ORIGINAL ARTICLE

Prognostic significance of PD-L1 expression in patients with colorectal cancer: a meta-analysis*

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Abstract

Background The association between the expression of programmed cell death 1 (PD-1) or its ligand [programmed cell death ligand-1 (PD-L1)] and colorectal cancer (CRC) survival rates remains unclear. Thus, we conducted a meta-analysis to investigate the prognostic value of PD-L1 expression in CRC patients.

Methods All eligible studies related to evaluation of PD-L1 expression and survival of CRC patients were searched in PubMed, Medline, Cochrane library, and the EMBASE database. Hazard ratios (HRs) and 95% confidence intervals (CI) of overall survival (OS) were examined to assess the effect of PD-L1 expression on the survival of CRC patients. The outcomes of this meta-analysis were synthesized based on random-effects model. Subgroup analyses were also performed.

Results Seven studies, wherein OS data were stratified according to the expression status of PD-L1, were analyzed. CRC patients showing positive PD-L1 expression were associated with significantly poorer prognoses in terms of overall survival, compared with those displaying negative PD-L1 expression (HR = 1.43, 95% CI: 1.07–1.92; P = 0.02). In the subgroup analyses, H-scores as well as the percentage of stained cells indicated that PD-L1 expression was significantly associated with poor prognosis (HR = 1.90, 95% CI: 1.38–2.62, P < 0.01; HR = 1.81, 95% CI: 1.08–3.03, P = 0.02). Immunohistochemical staining, utilizing a rabbit anti-PD-L1 antibody, revealed significantly superior survival in the PD-L1 negative group compared with the PD-L1 positive expression group (HR = 1.92; 95% CI, 1.40-2.63; P < 0.01). Moreover, PD-L1 expression was significantly associated with poor prognosis when polyclonal antibodies were used (HR = 1.84; 95% CI, 1.30–2.61; P < 0.01).

Conclusion Our meta-analysis indicated that PD-L1 expression status is a significant prognostic factor for CRC patients. Positive PD-L1 expression was associated with worse CRC survival. Evaluation via different immunohistochemistry based techniques may partly account for the contradictory results. Therefore, further investigative studies using larger sample sizes are felt to be needed to elucidate the prognostic value of PD-L1 expression in CRC patients.

Key words: colorectal cancer (CRC); programmed cell death ligand-1 (PD-L1); prognosis; Meta-analysis

Colorectal cancer (CRC) is a common cancer and one of the leading causes of cancer-related morbidity and mortality worldwide [1–2]. Although surgery, chemotherapy, and radiotherapy have significantly improved the clinical outlook for CRC patients, the 5-year survival rate still remains low [3–4]. Thus, alternative strategies, such as immunotherapy, are now being considered for the management of CRC [5]. Furthermore, many key molecular alterations are used as biomarkers for predicting prognosis. Programmed cell death 1 (PD-1) and PD-1 ligand 1 (PD-L1) expression have been observed in various malignancies and are reported to play an important role in modulating the strength of T cell response [6–7]. Blockade of the PD-1/PD-L1 signaling

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pathway can minimize damage to surrounding normal tissues by maintaining T cell activation [8–9]. Previous studies have found that PD-1/PD-L1 expression in tumor cells is correlated with poor prognoses [10–13]. Moreover, some clinical studies have shown that anti-PD-1 or PD-L1 antibodies may prolong the survival of melanoma patients, with particular reference to advanced and refractory patients [14–16].

Despite the development of antibodies against PD-1 and PD-L1, their predictive value of prognosis for CRC patients remains unclear. The association between PD-1/PD-L1 expression in CRC and patient survival also remains controversial. Previous meta-analyses has shown that PD-1/PD-L1 expression status was a significant prognostic factor in malignancies, and that positive PD-1/PD-L1 expression was associated with significantly poorer overall survival (OS), especially in patients with clear cell renal cell carcinoma and pancreatic cancer [17]. However, another meta-analysis contended that there was no statistically significant relationship between PD-L1 expression and the prognosis for non-small-cell lung cancer patients [18]. However, strong PD-L1 expression was observed in patients with CRC and was associated with a significant improvement in the 5-year survival rate [19].

