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REVIEW

Prognostic and clinicopathological value of PD-L1 in colorectal cancer: a systematic review and meta-analysis

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Purpose: The prognostic role of programmed death-ligand 1 (PD-L1) in colorectal cancer remains unclear. We employed a meta-analysis to explore the prognostic value of PD-L1 and to ascertain the relationship between PD-L1 expression and clinicopathological characteristics in CRC patients.

Methods: We systematically searched PubMed, Embase and the Cochrane Library until October 2018. Eligible studies about colorectal cancer that pay attention to PD-L1 expression and studies reporting survival information were included. In order to evaluate the prognostic role of PD-L1 for overall survival (OS) and recurrence-free survival (RFS)/disease-free survival (DFS), Hazard ratio (HR) with 95% confidence interval (CI) was used. Odds ratio (OR) with 95% CI was selected to appraise the correlation between PD-L1 with clinicopathological characteristics of colorectal cancer patients. Begg's funnel plot was used to assess publication bias.

Results: Twelve studies involving 4344 patients published from 2013 to 2018 were included in this meta-analysis. Pooled results revealed that PD-L1 overexpression was relevant to shorter OS (HR 1.47, 95% CI =1.01–2.15, p=0.04) and shorter RFS/DFS (HR 1.47, 95% CI =1.01–2.15, p=0.04). Moreover, Patients with high expression of PD-L1 associated with inferior tumor stage (OR=0.57, 95% CI: 0.45, 0.74, p<0.0001) and Vascular invasion-negativity (OR=0.75, 95% CI: 0.6, 0.94, p=0.01). But the expression of PD-L1 is not related to age, sex, tumor location, tumor differentiation, pT stage, pN stage, MSI/MMR status.

Conclusion: This meta-analysis revealed that PD-L1 can serve as a significant biomarker for negative prognosis and the adverse clinicopathological features of colorectal cancer and could facilitate the better management of individual patients.

Keywords: PD-L1, colorectal cancer, prognosis, meta-analysis

Introduction

Colorectal cancer (CRC) is the most commonly diagnosed cancer worldwide at present, being the third and fifth leading cause of cancer death in the United States and China, respectively.[1,2] About 39% of patients were diagnosed with localized stage CRC, for which the 5-year survival rates is 90%. However, the patients diagnosed with the regional and distant-stage disease and the survival rate descend on 71% and 14%.[3] New treatments for primary, regional and metastatic CRC have been developed, including laparoscopic surgery for primary; resection of the liver and lungs metastatic disease; radiotherapy for rectal cancer and some forms of metastatic disease; neoadjuvant and palliative chemotherapy; targeted therapy,

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immunotherapy, and vaccines.[4,5] Therefore, it is critical to early detection, the effectiveness of prevention, and management to improving treatment strategies and patient outcomes.

However, some locally advanced and distant metastatic CRC patients lost the chance of surgery, so chemotherapy is basically the only option for advanced and metastatic patients; but these have only modest efficacy and are ineffective against distant metastases.[6,7] Moreover, these treatments generate side effects that can limit their use. In recent years, more attention has been placed on developing immunotherapies, specially programmed death 1 (PD-1) and programmed death ligand-1 (PD-L1).PD-1/PD-L1 is one of the most important co-stimulatory signals; its-mediated immunosuppression is an important part of the dynamic balance of the immune system because it limits the immune response and prevents autoimmune diseases. The present study found that *CD274* (PD-L1, B7-H1) was first cloned in 1999.[8] The expression profiles of *CD274* (PD-L1) in human tumors have been revealed.[9,10] Hunmantumor-associated APCs include tumor microenvironment dendritic cells (DCs), tumor-draining lymph nodes DCs,[11,12] macrophages,[13,14] fibroblasts,[15] and T cells[16] were observed a high level of *CD274* (PD-L1) protein expression, except tumor cell. Many studies have found that engagement of PD-L1 with its receptor PD-1 on T cells delivers a signal that inhibits T cell proliferation, resulting in tumor immune evasion.[17] PD-1/PD-L1 immune checkpoint inhibitors have been used to treat melanoma, non-small cell lung cancer, renal cell carcinoma, lymphoma, and bladder cancer.[18] However, the efficacy of immune checkpoint inhibitors for the treatment of CRC is limited. Different research has studied the PD-L1 expression of the prognosis role of CRC; nevertheless, the results were not consistent. Some investigations showed that overexpression of PD-L1 forecasted poor survival in CRC,[19–24] but other investigations presented negative results.[25,26]

To tackle this problem, we employed meta-analysis to synthetic estimate the value of PD-L1 as a prognostic biomarker, and to clarify the relationship between PD-L1 expression and clinicopathological characteristic in CRC patients.

