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Correlation between PD-L1 expression ON CTCs and prognosis of patients with cancer: a systematic review and meta-analysis

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ABSTRACT

Circulating tumor cells (CTCs) are considered to be related to the prognosis of cancer patients. CTC is a powerful indicator for recurrence or metastasis. The relationship, however, between the expression of programmed cell death receptor ligand 1 (PD-L1) on CTCs in peripheral blood and the prognosis, is still controversial. Here, we conducted a meta-analysis to evaluate its prognostic value. A total of 20 articles were screened from PubMed, Embase, Cochrane, China National Knowledge Internet (CNKI) and WanFang Database, and the Hazard Ratio (HR) along with 95% confidence intervals (CIs) of each article were combined to study the relationship between PD-L1 expression on CTCs and prognosis. The expression of PD-L1 on CTCs in the peripheral blood of cancer patients is associated with poor prognosis. The pooled HRs for overall survival (OS) in cancer patients were 1.85 (95% CI, 1.29–2.66, $P = .001$). The pooled HRs for progression-free survival (PFS) in cancer patients were 1.50 (95% CI, 1.12–2.01; $P = .007$). This is the first meta-analysis to clarify the expression of PD-L1 on CTCs at baseline affects the prognosis of cancer patients. Patients with CTCs expressing PD-L1 had a shorter survival time than patients with CTCs not expressing PD-L1.

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Introduction

Circulating tumor cells were first described in 1869. CTCs are cells that are shed into the blood from the primary tumor and metastatic deposits.[1] With the latest development of reproducible detection technology, CTCs have been studied as diagnostic, prognostic and/or predictive biomarkers for various types of cancer.[2] CTCs are negatively correlated with the prognosis of tumor patients. Patients with CTCs detected in the peripheral blood have a worse prognosis and shorter survival time.[3,4] The existence of CTCs may be the cause of tumor recurrence and metastasis.[4,5] A study by Tamminga et al. showed that about one-third of patients with advanced non-small cell lung cancer could be detected with CTC, and this was related to the poor prognosis of patients receiving immune checkpoint therapy.[6] For patients with non-small cell lung cancer treated with tyrosine kinase inhibitors (TKI) or chemotherapy, the response rate of patients with CTC detected in peripheral blood to treatment was lower than that of patients without CTC detected.[7]

It is reported in the literature that the expression of PD-L1 is considered to be positively correlated with the efficacy of immune checkpoint inhibitor therapy,[8] but the relationship between PD-L1 on CTCs and the prognosis is still inconclusive.

Compared with tissue biopsy, circulating tumor cells have the following advantages: (1) easy to collect, (2) serial evaluation, (3) interrogation of the entire tumor burden instead of just a limited part of the tumor. Recent progress has been made in the phenotype and genotyping of CTC, which should provide insights into the predictive effect of CTC on treatment sensitivity or resistance. In addition, changes in CTC phenotypic markers during treatment can be used as a tool for drug efficacy monitoring. Therefore, CTCs collection can be considered a "liquid biopsy" that can provide prognostic and predictive clinical information and further understanding of tumor heterogeneity.[9]

Whether the expression of PD-L1 on CTCs can be used as a prognostic indicator has been explored,[10–12] but according to the current literature' results, there is no consensus. Boffa et al. found that PD-L1 expressed on circulating tumor cells in peripheral blood was associated with worse survival of lung cancer.[13] In the study by Khattak et al., patients with PDL1+ CTCs had longer PFS compared with patients with PD-L1− CTCs.[14]

Therefore, it is necessary to conduct a meta-analysis to study whether PD-L1 in the CTCs is related to the prognosis of cancer patients based on the current research status.

Materials and methods

Inclusion criteria

1. literatures with search terms in the title or abstract. 2. literatures restricted to human studies written in English or

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Chinese. 3. studies included the effect of PD-L1 on CTCs in the blood on the prognosis of cancer patients. 4. efficacy results expressed as PFS or OS had to be provided.

Exclusion criteria

1. reviews, case reports, notes, chapters, editorials and letters. 2. literatures were not relevant to this study. 3. literatures with insufficient data or no information available. 4. research on animal experiments.

Literature review

Titles and abstracts were screening by two investigators independently according to the inclusion criteria. After removing the duplicate literatures, the final selected literatures had been screened according to the exclusion criteria. If any disputes were encountered, the two reviewers negotiated to resolve or consulted with the third investigators, and the quality of the final enrolled literatures was evaluated after reading the full text.

Data extraction

The information was extracted from the full text includes: author, publication time and journal, region, sample size, age, tumor types, expression level of PD-L1 in CTCs or tissue specimens, cutoff value, CTCs detection methods, treatment methods, PFS, OS, HR for OS and PFS, etc. The information was extracted by two reviewers independently and when encountering controversial issues, the two reviewers consulted with a third investigator.