Studies related to the prognostic significance of PD-1/PD-L1 expression in CRC patients have yielded inconsistent results due to a lack of statistical power. Moreover, meta-analyses pertaining to CRC related expression of PD-1 and PD-L1 have not been performed. In order to address these issues, we conducted a meta-analysis to evaluate the association between prognostic value and PD-L1 status in CRC patients.

Material and methods

Literature search

All studies evaluating PD-L1 expression and survival of CRC patients were retrieved by searching PubMed, Medline, Cochrane library, and the EMBASE database. Different search term combinations were used, including "colorectal cancer," "PD-L1," "B7-H1," "survival," and "prognosis." A manual search through all references of the relevant articles was also performed.

Inclusion and exclusion criteria

To be eligible for the current meta-analysis, studies had to meet the following criteria: (1) investigation of the association between PD-L1 expression and the prognosis for CRC patients; (2) the expression level of PD-L1 was scored as either "positive" or "negative" via immunohistochemistry (IHC) staining; (3) The primary outcome of OS according to PD-L1 status was available for estimation. Studies with insufficient data were excluded.

Data extraction and quality assessment

We extracted the required data from all eligible studies; the name of the first author, the year of publication, IHC evaluation method, cut off value for positive PD-L1 expression, primary antibody, and OS. OS data were extracted in the form of hazard ratios (HRs) with 95% confidence intervals (CI). In order to ensure the quality of our meta-analysis, two authors used the Methodological Index for Nonrandomized Studies (MINORS) to independently evaluate the quality of the eligible studies.

Statistical analysis

All statistical analyses were performed using RevMan 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) analysis software and Stata software. HRs for OS with 95% CIs was used to assess the effect of PD-L1 expression on the survival of CRC patients. Subgroup analyses were performed according to patients from different countries, IHC evaluation methods and primary antibodies (source, type, and catalog), respectively. Heterogeneity among studies was assessed using the Q and I^2 statistics [20]. The random effect model was utilized in case of potential heterogeneity. Additionally, publication bias was evaluated using Egger's [21] and Begg-Mazumdar [22] procedures. For all tests, statistical significance was set at $P < 0.05$ for a two tailed test.

Results

Search results

The search results were shown (Fig. 1). The primary literature research retrieved a total of 690 potentially relevant articles. After screening titles and abstracts, 569 references were excluded due to being irrelevant to the
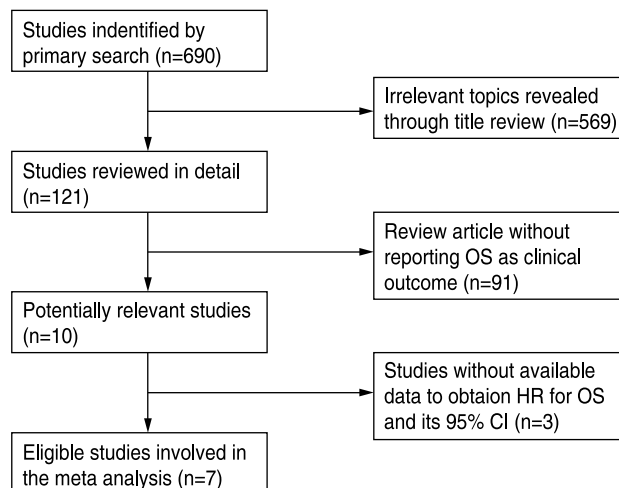

Fig. 1 Process for identification of eligible studies.

subject of the analysis. Additionally, 91 studies, which did not report OS as a clinical outcome, were excluded. Next, three studies with insufficient survival data were excluded after full-texts were read. Ultimately, the seven remaining studies were included for further statistical evaluation [23–29].

Characteristics of included trials

The characteristics of analyzed studies were summarized (Table 1). In the trials that were included, CRC patients had been used to evaluate PD-L1 expression and its relationship with OS in CRC. PD-L1 expression was evaluated via the IHC method in all included studies.

Meta-analyses of PD-L1 expression in terms of OS

Seven studies provided 5-year OS for CRC. In CRC patients, positive PD-L1 expression was associated with significantly poorer OS when compared to negative PD-L1 expression (Random-effects model, HR = 1.43, 95% CI: 1.07–1.92; P = 0.02; Fig. 2). There was significant heterogeneity among studies (I^2 = 51%, P = 0.06). However, no evidence of significant publication bias was detected (Egger test, t = 2.42, P = 0.06; Begg test, Z = 0.62, P = 0.54).

