8%
2022 Leddon	-0.8210	0.7059		0.4400	[0.1100; 1.7500]	0.8%	1.3%
2018 Seiwert	-0.5447	0.3713		0.5800	[0.2800; 1.2000]	2.8%	3.8%
2018 Ferris	-0.0834	0.2041	達	0.9200	[0.6200; 1.3800]	9.4%	8.2%
Common effect model			1	0.6950	[0.6149; 0.7856]	100.0%	
Random effects model				0.6685	[0.5689; 0.7856]		100.0%

0.01

0.1

1

10

100

Heterogeneity: $I^2 = 42\%$, $\tau^2 = 0.0413$, p = 0.02

b

с

Study logHR	SE(logHR)	Hazard Ratio	HR	95%-CI	Weight (common)	Weight (random)
2022 Chang 0.1655	0.2317	<u>:: </u>	1.1800	[0.7500; 1.8600]	11.3%	9.4%
2020 Kim 0.2311	0.6207		1.2600	[0.3800; 4.3300]	1.6%	3.9%
2022 Bai -0.9416	0.4597		0.3900	[0.1600; 0.9700]	2.9%	5.7%
2022 Liu -1.6503	0.3975		0.1920	[0.0880; 0.4180]	3.9%	6.5%
2022 Wu -0.4700	0.3467		0.6250	[0.3170; 1.2340]	5.1%	7.4%
2021 Yao 0.4055	0.3196	34 - 2	1.5000	[0.8000; 2.8000]	6.0%	7.8%
2022 Sun 0.0198	0.3586		1.0200	[0.5100; 2.0800]	4.7%	7.2%
2022 Ju -0.0356	0.4861		0.9650	[0.3720; 2.5010]	2.6%	5.3%
2022 Xin -0.5276	0.6065		0.5900	[0.1800; 1.9400]	1.7%	4.0%
2022 Tomonari -0.2904	0.3508		0.7480	[0.3760; 1.4870]	4.9%	7.3%
2022 Tada -0.0222	0.1403		0.9780	[0.7430; 1.2880]	30.9%	11.0%
2020 Powell -1.9661	0.6392	!!	0.1400	[0.0400; 0.4900]	1.5%	3.8%
2017 Bauml -0.1508	0.1956		0.8600	[0.5900; 1.2700]	15.9%	10.1%
2020 Kim 0.0100	0.8056		1.0100	[0.2100; 4.9400]	0.9%	2.7%
2018 Seiwert -0.1985	0.3129		0.8200	[0.4400; 1.5000]	6.2%	7.9%
Common effect model		i	0.8493	[0.7289; 0.9896]	100.0%	
Random effects model		· · · · · · · · · · · · · · · · · · ·	0.7486	[0.5588; 1.0030]		100.0%
		0.1 0.5 1 2 10				

Heterogeneity: $I^2 = 58\%$, $\tau^2 = 0.1825$, p < 0.01

Study	logOR	SE(logOR)	Odds Ratio	OR	95%-CI	Weight (common)	Weight (random)
Kim-2020	1.5261	0.9829		4.6000	[0.6700; 31.5800]	1.4%	2.4%
Yang-2021	-0.7985	0.3877		0.4500	[0.2100; 0.9600]	8.9%	10.2%
Liu-2022	1.5686	0.7950		4.8000	[1.0100; 22.7900]	2.1%	3.5%
Yau-HBV-2019	-0.1278	0.5051		0.8800	[0.3300; 2.3900]	5.3%	7.2%
Yau-HCV-2019	0.4700	0.5204	<u>1</u>	1.6000	[0.5800; 4.4600]	4.9%	6.9%
Wu-HBV-2022	0.6259	1.0048	<u>_</u>	1.8700	13.3500	1.3%	2.3%
Wu-HCV-2022	0.2231	1.3440	<u>.</u>	1.2500	17.4700	0.7%	1.3%
El-Khoueiry-2017	0.0000	0.5140	_	1.0000	[0.2200; 1.6500]	5.1%	7.0%
Verset-2020	0.4447	0.7752		1.5600	0.3400: 7.1000	2.2%	3.6%
Yao-2021	0.5306	0.1768		1.7000	[0.7000: 1.4000]	42.9%	19.5%
Ferris-2021	0.5766	0.5743	<u></u>	1.7800	[0.5800: 5.5100]	4.1%	5.9%
Powell-2020	-0.0202	0.9575		0.9800	[0.1500; 6.4000]	1.5%	2.5%
Bauml-2017	0.0677	0.5062		1.0700	0.4000: 2.91001	5.2%	7.2%
Chow-2016	1.0332	0.4786	4	2.8100	[1.1000: 7.1800]	5.8%	7.8%
Seiwert-2018	0.7324	0.7810	<u>_</u>	2.0800	[0.4500: 9.6100]	2.2%	3.6%
Colevas-2018	-0.0943	1.0842		0.9100	[0.1100: 7.7100]	1.1%	2.0%
Ferris-2018	0.2231	0.5065		1.2500	[0.4600; 3.3500]	5.2%	7.2%
Common effect mod	el		į	1.4345	[1.1433: 1.7998]	100.0%	
Random effects mod	lel		\	1.3893	[1.0163; 1.8993]		100.0%
2	2		0.1 0.5 1 2 10				
	/	0.04					