Quality assessment

The literatures were evaluated according to the Newcastle–Ottawa scale (NOS), which was used to assess the quality of cohort studies and case–control studies. The included literatures were evaluated by two reviewers independently, and the disagreement was resolved through discussion or consultation with a third investigator. The highest score is 9 points, and studies with a score of six or more are considered to be high-quality.[15]

Statistical analysis

Stata 16.0 statistical software was used for meta-analysis. Hazard ratios for OS and PFS and 95% confidence intervals were pooled to measure the time to event relationship (between the expression of PD-L1 in CTCs and prognosis of cancer patients). HRs were derived from the multivariate analysis first, followed by univariate analysis, or calculated from Kaplan–Meier survival curves using the methods previously proposed by Tierney and colleagues.[16] Heterogeneity was evaluated by Q test. $P > .10$ was considered to have no heterogeneity or slight heterogeneity, while $P < .10$ implied significant heterogeneity.[17] Besides, heterogeneity was assessed by the I^2 statistics. I^2 values of 25%, 50%, and 75% were considered low, moderate, and high heterogeneity, respectively.[18] When obvious heterogeneity was observed, the random effect model was used; otherwise, the fixed-effect model was used. In addition, to find the source of significant heterogeneity, sensitivity analysis and subgroup analysis were performed. Publication bias was assessed by visual inspection of the funnel plot first and further by the Egger test[19] and the Begg test.[20]

Subgroup analysis

Subgroup analysis in this meta-analysis included the characteristics of the patients, such as area, tumor type, gender, age, methods for detecting CTCs, PD-L1 antibody, data type and treatment methods.

Results

Literature search

A total of 546 documents from five databases were obtained. The five databases are PubMed, Embase, Cochrane, CNKI, and WanFang Database. Among them, 270 documents were excluded because they overlapped in various databases. 183 articles were removed due to lack of full text. 86 articles were reviewed for full-text evaluation. 66 full texts were excluded for the following reasons. 1. They were reviews, case reports, notes, chapters, editorials, and letters. 2. They were not relevant to this study. 3. There was insufficient data or no information available. 4. They were researchers on animal experiments. Finally, 20 articles[12–14,21–37] were recruited for qualitative synthesis and meta-analysis (Figure 1). The remaining documents were unanimously regarded as high-quality documents by researchers.

Study characteristics

The study included 20 studies with a total of 1,344 patients from five countries: the United States, Australia, Greece, France and China. The characteristics of 20 studies are summarized in Table 1. The patients were between 21 and 91 y old. These studies included a variety of tumor types such as non-small cell lung cancer (NSCLC), squamous cell carcinoma of head and neck (HNSCC), prostate cancer, melanoma, colon cancer, gastrointestinal tumors and breast cancer. CTCs in the peripheral blood of 617 out of 1344 patients expressed PD-L1.

In five articles, percentages were used to define the threshold cutoff point for CTCs expressing PD-L1. Other articles used the number of CTCs expressing PD-L1 as the cutoff point. Eight articles received immune checkpoint inhibitor therapy. These documents applied CTC detection platforms based on different detection mechanisms. The researchers stained CTCs with PD-L1 antibody to identify how many cells in the peripheral blood expressed PD-L1, even though the antibodies selected were different (Table 1).

OS of cancer patients with PD-L1 expression on CTCs in the peripheral blood

The pooled HRs for OS in cancer patients were 1.85 (95% CI, 1.29–2.66, $P = .001$; heterogeneity: $I^2 = 43.1\%$, $P = .055$; Figure 2a). Although no significant heterogeneity observed among the selected studies, the P value is close to 0.05