Subgroup analysis between PD-L1 expression and OS

PD-L1 expression was not significantly associated with poor prognosis for both Chinese and non-Chinese patients (Fig. 3). With respect to the different methods of IHC evaluation, the H-score system method, as well as the percentage of stained cells method, indicated that positive PD-L1 expression was significantly associated with poor prognosis when compared with negative PD-L1 expression (HR = 1.90, 95% CI: 1.38–2.62, P < 0.01; HR = 1.81, 95% CI: 1.08–3.03, P = 0.02; Fig. 4). Furthermore, significantly superior survival was shown in the negative PD-L1 expression group compared with the positive PD-L1 expression group when rabbit antibody was used as the primary anti-PD-L1 antibody (HR = 1.92; 95% CI, 1.40–2.63; P < 0.01; Fig. 5). Moreover, PD-L1 expression was significantly associated with poor prognosis when the polyclonal antibody (PAB) was used (HR = 1.84; 95% CI, 1.30–2.61; P < 0.01; Fig. 6). No statistical relationships between PD-L1 expression and CRC prognosis were detected in the remaining subgroups.

Table 1 Characteristics of included studies

| Study | Year | Country | IHC Evaluation | Cutoff Value for PD-L1/ PD-1 Positive | Antibody (Company) | Antibody | | | HR for OS | Lower limit of 95% CI | Upper limit of 95% CI |
						Source	Type	Catalog			
Shi SJ	2013	China	H-score	> 200	Abcam, UK	Rabbit	PAB	ab58810	China	China	3.576
Song MM	2013	US	DIA	NR	Abcam, UK	NR	NR	NR	US	US	1.979
Liang M	2014	China	H-score	> 20	Santa Cruz Biotechnology, USA	Rabbit	PAB	NR	China	China	2.713
Zhu JJ	2014	China	NR	NR	Boster, China	Mouse	MAB	Clone 2H11	China	China	0.98
Zhu HL	2015	China	Percentage	1%	Abcam, UK	Rabbit	MAB	NR	China	China	4.684
Saigusa	2016	Japan	H-score	NR	LifeSpan BioSciences, USA	Mouse	MAB	Clone 27A2	Japan	Japan	5.016
Wang LS	2016	China	Percentage	1%	Spring Bioscience, USA	NR	MAB	SP142	China	China	2.89

DIA : Digital image analysis; HR: Hazard ratio; MAB: Monoclonal antibody; NR: Not reported; PAB: Polyclonal antibody; H-score: SI (Staining intensity)*PP (Percentage of positive cells) (SI: 0, negative; 1, weak; 2, moderate; and 3, strong; PP: 0, negative; 1 to 100, 1% to 100% positive cells).

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Liang M 2014	0.5539	0.1917	20.6%	1.74 [1.20, 2.53]
Saigusa 2016	0.823	0.4029	9.5%	2.28 [1.03, 5.02]
Shi SJ 2013	0.3577	0.1292	25.3%	1.43 [1.11, 1.84]
Song MM 2013	0.1601	0.2666	15.6%	1.17 [0.70, 1.98]
Wang LS 2016	0.3229	0.3767	10.4%	1.38 [0.66, 2.89]
Zhu HL 2015	0.8345	0.3621	10.9%	2.30 [1.13, 4.68]
Zhu JJ 2014	-0.9264	0.4624	7.8%	0.40 [0.16, 0.98]
Total (95% CI)			100.0%	1.43 [1.07, 1.92]