Heterogeneity: I^2 = 12%, τ^2 = 0.0992, p = 0.31

Fig. 2 Forest plots for a overall survival (OS), b progression-free survival (PFS), and c objective response rate (ORR)



Fig. 3 a The pooled HRs for overall survival (OS) stratified on viral types (EBV, HBV/HCV, and HPV); b treatment regions (monotherapy or combined therapy); c patients locations (western countries and eastern countries); d the pooled HRs for progression-free survival

an increased ORR [OR = 1.43, 95%CI (1.14–1.80), P = 0.0018] in viral positive group according to a fixed-effect model (I2 = 12%, P = 0.31) (Fig. 2c).

Subgroup analysis for the impact of viral status

We performed subgroup based on the viral types, treatment regimen, and patient locations (Fig. 3a–i). The result showed that patients treated with ICIs who were exposed to HBV/ HCV or HPV infection exhibited an evidently superior OS without heterogeneity, compared to those without HBV/ HCV [HR=0.79, 95%CI (0.65–0.96)] and HPV [HR=0.64, 95%CI (0.53–0.76)]. While the OS was similar between the EBV-positive group and the EBV-negative group [HR=0.58, 95%CI (0.21–1.63)] (Fig. 3a). Furthermore, we found that patients with viral infection who received ICIs had a significantly better OS, in contrast to those without

(PFS) stratified on viral types; **e** treatment regions; **f** patients locations; **g** the pooled ORs for objective response rate (ORR) stratified on viral types; **h** treatment regions; **i** patients locations

infection, regardless of the treatment types (monotherapy or combined therapy) [HR = 0.64, 95%CI (0.54–0.75) and HR = 0.78, 95%CI (0.64–0.94), respectively] (Fig. 3b) and patient locations (eastern countries or western countries) [HR = 0.68, 95%CI (0.55–0.84) and HR = 0.57, 95%CI (0.45–0.71), respectively] (Fig. 3c). Additionally, the groups with HBV/HCV or HPV infection achieved a higher ORR compared to the groups without HBV/HCV or HPV infection)[OR = 1.58, 95%CI (1.19–2.10) and OR = 1.57, 95%CI (1.0–2.47), respectively] (Fig. 3g).

Publication bias

The shape of the funnel plot suggested no publication bias for recruited studies on PFS (Egger: P = 0.11) (Fig. 4a) and ORR (Egger: P = 0.98) (Fig. 4b). However, there was a



Fig. 4 Funnel plot of publication bias on \mathbf{a} progression-free survival (PFS), \mathbf{b} objective response rate (ORR), and \mathbf{c} overall survival (OS) in the meta-analysis; \mathbf{d} the corrected HRs for OS based on the trim and fill method

publication bias for OS (Egger: P = 0.02) (Fig. 4c). Nevertheless, in the results of the trim and fill method, the publication bias corrected overall effect size was 0.76 (95% CI: 0.62–0.93) (Fig. 4d), even though the effect size increased compared to the original ones. This implied that the results obtained for this study were reliable and consistent.

The sensitivity analysis

Sensitivity analyses were performed by excluding one single study from the primary analyses. The results showed that no single study significantly influenced the pooled HRs or ORs, suggesting that the data of this meta-analysis were relatively credible and stable (Fig. 5).