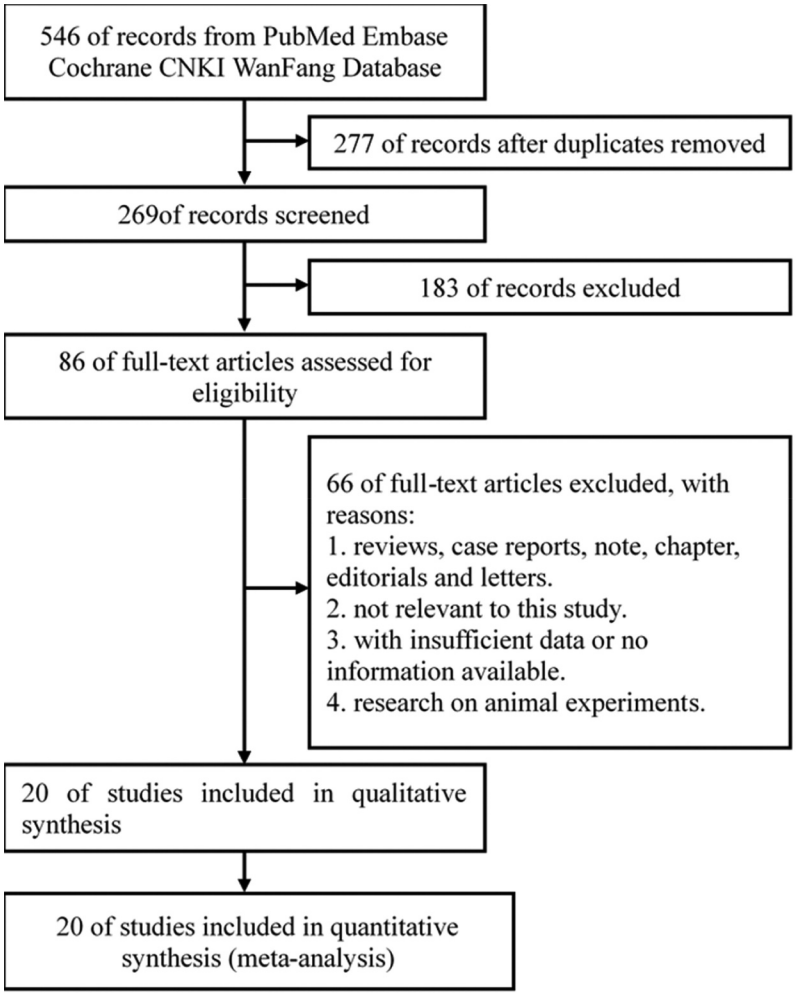

Figure 1. Flow Diagram of the Study Selection Process. CNKI, China National Knowledge Internet.

(0.055), we conducted a sensitivity test and found that omitting any single study did not influence the result of OS. Hence, subgroup analyses were proposed. Among patients whose cut-off≤1 group, pooled HRs of OS were 1.82 (95% CI, 1.22–2.74, P = .004; heterogeneity: I^2 = 0.0%, P = .543). Among patients under 65 y of age, the combined HRs of OS were 1.74 (95% CI, 1.18–2.56; heterogeneity: I^2 = 33.7%, P = .071). When the included studies were analyzed by subgroups based on region, there were no heterogeneity in the studies from the United States (2.39,95% CI, 1.62–3.52; heterogeneity: I^2 = 0.0%, P = .652), China (3.03,95% CI, 1.61–5.72; heterogeneity: I^2 = 0.0%, P = .440), and France (1.23,95% CI, 0.68–2.21; heterogeneity: I^2 = 0.0%, P = .625), and the heterogeneity came from the researches in Greece (1.43,95% CI, 0.40–5.05; heterogeneity: I^2 = 69.9%, P = .068). According to the pooled HRs for OS in cancer patients, the expression of PD-L1 on CTCs in the peripheral blood of cancer patients was associated with poor prognosis.

PFS of cancer patients with PD-L1 expression on CTCs in the peripheral blood

The pooled HRs for PFS in cancer patients were 1.50 (95% CI, 1.12–2.01; P = .007; heterogeneity: I^2 = 64.7%, P = .000; Figure 2b). Because of significant heterogeneity observed, we also performed a similar sensitivity analysis. The sensitivity analysis result showed that omitting any single study did not influence the result of PFS. We then conducted subgroup analyses of the included studies. In the cutoff≤1 subgroup, the pooled HRs for PFS in cancer patients were 1.85 (95% CI, 1.26–2.72; P = .002; heterogeneity: I^2 = 24.2%, P = .244). Differences had also been observed in age groups. In the under 65-y-old group, the pooled HRs for PFS in cancer patients were 1.82 (95% CI, 1.35–2.45; P = .000; heterogeneity: I^2 = 15.3%, P = .303). When analyzing the subgroups by region, no heterogeneity was found in the China (2.85, 95% CI, 1.93–4.20; P = .000; heterogeneity: I^2 = 0.0%, P = .924) and France (1.29, 95% CI, 0.84–1.97; P = .239; heterogeneity: I^2 = 0.0%, P = .303) subgroups.

Whether the expression of PD-L1 on CTCs can be a prognostic indicator for immune checkpoint inhibitor therapy.

In the subgroup analysis, among studies that did not use immune checkpoint inhibitor (ICI) therapy, the pooled HRs for OS were 2.02 (95% CI, 1.44–2.83; P = .000; heterogeneity: I^2 = 18.0%, P = .288; Figure 2c, Table 2). This suggested that without the use of immune checkpoint inhibitors, the expression of PD-L1 on CTCs indicated a worse prognosis. However, in the group treated with immune checkpoint inhibitors, the expression of PD-L1 on CTCs

Table 1. Characteristics of studies included in the meta-analysis.