Heterogeneity: Tau² = 0.07; Chi² = 12.32, df = 6 (P = 0.06); I² = 51%
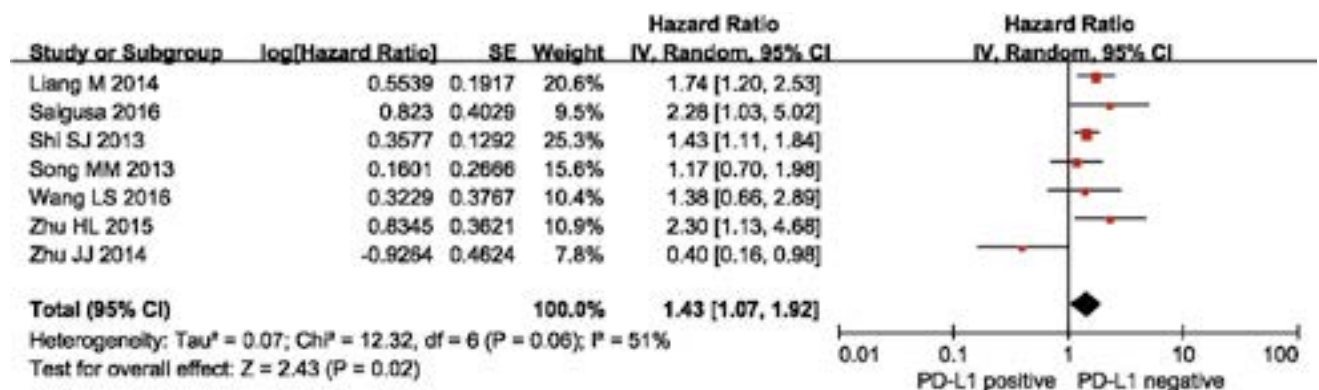Test for overall effect: Z = 2.43 (P = 0.02)

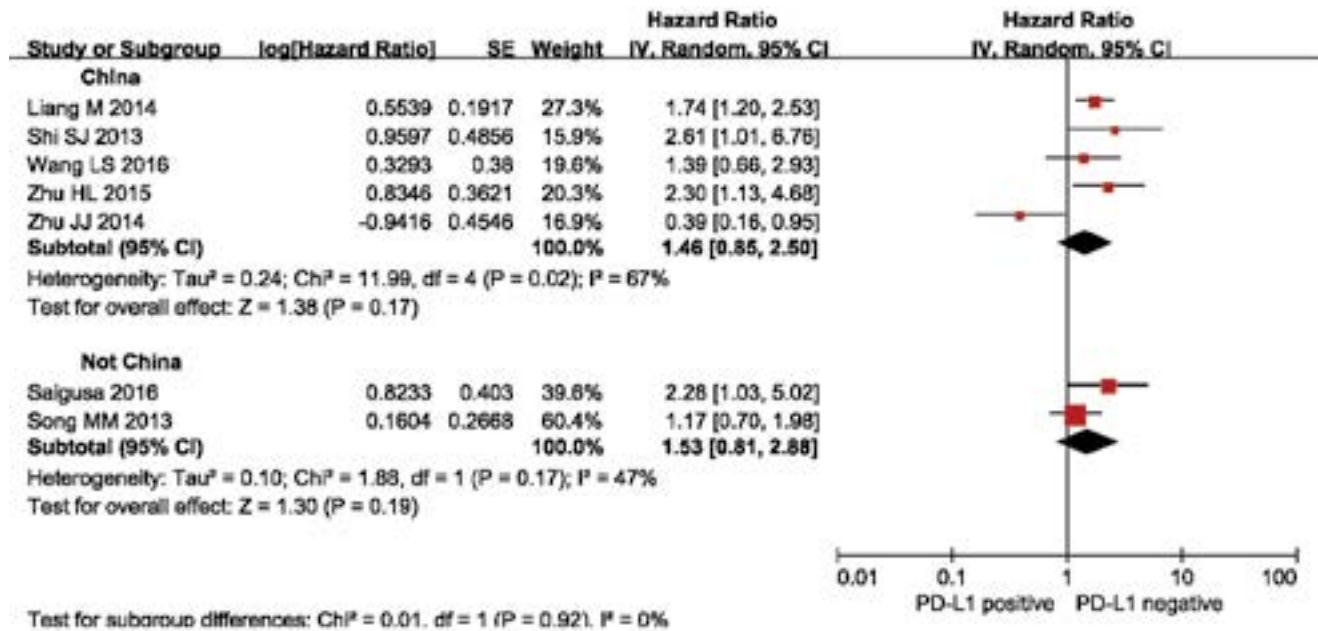**Fig. 2** Meta-analysis of PD-L1 positive versus PD-L1 negative on CRC tissues.