Materials and methods

This meta-analysis is based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[30] Our research was based on data from previously published studies; thus ethical ratify was unnecessary.

Search strategy

The Cochrane Library, Embase and PubMed were systematically searched. The strategy used was to search for the following words in relevant literature: ("Colorectal Neoplasms" OR "Neoplasms, Colorectal" OR "Colorectal Neoplasm" OR "Neoplasm, Colorectal" OR "Colorectal Tumors" OR "Colorectal Tumor" OR "Tumor, Colorectal" OR "Tumors, Colorectal" OR"Colorectal Carcinoma" OR "Carcinoma, Colorectal" OR "Carcinomas, Colorectal" OR "Colorectal Carcinomas" OR "Colorectal Cancer" OR "Cancer, Colorectal" OR "Cancers, Colorectal" OR "Colorectal Cancers") AND ("*CD274*" OR "B7-H1" OR "PD-L1" OR "PD-L1" OR "*CD274* Antigens" OR "B7-H1 Immune Costimulatory Protein" OR "B7 H1 Immune Costimulatory Protein" OR "B7-H1 Antigen" OR "Antigen, B7-H1" OR "B7 H1 Antigen" OR "PD-L1 Costimulatory Protein" OR "Costimulatory Protein, PD-L1" OR "PD L1 Costimulatory Protein" OR "Programmed Cell Death 1 Ligand 1 Protein" OR "*CD274* Antigen" OR "Antigen, *CD274*" OR "Programmed Cell Death 1 Ligand 1" OR "B7H1 Immune Costimulatory Protein"). To recognize more research, we also retrospect the reference lists of relevant articles.

Selection criteria

The eligible researches were contained in this meta-analysis based on the following criteria: (1) Patients with colorectal cancer confirmed by pathology. (2) Immunohistochemistry (IHC) was used to detect the expression of PD-L1 in colorectal cancer tissue. (3) Studies reported 5-year OS, HR with 95% confidence interval (95% CIs), or reported original survival curves. (4) Their full texts were available. This analysis exclude articles based on the following standards: (1) non-English; (2) animal experiments; (3) comment, letters, review or case reports; (4) deficiency data to report the risk ratios (RR) and 95% confidence interval (95% CI), or the Kaplan-Meier curve could not be extracted. When duplicate publications were identified, only the most complete or most recent article was included.

Data extraction

All relevant articles data were extracted by two independent reviewers (Lianzhou Yang, Rujun Xue). The information was extracted from each study included: first author, country, date of publication, number of patients, duration of follow up, age, histological type of tumor, tumor site,

grade at diagnosis, number of patients with PD-L1 positive, cut-off value, antibody, survival data, Kaplan-Meier curves. ALL divergences were settled by discussion and the achievement of consensus.

Quality assessment

According to the Newcastle-Ottawa Scale (NOS), two researchers independently assessed each study for quality. (Lianzhou Yang, Rujun Xue). The NOS maximum possible score is 9 points. Each study included was judged on three perspectives: (I) the selection (representativeness, selection of the non-exposed, ascertainment of exposure and outcome of interest); (II) the comparability; and (III) the ascertainment of either the exposure or outcome of interest (assessment and follow-up). A study that received a score of 6 or higher was considered the high-quality study.

Statistical analysis

The software used in this work was Review Manager Software, Version 5.3 and Stata version12.0. The hazard ratio (HR) with 95% CI was utilized to assess the relationship between the expression of PD-L1 and OS, DFS, and RFS. The merged ORs and the 95% CIs were utilized to quantitatively determine the relationship between PD-L1 and clinicopathological feature of the patient. The heterogeneity between included studies was examined using I^2 and Q text. If $p<0.1$ or $I^2>50\%$, which demonstrated significant heterogeneity, the fixed effect model was used for meta-analysis. If there was significant heterogeneity, the random model was used. In this analysis, p-values <0.05 were considered statistically significant.

Results
Search results

After the primary retrieval, 675 potentially relevant articles were initially identified with three databases searched. After removing 156 duplicates, still 519 studies were identified for the title/abstract; however, 422 manuscripts were excluded for the following reasons: not original papers (eg, case report, review, and meta-analysis), animal studies, not colorectal cancer-related studies, not PD-L1-related studies, irrelevant, or were not published in English. Subsequently, 95 articles remained for further full-text assessment. Thereafter, 36 articles were excluded due to insufficient data, 2 articles lack of survival outcomes, 13 were no-original articles and 7 were unfinished clinical trials. Ultimately, twelve studies[19–26,31–34] were

published from 2013 to 2018 were included in this meta-analysis (Figure 1).