Author	Year	Journal	Region	N total	Age mean (range)	Tumor type	PD-1+ CTC	Cutoff PD-L1+ CTC/mL	CTC detection Method	PD-L1 antibody
Anantharaman	2016	BMC Cancer	America	25	67(43–89)	Bladder cancer	7	1	EPIC Sciences Platform	CST
Boffa	2017	Cancer Epidemiol Biomarkers Prev	America	112	67.5(59–76.5)	NSCLC	26	1.1	EPIC Sciences Platform	CST
Cheng	2020	Cancer Management and Research	China	66	62(48–79)	NSCLC	22	1%	HE pathological staining	Abcam
Dhar	2018	Scientlfic Reports	America	22	69.4(51–91)	NSCLC	7	2	Vortex HT chip	ProSci Inc
Dong	2019	Front Oncol	China	114	60.9	NSCLC	56	-	CanPatrolTM	RNA-ISH
Guibert	2018	Lung Cancer	France	96	60 (30–81)	NSCLC	74	1% 5% 10%	ISET platform	CST
Ilie′	2018	Annals of Oncology	France	106	65 (41–86)	NSCLC	71	1	ISET platform	Ventana
Kallergi	2018	Therapeutic Advances In Medical Oncology	Greece	30	-	NSCLC	9	3	ISET platform	Biolegend Novus Biologicals
Khattak	2020	The Oncologist	Australia	40	71	Melanoma	14	-	Flow Cytometric Staining	R&D System
Kulasinghe	2018	Cancer Medicine	Australia	56	60 (21–82)	HNSCC NSCLC	17	-	ClearCell FX system	Abcam
Liu	2020	Molecular Oncology	China	70	63	Gastric cancer	50	8	Flow Cytometric Staining	CST
Papadaki	2020	Cancers	Greece	198	60(29–84)	Breast cancer	60	1	-	CST
Satelli	2016	Scientlfic Reports	America	92	-	Colon cancer prostate cancer	64	50%	Flow Cytometric Staining	Flow cytometry
Tada	2020	Oral Oncology	America	44	66	HNSCC	11	-	CellSieve™ microfilter	RT-qPCR
Yue	2018	Oncoimmunology	China	35	-	Gastrointestinal cancer	26	2 20%	Pep@MNPs isolated system	KN802
Adams	2017	Clinical Cancer Research	America	41		Lung cancer	17	2	CellSieve™ microfilter	R&D systems
Manjunath	2019	Cancers	America	30	65(50–79)	NSCLC	30	3	CellSieve™ microfilter	CST
Strati	2017	Annals of Oncology	Greece	113	65	HNSCC	24	-	RosetteSep System	CellSearchTM analysis
Wang	2019	Scientlfic Reports	America	38	67(57–89)	NSCLC	25	5%	GO chip Immunofluorescence staining	BioLegend
Zhang	2020	Cancer Letters	China	16	-	NSCLC	7	-	SE-iFISH	IF(-)

Aberrations: NSLCC: Non-small cell lung carcinoma, HNSCC: Head and neck squamous cell carcinoma, PD-1: Programmed cell death-1, QA: Quality Assessment.

in the peripheral blood was not found to be related to the patient's prognosis. The pooled HRs for OS were 1.31 (95% CI, 0.46–3.75; P = .618; heterogeneity: I^2 = 70.1%, P = .018; Figure 2d, Table 2).

Sensitivity analyses

Sensitivity analysis results showed that the heterogeneity of HRs for OS was mainly derived from two studies conducted by Khattak and colleagues and Strati and

Table 2. Subgroup analysis of the pooled HRs for OS and PFS in cancer patients with PD-L1 expressed in the CTCs.