Fig. 3 Subgroup analysis of PD-L1 positive versus PD-L1 negative on CRC tissues of patients from different countries.
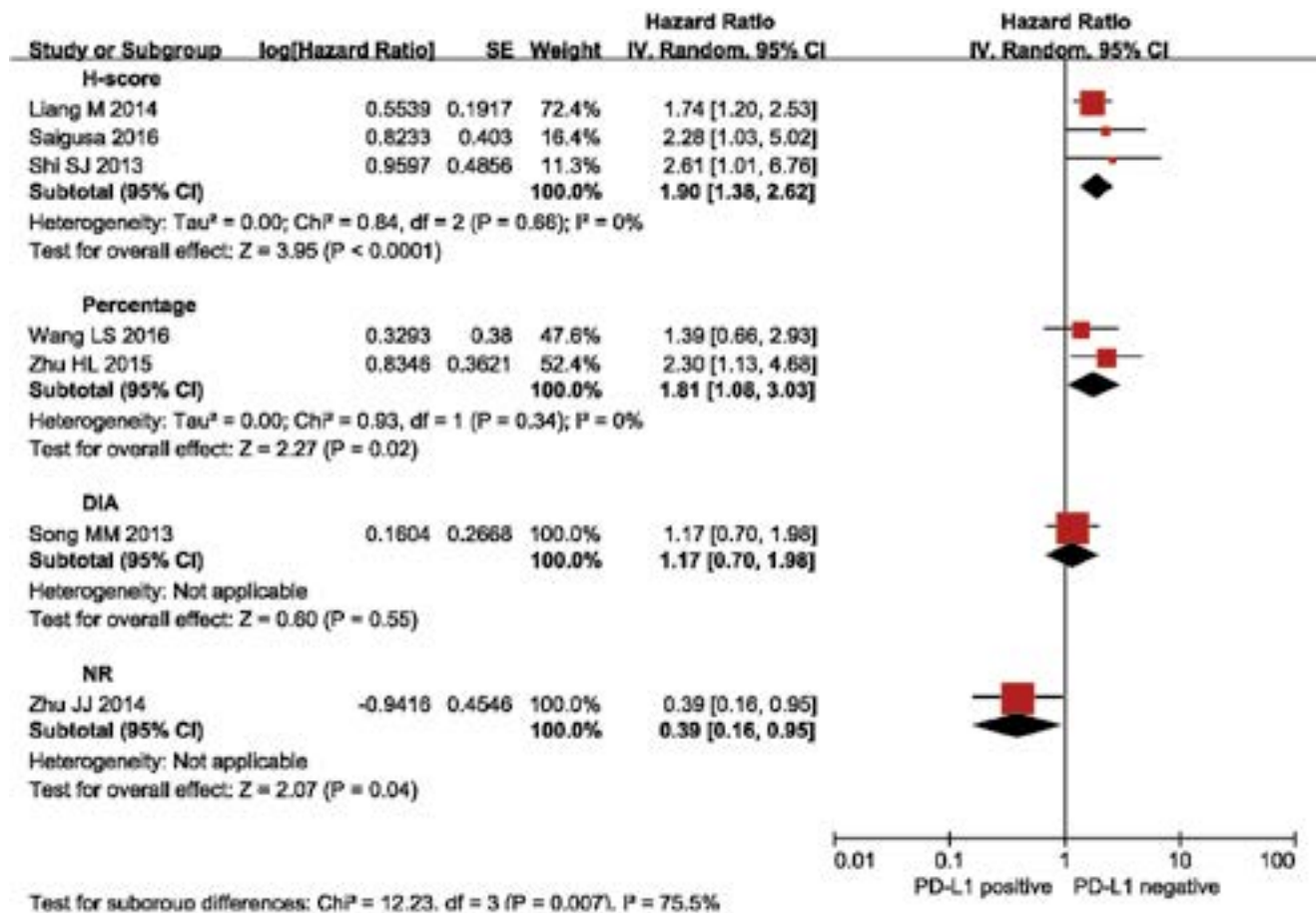