Characteristics of included studies

Twelve studies involving 4344 patients published from 2013 to 2018 were included in this meta-analysis. The number of patients in each study arranged from 90 to 1420. The immunochemical staining (IHC) was used to confirm PD-L1 expression oftumor tissues in all studies. Three pieces of research were performed in Western countries and nine kinds of research were implemented in Asian countries. The quality of the selected researches wasassessed by using the Newcastle-Ottawa Scale and found to range from 6 to 8, indicating that the studies were of high quality. Table 1 describes the detailed characteristics of the twelve studies.

Correlation between PD-L1 expression and survival

We evaluated the prognostic role of PD-L1 expression of OS, RFS, and DFS. Eight researches (n=3198) reported OS, as significant heterogeneity existed (Cochran's Q, $p<0.00001$, $I^2=88\%$).Pooled result by random model revealed high expression of PD-L1 was correlated with poor OS than the absence of PD-L1 expression (HR 1.47, 95% CI =1.01–2.15, $p=0.04$) (Figure 2A). Because heterogeneity existed, subgroup analysis was performed. Subgroup analysis based on different analytical methods, integrated HR for OS was 1.29 (95% CI: 0.90–1.86, $p=0.16$) (Figure 2B). Elucidating the effect of different cut-off of PD-L1 expression of the results, we performed subgroup analysis stratified by cut-off. When score<4 or cut-off ≤5% the heterogeneity was negligible, but there was no statistical significance in all subgroup between PD-L1 expression and overall survival (Figure 3A).

Seven (n=1697) reported RFS/DFS. As significant heterogeneity existed (Cochran's Q, $p<0.0001$, $I^2=80\%$). Pooled result by random model revealed PD-L1 overexpression was associated with shorter RFS/DFS than the absence of PD-L1 expression (HR 1.47, 95% CI =1.01–2.15, $p=0.04$) (Figure 2C). Because heterogeneity existed, subgroup analysis was performed. Subgroup analysis based on different analytical methods, integrated HR for RFS/DFS was 1.86 (95% CI: 1.10–3.14, $p=0.02$) (Figure 2D). Elucidating the effect of different cut-off of PD-L1 expression of the results, we performed subgroup analysis stratified by cut-off. When cut-off score <4 or
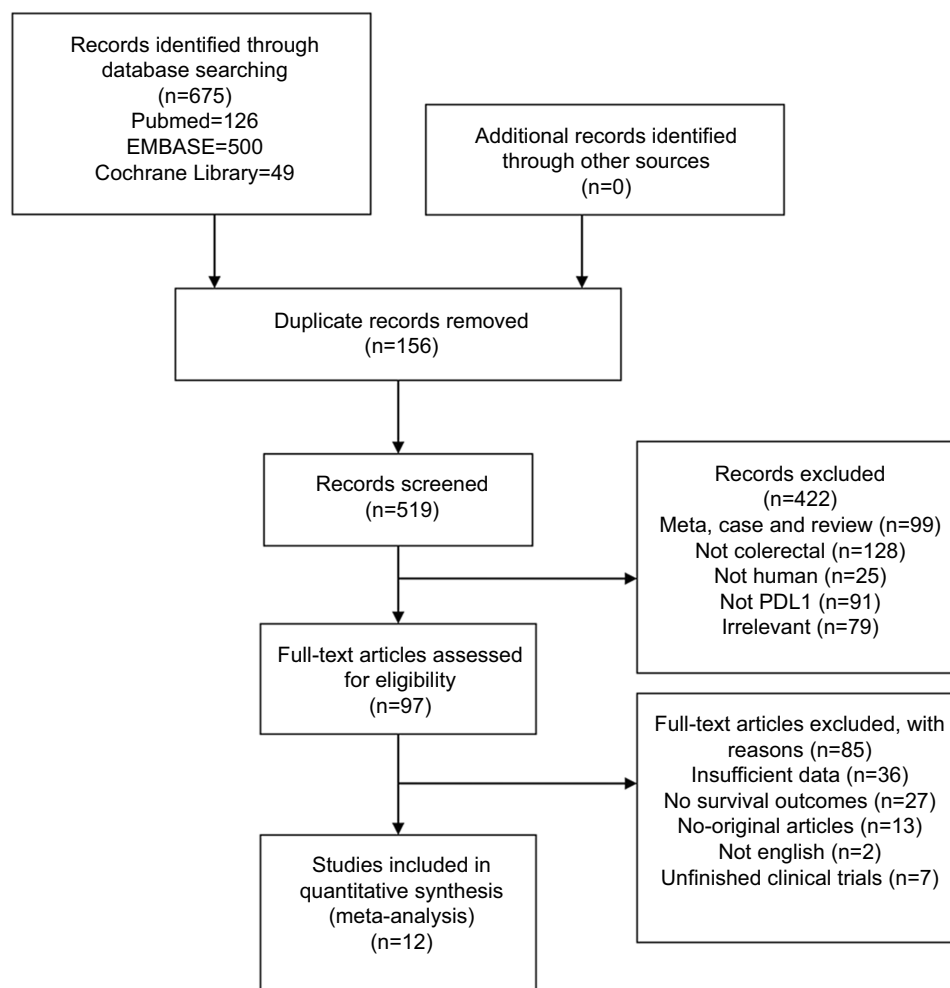
Figure 1 Flow chart of the literature search and study selection protocols.