	OS			PFS		
	Number of studies Heterogeneity I^2%, p	Pooled HRs (95% CI)	Interaction (p)	Number of studies Heterogeneity I^2%, p	Pooled HRs (95% CI)	Interaction (p)
Total	43.1(0.055)	1.96(1.34–2.88)	0.001	64.7(0.000)	1.50 (1.12–2.01)	0.007
Cutoff						
>1	32.5(0.227)	2.74(1.63–4.60)	0.000	57.8(0.037)	1.37(0.83–2.24)	0.217
≤1	0.0(0.543)	1.82(1.22–2.74)	0.004	24.2(0.244)	1.85(1.26–2.72)	0.002
unknown	64.3(0.061)	0.9(0.32–2.54)	0.835	78.3(0.000)	1.19(0.48–2.98)	0.710
Median Age						
>65	77.2(0.012)	1.37(0.27–7.06)	0.707	82.9(0.001)	0.59(0.16–2.12)	0,417
≤65	33.7(0.171)	1.74(1.18–2.56)	0.005	15.3(0.303)	1.82(1.35–2.45)	0.000
unknown	0.0(0.587)	2.67(1.31–5.45)	0.007	67.3(0.009)	1.85(0.90–3.80)	0.093
Area						
America	0.0(0.652)	2.39(1.62–3.52)	0.000	67.4(0.005)	1.17(0.51–2.66)	0.707
Australia	-	-	-	82.7(0.003)	1.08(0.16–7.24)	0.938
China	0.0(0.440)	3.03(1.61–5.72)	0.001	0.0(0.924)	2.85(1.93–4.20)	0.000
France	0.0(0.625)	1.23(0.68–2.21)	0.494	0.0(0.788)	1.29(0.84–1.97)	0.239
Greece	69.9(0.068)	1.43(0.40–5.05)	0.579	38.8(0.195)	1.32(0.84–2.08)	0.231
Tumor type						
Gastrointestinal cancer	0.00(0.459)	2.99(1.68–5.30)	0.000	0.0(0.859)	2.86(1.61–5.09)	0.000
Lung cancer	39.1(0.145)	1.64(1.07–2.51)	0.022	53(0.010)	1.36(1.00–1.84)	0.047
Treatment method						
ICI	70.1(0.018)	1.31(0.46–3.75)	0.618	66.9(0.000)	1.41(0.67–2.96)	0.370
No ICI	18.0(0.288)	2.02(1.44–2.83)	0.000	65.7(0.000)	1.55(1.08–2.23)	0.018
Data types						
Multivariate	73.4(0.010)	1.18(0.46–3.02)	0.728	75.4(0.017)	0.74(0.26–2.11)	0.575
Others	0.0(0.572)	2.15(1.57–2.94)	0.000	64.5(0.000)	1.71(1.21–2.42)	0.002