Fig. 4 Subgroup analysis of positive expression of PD-L1 on tumor cells according to IHC evaluation method.
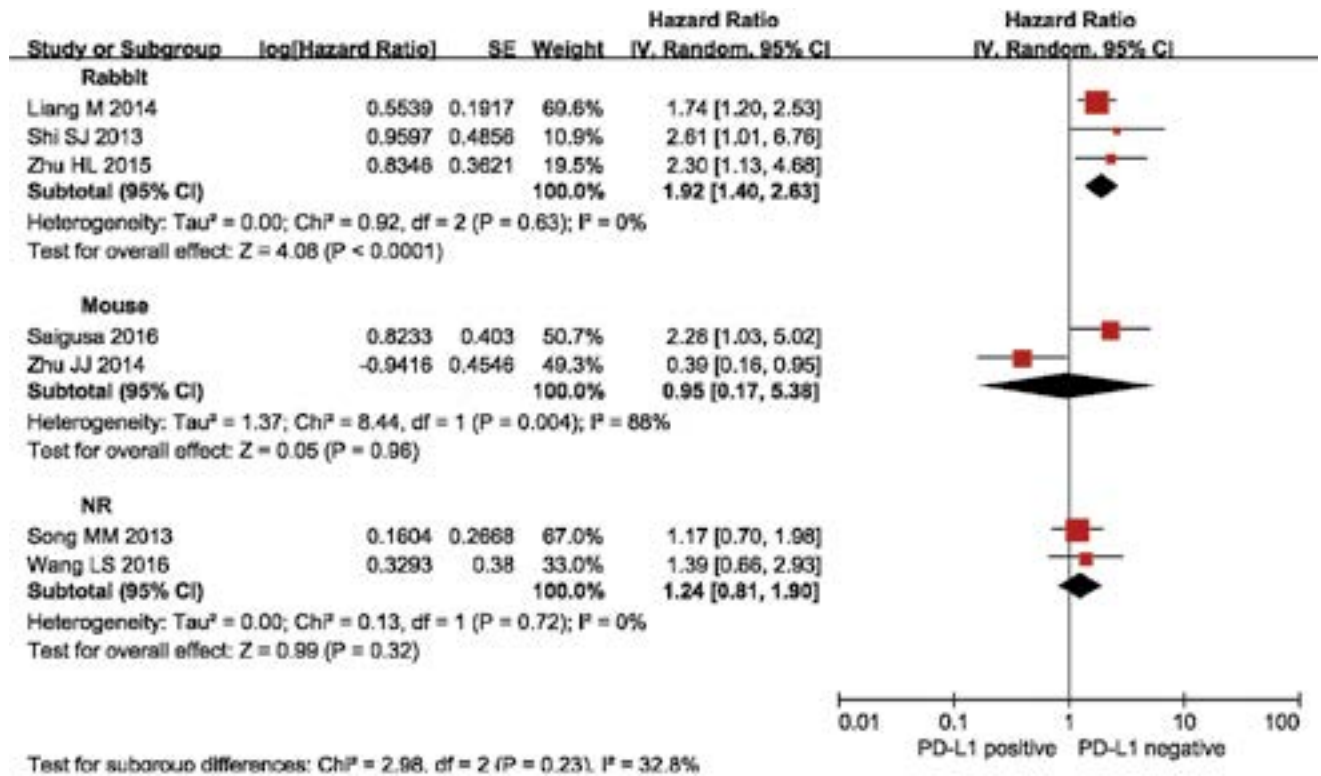
				Hazard Ratio	
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Rabbit					
Liang M 2014	0.5539	0.1917	69.6%	1.74 [1.20, 2.53]	
Shi SJ 2013	0.9597	0.4856	10.9%	2.61 [1.01, 6.76]	
Zhu HL 2015	0.8346	0.3621	19.5%	2.30 [1.13, 4.68]	
Subtotal (95% CI)			100.0%	1.92 [1.40, 2.63]	

Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 2 (P = 0.63); I² = 0%
Test for overall effect: Z = 4.08 (P < 0.0001)

Mouse					
Saigusa 2016	0.8233	0.403	50.7%	2.28 [1.03, 5.02]	
Zhu JJ 2014	-0.9416	0.4546	49.3%	0.39 [0.16, 0.95]	
Subtotal (95% CI)			100.0%	0.95 [0.17, 5.38]	

Heterogeneity: Tau² = 1.37; Chi² = 8.44, df = 1 (P = 0.004); I² = 88%
Test for overall effect: Z = 0.05 (P = 0.96)

NR					
Song MM 2013	0.1604	0.2668	67.0%	1.17 [0.70, 1.98]	
Wang LS 2016	0.3293	0.38	33.0%	1.39 [0.66, 2.93]	
Subtotal (95% CI)			100.0%	1.24 [0.81, 1.90]	

Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%
Test for overall effect: Z = 0.99 (P = 0.32)

0.01   0.1   1   10   100
PD-L1 positive   PD-L1 negative

Test for subgroup differences: Chi² = 2.98, df = 2 (P = 0.23), I² = 32.8%

Fig. 5 Subgroup analysis of the association between PD-L1 expression and different source of antibody.