Discussion

Recently, increasing evidences highlighted the importance of viral infection in influencing the efficacy of immunotherapy. Pre-clinical and clinical evidences have recognized that the viral infection may play a crucial role in boosting the immune response and improve prognosis of cancer patients undergoing ICIs treatment [11–14]. To the best of **Fig. 5** Sensitivity analysis of **a** overall survival (OS), **b** progression-free survival (PFS), and **c** objective response rate

(ORR)

а								
Study	Hazar	d Ratio	HR	95%-CI	P-value	Tau2	Tau	12
Omitting 2022 Chang			0.65	[0.55; 0.77]	< 0.01	0.0420	0.2049	42%
Omitting 2022 Bai	<u> </u>		0.71	[0.62; 0.82]	< 0.01	0.0130	0.1139	33%
Omitting 2022 Liu			0.68	[0.58; 0.81]	< 0.01	0.0374	0.1934	42%
Omitting 2022 Wu			0.67	[0.57; 0.79]	< 0.01	0.0455	0.2133	45%
Omitting 2019 Yau-HBV			0.65	[0.55; 0.76]	< 0.01	0.0313	0.1769	38%
Omitting 2019 Yau-HCV			0.65	[0.55; 0.78]	< 0.01	0.0493	0.2220	44%
Omitting 2022 Wu			0.68	[0.58; 0.79]	< 0.01	0.0391	0.1977	42%
Omitting 2021 Yao			0.67	[0.56; 0.79]	< 0.01	0.0461	0.2147	45%
Omitting 2022 Sun			0.66	[0.56; 0.78]	< 0.01	0.0447	0.2113	43%
Omitting 2021 Kim			0.67	[0.57; 0.79]	< 0.01	0.0419	0.2048	45%
Omitting 2022 Ju			0.67	[0.57; 0.79]	< 0.01	0.0440	0.2097	45%
Omitting 2022 Tada			0.65	[0.55; 0.77]	< 0.01	0.0473	0.2175	43%
Omitting 2021 Ferris			0.69	[0.59; 0.80]	< 0.01	0.0300	0.1733	34%
Omitting 2020 Powell			0.69	[0.59; 0.80]	< 0.01	0.0293	0.1711	30%
Omitting 2017 Bauml			0.66	[0.56; 0.79]	< 0.01	0.0535	0.2313	45%
Omitting 2023 Black-Mono			0.67	[0.56; 0.80]	< 0.01	0.0545	0.2336	44%
Omitting 2023 Black-Combination			0.67	[0.56; 0.80]	< 0.01	0.0515	0.2269	45%
Omitting 2019 Zandberg			0.67	[0.56; 0.79]	< 0.01	0.0523	0.2287	45%
Omitting 2022 Leddon			0.67	[0.57; 0.79]	< 0.01	0.0416	0.2040	44%
Omitting 2018 Seiwert			0.67	[0.57; 0.79]	< 0.01	0.0459	0.2142	45%
Omitting 2018 Ferris			0.65	[0.55; 0.77]	< 0.01	0.0430	0.2074	42%
Random effects model			0.67	[0.57; 0.79]	< 0.01	0.0413	0.2033	42%
	0.75	1 1.5						

b							
Study	Hazard Ratio	HR	95%-CI	P-value	Tau2	Tau	12
Omitting 2022 Chang Omitting 2020 Kim Omitting 2022 Bai Omitting 2022 Liu Omitting 2022 Wu Omitting 2022 Wu Omitting 2022 Sun Omitting 2022 Ju Omitting 2022 Xin Omitting 2022 Tomonari		0.71 0.73 0.78 0.90 0.75 0.71 0.73 0.73 0.75 0.74	$\begin{matrix} [0.52; \ 0.97] \\ [0.54; \ 0.99] \\ [0.58; \ 1.05] \\ [0.77; \ 1.05] \\ [0.55; \ 1.04] \\ [0.53; \ 0.95] \\ [0.53; \ 1.00] \\ [0.54; \ 1.02] \\ [0.54; \ 1.02] \end{matrix}$	0.03 0.04 0.10 0.19 0.08 0.02 0.05 0.05 0.05 0.07 0.07	0.1929 0.1972 0.1707 < 0.0001 0.2115 0.1642 0.2105 0.2074 0.1984 0.2179	0.4392 0.4440 0.4131 < 0.0001 0.4599 0.4052 0.4558 0.4555 0.4455 0.4668	58% 60% 57% 30% 60% 56% 61% 60% 61%
Omitting 2022 Tada Omitting 2020 Powell Omitting 2017 Bauml Omitting 2020 Kim Omitting 2018 Seiwert Random effects model		0.72 0.81 0.73 0.74 0.74	[0.52; 1.00] [0.62; 1.05] [0.53; 1.02] [0.55; 1.00] [0.53; 1.02] [0.56; 1.00]	0.05 0.11 0.06 0.05 0.06 0.05	0.2187 0.1140 0.2272 0.1961 0.2208 0.1825	0.4676 0.3377 0.4766 0.4428 0.4699 0.4272	59% 48% 61% 61% 61% 58%
	0.75 1 1.5						