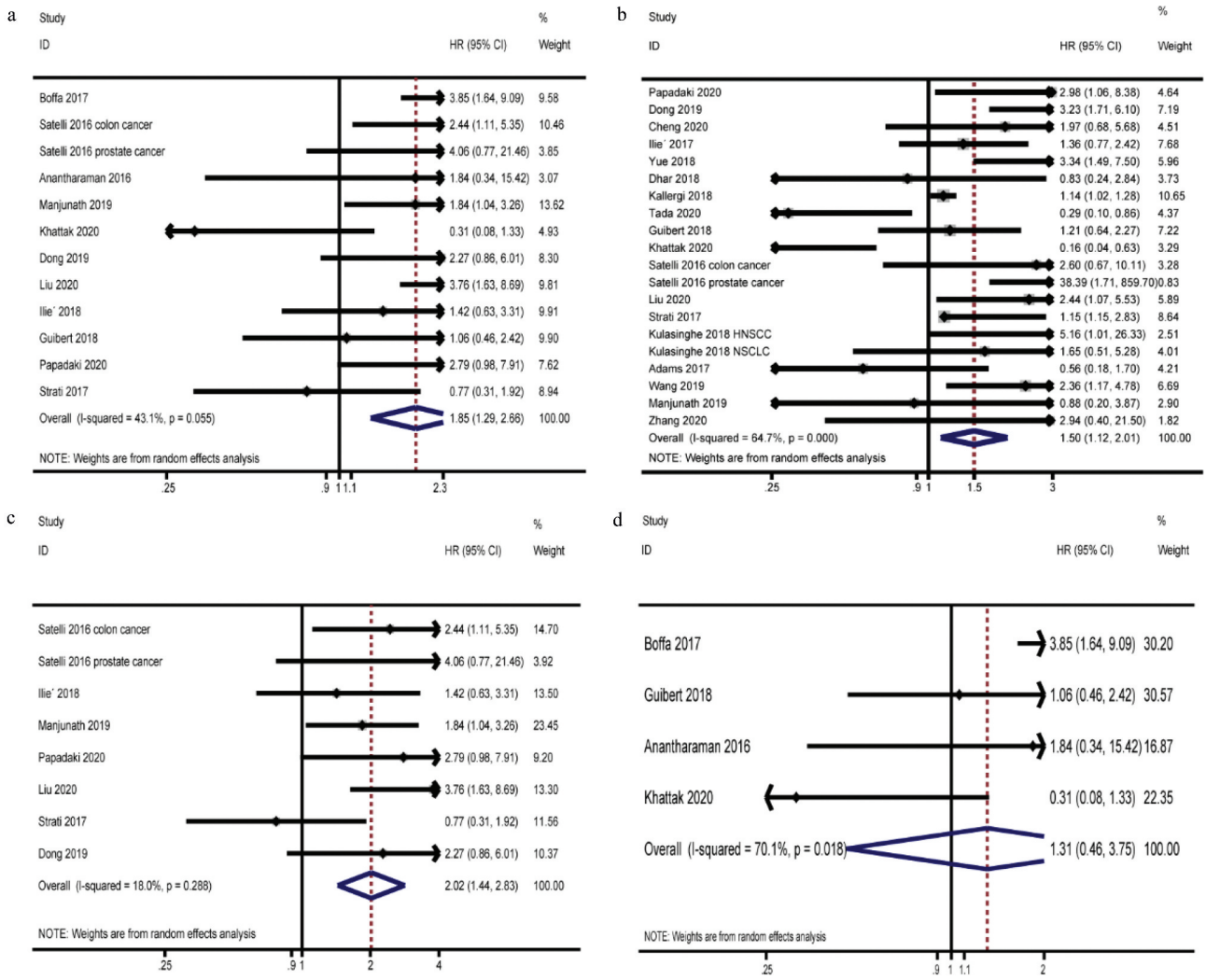

Figure 2. Prognosis of cancer patients with PD-L1 expression on CTCs in the peripheral blood. A, Pooled HRs and 95% CI for OS. B, Pooled HRs, and 95% CI for PFS. C, Pooled HRs, and 95% CI for OS in the subgroup that did not use ICI therapy. D, Pooled HRs and 95% CI for OS in the subgroup that uses ICI therapy.

colleagues. Khattak and colleagues conducted a melanoma study. Because patients in this cohort were treated with the immune checkpoint inhibitor Pembrolizumab. The application of immune checkpoint inhibitors made the prognosis of patients with PD-L1 positive CTCs better than that of patients with PD-L1 negative CTCs.

Strati and colleagues conducted a prospective cohort study of head and neck squamous cell carcinoma. The sample size of this study was relatively large, with a total of 113 patients and 24 patients with PD-L1 positive on CTCs. The expression of PD-L1 on CTCs was detected by Quantitative Reverse Transcription Polymerase Chain Reaction (RT-qPCR) method. This method represented the transcription level of PD-L1 gene to a certain extent, but might not completely represent the expression level of PD-L1 protein.

After removing these two studies, the pooled HRs for OS were 2.18 (95% CI, 1.65–2.88; P = .000; heterogeneity: I^2 = 0.0%, P = .489; Figure 3e).

Excluding the literature one by one in the sensitivity analysis did not affect the results and heterogeneity of PFS, and then we conducted a subgroup analysis.

Subgroup analyses

Because the pooled HRs for PFS in cancer patients had obvious heterogeneity and the pooled HRs for OS in cancer patients had moderate heterogeneity, we conducted a subgroup analysis of the selected literatures to explore the source of heterogeneity. We had set up a total of eight subgroups, namely the CTCs detection platform, the threshold of CTCs expressing PD-L1, the type of PD-L1 antibody, the research area, the median age of the enrolled patients, the data analysis method, the treatment method and tumor type.

Taken the expression of PD-L1 on 1 CTC as the dividing point, in cutoff≤1 group, the pooled HRs of OS were 1.82 (95% CI, 1.22–2.74, P = .004; heterogeneity: I^2 = 0.0%, P = .543; Table 2). The pooled HRs for PFS were 1.85 (95% CI, 1.26–2.72; P = .002; heterogeneity: I^2 = 24.2%, P = .244; Table 2).