				Hazard Ratio	
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
PAB					
Liang M 2014	0.5539	0.1917	86.5%	1.74 [1.20, 2.53]	
Shi SJ 2013	0.9597	0.4856	13.5%	2.61 [1.01, 6.76]	
Subtotal (95% CI)			100.0%	1.84 [1.30, 2.61]	

Heterogeneity: Tau² = 0.00; Chi² = 0.60, df = 1 (P = 0.44); I² = 0%
Test for overall effect: Z = 3.41 (P = 0.0006)

MAB					
Saigusa 2016	0.8233	0.403	24.9%	2.28 [1.03, 5.02]	
Wang LS 2016	0.3293	0.38	25.7%	1.39 [0.66, 2.93]	
Zhu HL 2015	0.8346	0.3621	26.3%	2.30 [1.13, 4.68]	
Zhu JJ 2014	-0.9416	0.4546	23.2%	0.39 [0.16, 0.95]	
Subtotal (95% CI)			100.0%	1.34 [0.63, 2.85]	

Heterogeneity: Tau² = 0.43; Chi² = 11.24, df = 3 (P = 0.01); I² = 73%
Test for overall effect: Z = 0.75 (P = 0.45)

NR					
Song MM 2013	0.1604	0.2668	100.0%	1.17 [0.70, 1.98]	
Subtotal (95% CI)			100.0%	1.17 [0.70, 1.98]	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.60 (P = 0.55)

0.01   0.1   1   10   100
PD-L1 positive   PD-L1 negative

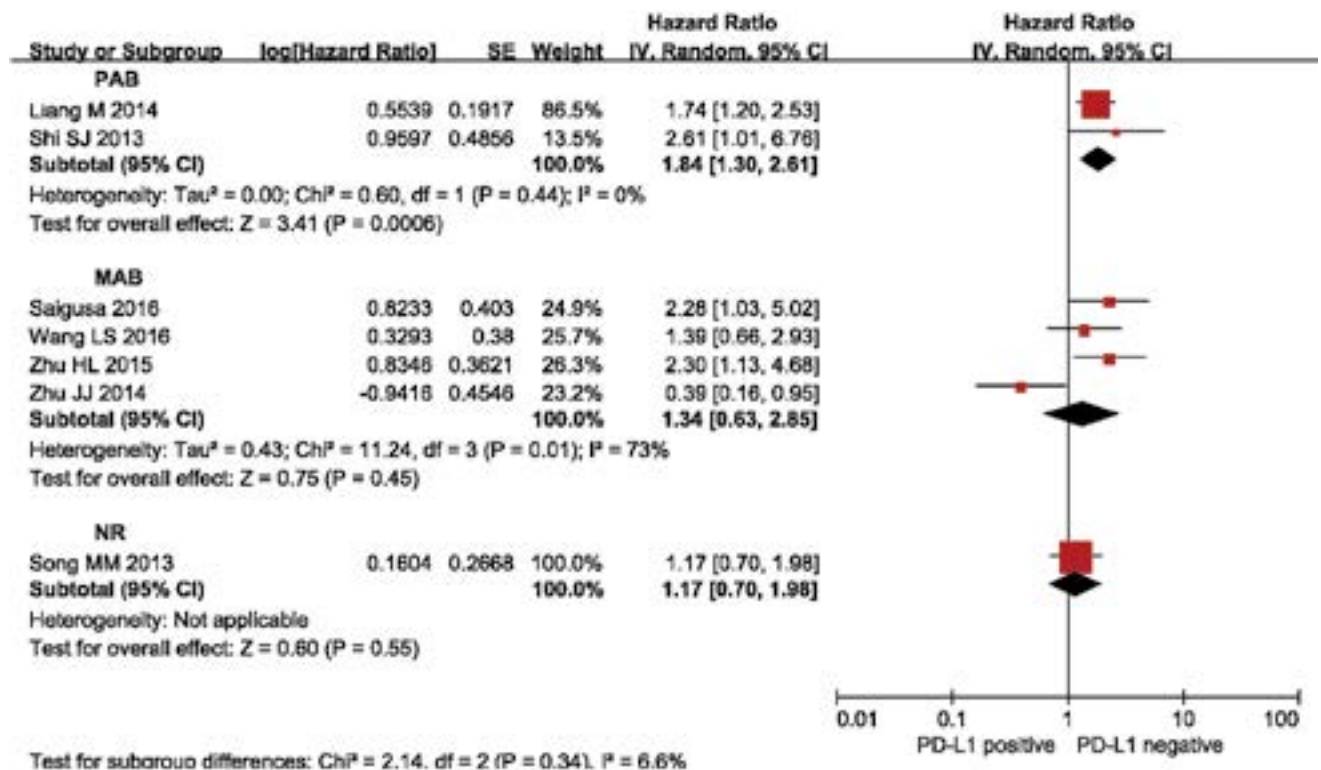Test for subgroup differences: Chi² = 2.14, df = 2 (P = 0.34), I² = 6.6%