c							
Study	Odds Ratio	OR	95%-CI	P-value	Tau2	Tau	12
Omitting Kim-2020	<u> </u>	1.35	[0.98; 1.85]	0.06	0.0969	0.3113	11%
Omitting Yang-2021		1.61	[1.27; 2.04]	< 0.01	0	0	0%
Omitting Liu-2022	- <u>-</u>	1.33	[0.97; 1.82]	0.07	0.0893	0.2988	5%
Omitting Yau-HBV-2019		1.44	[1.04; 2.00]	0.03	0.1091	0.3302	13%
Omitting Yau-HCV-2019		1.38	[0.99; 1.92]	0.06	0.1186	0.3444	17%
Omitting Wu-HBV-2022	· · · · · · · · · · · · · · · · · · ·	1.38	[1.00; 1.90]	0.05	0.1054	0.3247	17%
Omitting Wu-HCV-2022		1.39	[1.01; 1.91]	0.04	0.1033	0.3214	18%
Omitting El-Khoueiry-2017		1.43	[1.02; 1.99]	0.04	0.1151	0.3393	15%
Omitting Verset-2020		1.38	[1.00; 1.91]	0.05	0.1100	0.3316	18%
Omitting Yao-2021		1.33	[0.93; 1.91]	0.12	0.1263	0.3553	10%
Omitting Ferris-2021		1.37	[0.98; 1.91]	0.06	0.1140	0.3376	17%
Omitting Powell-2020		1.40	[1.02; 1.93]	0.04	0.1064	0.3261	17%
Omitting BaumI-2017		1.42	[1.02; 1.98]	0.04	0.1177	0.3430	16%
Omitting Chow-2016		1.31	[0.95; 1.80]	0.10	0.0852	0.2919	7%
Omitting Seiwert-2018	<u> </u>	1.37	[0.99; 1.89]	0.06	0.1071	0.3273	17%
Omitting Colevas-2018		1.40	[1.02; 1.93]	0.04	0.1048	0.3238	17%
Omitting Ferris-2018		1.40	[1.00; 1.96]	0.05	0.1209	0.3477	17%
		4 00					400/
Kandom effects model		1.39	[1.02; 1.90]	0.04	0.0992	0.3150	12%
0.5	1 2						

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our knowledge, this study was firstly investigated the impact of viral infection on outcomes of cancer patients treated with ICIs based on a comprehensive survey (29 cohorts incorporating 3,255 individuals), multiple viruses types (EBV, HBV, HCV, and HPV) and multiple tumor types (including GC, NPC, HCC and HNSCC). The result demonstrated a significant association between viral infection and improved outcomes for cancer patients receiving ICIs treatment.

Mechanically, PD-1 and its ligands played a crucial role in enabling tumor cells to evade the anti-tumor response of immune system [20]. Less widely recognized was that the PD-1/PD-L1 axis also played a role in regulating immune responses against viral infection and can be influenced by various viruses [21, 22]. Upregulation of PD-1 and its ligands PD-L1 were observed during acute viral infection and after infection with persistent viruses including important human pathogens such as HBV, HCV, and EBV [23–26]. Moreover, viral infection associated carcinomas were typically characterized by abundant immune cell infiltration [11, 12], which might further positively affect the efficacy of ICIs.

Notably, our study exhibited that EBV infection did not impact the efficacy of ICI treatment, despite the frequent association of EBV infection with high PD-L1 expression in tumors was discovered [25, 26]. The reason remains to be elucidated. However, it should be noted this study comprising EBV associated tumors was only included 4 cohorts with a total of 408 participants. Therefore, caution should be advised when interpreting the result.

However, this study encountered two flaws: firstly, some of recruited studies were retrospective, although we had comprehensively analyzed the articles; secondly, due to the limited availability of comprehensive data, subgroup analysis based on specific ICI agents could not be conducted.

In conclusion, this study demonstrated that the presence of viral infection was positively associated with better outcomes, with improved OS, increased ORR, and potential benefits in PFS in cancer patients undergoing ICIs therapy. And subgroup analyses on therapy regimen and patient locations exhibited similar results, indicating the positive impact of viral infection on ICIs therapy in clinical practice.

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Declarations

Conflict of 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.

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