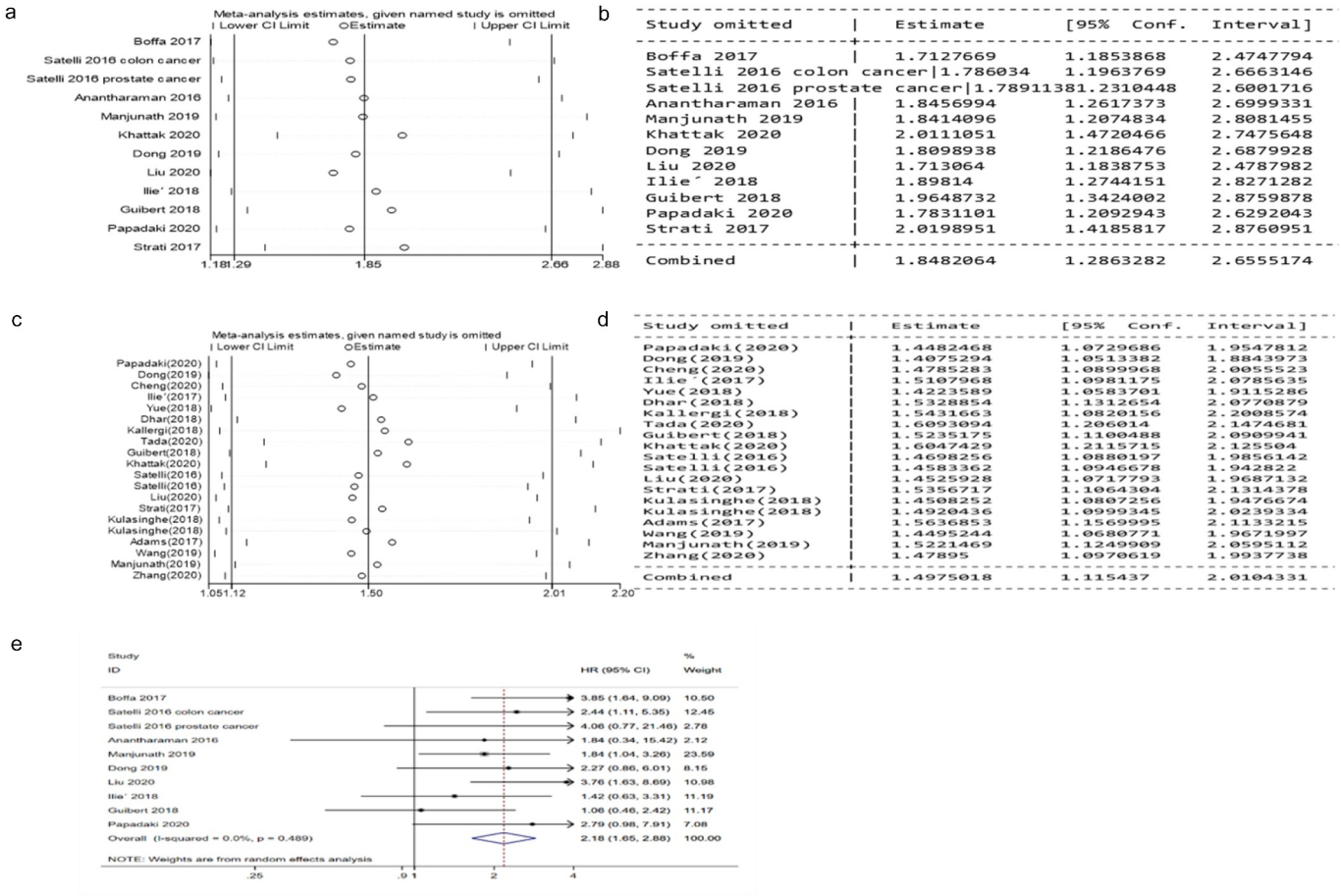

Figure 3. Sensitivity analyses of the pooled HRs for OS and PFS of cancer patients with PD-L1 expression on CTCs in the peripheral blood. A, B, Sensitivity analyses of the pooled HRs for OS. C, D, Sensitivity analyses of the pooled HRs for PFS. E, Pooled HRs and 95% CI for OS after removing two studies.

There was heterogeneity between research in different regions. The pooled HRs for OS in the American subgroup were 2.39 (95% CI, 1.62–3.52; heterogeneity: I^2 = 0.0%, P = .652; Table 2), the pooled HRs for OS in the China subgroup were 3.03 (95% CI, 1.61–5.72; heterogeneity: I^2 = 0.0%, P = .440; Table 2), and the pooled HRs for OS in the France subgroup were 1.23 (95% CI, 0.68–2.21; heterogeneity: I^2 = 0.0%, P = .625; Table 2). The pooled HRs for PFS in the China subgroup were 2.85 (95% CI, 1.93–4.20; P = .000; heterogeneity: I^2 = 0.0%, P = .924; Table 2) and the pooled HRs for PFS in the France (1.29, 95% CI, 0.84–1.97; P = .239; heterogeneity: I^2 = 0.0%, P = .303; Table 2).

Among patients under 65 y of age, the combined HRs for OS was 174 (95% CI, 1.18–2.56; heterogeneity: I^2 = 33.7%, P = .071; Table 2). The pooled HRs for PFS in cancer patients were 1.82 (95% CI, 1.35–2.45; P = .000; heterogeneity: I^2 = 15.3%, P = .303; Table 2). This indicated that the expression of PD-L1 on CTCs in younger patients had a poor prognosis.

When we performed subgroup analyses on tumor types, the pooled HRs for OS in gastrointestinal cancer were 2.99 (95% CI, 1.68–5.30; P = .000; heterogeneity: I^2 = 0.0%, P = .459; Table 2). The pooled HRs for OS in Lung cancer were 1.64 (95% CI, 1.07–2.51; P = .000; heterogeneity: I^2 = 39.1%, P = .145; Table 2). And the pooled HRs for PFS in gastrointestinal cancer were 2.86 (95% CI, 1.61–5.09; P = .000; heterogeneity: I^2 = 0.0%, P = .859; Table 2). This represented that the conclusions in respiratory system tumors and digestive system tumors were consistent.

The pooled HRs for OS in multivariate analyses group were 1.18 (95% CI, 0.46–3.02; P = .728; heterogeneity: I^2 = 73.4%, P = .010; Table 2). The pooled HRs for OS in the other group were 2.15 (95% CI, 1.57–2.94; P = .000; heterogeneity: I^2 = 0.0%, P = .572; Table 2).