Fig. 6 Subgroup analysis of the association between PD-L1 expression and different type of antibody.

Discussion

Recent studies have shown that PD-1/PD-L1 is highly expressed in a variety of human cancers [30–31]. High PD-1/PD-L1 expression may contribute to tumor immune evasion [32]. However, correlation between PD-1/PD-L1 expression levels and cancer progression remains a controversial subject. Previous studies have shown that PD-1/PD-L1 expression levels are indicators of poor prognoses for patients with renal cell carcinoma, gastric carcinoma, and pancreatic cancer [17].

Our meta-analysis explored the association between PD-L1 expression and prognosis for CRC patients. The results indicated that PD-L1 expression was associated with a poor prognosis for CRC. Moreover, subgroup analysis showed that positive PD-L1 expression was associated with poor prognosis for CRC patients when different antibodies or different IHC methods were used. As a whole, these results confirmed that PD-L1 plays a key role in cancer immune escape and that activation of the PD-L1 pathway had a profoundly adverse prognostic impact on CRC patients. Thus, therapies targeting PD-L1, such as blockading PD-L1, may improve antitumor immunity and display clinical responses in CRC patients expressing high PD-L1 levels.

PD-L1 and PD-1 were found to play an important role in cell proliferation, apoptosis, migration, and invasion, leading to the prevention of tumor destruction [10]. Results of previous studies have confirmed the role of PD-L1/PD-1 in CRC development [33]. Our results indicated that CRC patients with positive PD-L1 expression have a worse 5-year outcome. Previous studies reporting on OS demonstrated that PD-L1 overexpression and PD-1 expression were associated with prognoses for CRC patients [26-29]. Potential association between PD-L1/PD-1 expression and prognosis for other tumors has also been assessed by previous meta-analyses [10, 17]. PD-1 overexpression in non-small-cell lung cancer (NSCLC) was associated with a poor prognosis for NSCLC [34-35]. However, no significant correlation was found between PD-L1 expression and prognosis for NSCLC, suggesting that PD-L1 was not a prognostic predictor for NSCLC patients [10]. Differences between methods used in these studies, such as different methods of defining positive vs negative PD-L1/PD-1 expression and the use of different batches of PD-L1/PD-1 antibodies, may partly account for the contradictory results.

Subgroup analyses of IHC methods, definition of positive PD-L1 expression and the sources and types of primary antibodies used showed that both IHC evaluation methods and primary antibodies displayed a consistent prognostic correlation with overall results. Positive PD-L1 expression in tumor-infiltrating immune cells was associated with a worse prognosis compared with the negative PD-L1 expression group when both rabbit and PAB antibodies were used, as well as when both percentage evaluation method and H-score system were used. A previous study reported that positive PD-1 expression was an independent predictor for colorectal carcinoma prognosis when the H-score system was used as the IHC evaluation method [17]. Another study has indicated that PD-L1 expression was a prognostic indicator for CRC patients when digital image analysis was used as the IHC evaluation method [36]. These results implied that further studies with larger sample sizes might be needed to confirm the relationship between PD-L1/PD-1 expression and prognosis for CRC patients with different baseline characteristics.

In conclusion, our meta-analysis provided evidence that PD-L1 expression was an independent predictor of prognosis for CRC. Overexpression of PD-L1, as measured via IHC, was associated with a worse prognosis for CRC. These new findings have improved understanding of the association between PD-L1 and the progression of CRC. Moreover, antibody-mediated blockade of PD-L1 may represent a promising treatment target for CRC.

Conflict of interest

The authors declare that they have no conflict of interest.

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