Detection platform for CTCs in peripheral blood had no effect on OS. The reason was that the number of studies using the same platform was too small. When analyzing PFS, there were differences between different platforms. The pooled HRs of ISET platform subgroup were 1.15 (95% CI, 1.03–1.28; P = .015; heterogeneity: I^2 = 0.0%, P = .554; Figure S1A). The pooled HRs of CellSieve™ microfilter were 0.47 (95% CI, 0.24–0.84; P = .034; heterogeneity: I^2 = 0.0%, P = .461; Figure S1B). The pooled HRs of ClearCell FX system were 2.51 (95% CI, 0.85–7.41; P = .095; heterogeneity: I^2 = 19.9%, P = .264; Figure S1C). The pooled HRs of Flow Cytometric Staining were 1.81 (95% CI, 0.35–9.50; P = .481; heterogeneity: I^2 = 81.8%, P = .001; Figure S1D).

The pooled HRs for OS in CST subgroup were 2.27 (95% CI, 1.49–3.45; P = .000; heterogeneity: I^2 = 26.4%, P = .236; Figure

S1E). The pooled HRs for PFS in CST subgroup were 1.71 (95% CI, 1.03–2.81; $P = .036$; heterogeneity: $I^2 = 19.6\%$, $P = .292$; Figure S1F). The pooled HRs for PFS in Abcam subgroup were 1.65 (95% CI, 1.08–2.57; $P = .028$; heterogeneity: $I^2 = 0.0\%$, $P = .489$; Figure S1G).

Publication bias

Egger and Begg tests were performed to evaluate publication bias and funnel plot symmetry was examined. Publication bias was not observed based on the visual distribution of funnel plot and *P* values in Egger and Begg tests (Figure S2).

Comparing results from random effect model with those from fixed effect model

As shown in Supplementary Table S1 and S2, in the absence of heterogeneity ($I^2 = 0.00\%$), the HRs and 95% CIs obtained by the random effects model and the fixed effects model were consistent. Additionally, HRs and 95% CIs from the analyses with heterogeneity ($I^2 > 0.00\%$) were slightly changed from random effect model to fixed effect model but it had no impact on prognostic analyses.

Discussion

There had been many studies on the relationship between the expression of PD-L1 on CTCs and the prognosis of cancer patients.[26,35,38] Articles showed that patients with PD-L1 expression had a worse prognosis.[38,39] However, there were also studies that have found that patients with PD-L1 expression can benefit from immune checkpoint inhibitor therapy.[40] For a unified conclusion that has not been reached, a meta-analysis could be done to guide clinical treatment. However, no one has done a meta-analysis in this direction. Our study is the first study, which can bring important evidence for whether the expression of PD-L1 on CTCs can be used as a prognostic assessment marker.

We found that the PD-L1 expression of CTCs in the peripheral blood of patients at baseline was related to the poor prognosis of patients. Patients with 1 or more CTCs expressing PD-L1 had shorter OS and PFS. PD-L1 on tumor cells can bind to PD-1 expressed on T cells, leading to immune escape of tumors, which may be the advantage of tumor metastasis and a feature of high malignancy.

Among patients treated with immune checkpoint inhibitors, studies showed that PD-L1 expression responds better to ICI treatment and had a longer survival benefit.[41,42] However, less than 30% of patients with PD-L1 expression could benefit from immune checkpoint inhibitor therapy.[43] The expression of PD-L1 on CTCs in peripheral blood could not yet be used as a basis for patients to benefit from immune checkpoint inhibitor therapy. A large number of prospective randomized controlled clinical trial studies are needed.

Some limitations existed in our meta-analysis. All the comprehensive studies were selected from Chinese and English databases, so articles in other languages or unpublished articles were overlooked. Some data were obtained from univariate analyses or calculated from Kaplan–Meier survival curves,[16] which might be in slight disparity with the fact. The results of some subgroup analyses might not be representative enough, because the number of studies in some subgroups was too small, such as the detection platform of CTCs and the use of PD-L1 antibodies.

Immune checkpoint inhibitor therapy currently lacks effective prognostic indicators. At present, immunohistochemical detection of PD-L1 expression level in tissues was commonly used.[44] At the same time, there were studies on the relationship between microsatellite instability,[45] tumor mutation burden,[46]the density of tumor-infiltrating lymphocyte (TIL),[47] gut microbiota,[48] circulating biomarkers,[49] and patient previous history,[50] and driving gene mutations.[51–53] However, there was no perfect index, and due to the existence of tumor heterogeneity, there were certain limitations in the extraction of tissues. If a marker can be found in the peripheral blood to judge the prognosis, it will be of great significance to the patient. It will not only be able to quickly and non-invasively detect whether it is effective for immune checkpoint inhibitors and can also reduce the risk of tumor metastasis, bleeding, and spread caused by a puncture.

Systematic review registration

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Disclosure of potential conflicts of interest

The authors report no conflict of interest.

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