≤5% the heterogeneity was negligible. There was no statistical significance in cut-off >5% or score >4 subgroups between PD-L1 expression and RFS/DFS (Figure 3B).

Correlation between PD-L1 expression and tumor clinicopathlogical parameters

Moreover, we investigated the relationship between PD-L1 expression and clinicopathological parameters, including sex, age, tumor location, tumor differentiation, tumor stage, pT stage, pN stage, vascular invasion, MSI/MMR status. The analysis of each parameter includes at least three studies. The merged results demonstrated that PD-L1 expression suggests in patients with poorer tumor stage (OR =0.57, 95%CI: 0.45, 0.74, $p<0.0001$) and Vascular invasion-negativity (OR =0.75, 95%CI: 0.6, 0.94, $p=0.01$) (Figure 4). However, there was no association between PD-L1 expression and age (OR =0.95, 95%CI: 0.73, 1.22, p=0.67), sex (OR =0.97, 95% CI: 0.84, 1.13, $p=0.72$), tumor location (OR =1.12, 95%CI:

0.87, 1.45, p=0.37), tumor differentiation (OR =1.18, 95%CI: 0.94,1.48, $p=0.15$), pT stage (OR =0.81, 95%CI: 0.44, 1.48, p=0.49), pN stage (OR =0.72, 95%CI: 0.44, 1.17, p=0.18), MSI/MMR status (OR =0.54, 95%CI: 0.16, 1.90, p=0.34) (Figure S1).

Sensitivity analyses

We delete any single study at a time individually, which to assess the stability of the results. The results show that there is no separate study significantly affected the total HRs, this meta-analysis of the results are credible.

Publication bias

The funnel plot did not indicate any evidence of publication bias (Figure 5).

Discussion

The PD-1/PD-L1 pathway has become a promising therapeutic target for various human malignancies, including

Table I Characteristics of the studies included in the meta-analysis

Study	Year	Country	Number of patients	Age	Study period	Follow up Median(M)	Detection method	Cut-off	Antibody	PD-LI positive/ negative	Quality assess-ment
Droeser et al[25]	2013	Switzerland	1420	69.9 (30–96)	1987–1996	-	IHC	Percentages of PD-LI staining intensity	Clone 27A2, ab82059	495/913	8
Hamada et al[19]	2017	USA	617	68.6±8.8	1976–2012	Patients were observed until death or January 1, 2012	IHC	Score^{3}2	Anti-CD274 antibody, eBioscience	384/233	8
Koganemaru et al[31]	2017	Japan	235	63 (32–84)	2009–2012	52.9 (4.6–78.8)	IHC	>5%	SP142	19/216	6
Lee et al[33]	2016	USA	395	55±15 (18–90)	-	55±40 (0.4–393)	IHC	>1%	Clone EIL3N	19/375	6
Li et al[26]	2016	China	276	57 (27–85)	2007–2009	61	IHC	Score^{3}4	ab174838	138/138	7
Liang et al[20]	2014	China	185	52 (29–72)	-	60	IHC	Score^{3}4	Polyclonal anti-bodies, Santa Cruz Biotechnology	102/83	6
Saigusa et al[21]	2016	Japan	90	64 (33–80)	2003–2014	46 (2–139)	IHC	Score^{3}2	Clone 27A2	36	6
Shi et al[22]	2013	China	143	59.8±12.5	2006–2007	43 (1–56)	IHC	Presence of PD-LI staining	Abcam, ab58810	64	6
Song et al[23]	2013	China	347	65	2000–2006	(1–122)	IHC	Score^{3}1.49, ran-ged from 0 to 15.9 (median: 2.33)	Abcam	-	8
Wang et al[32]	2017	China	254	56 (28–75)	2007–2009	42 (21–68)	IHC	Percentages of PD-LI staining intensity	sp142	46/208	7
Wang et al[34]	2016	China	262	56.5 (28–75)	2007–2009	43.5 (21–68)	IHC	>5%	SP142	54/208	8
Zhu et al[24]	2015	China	120	67 (54–80)	2008–2013	39	IHC	Score^{3}4	Abcam	28	7
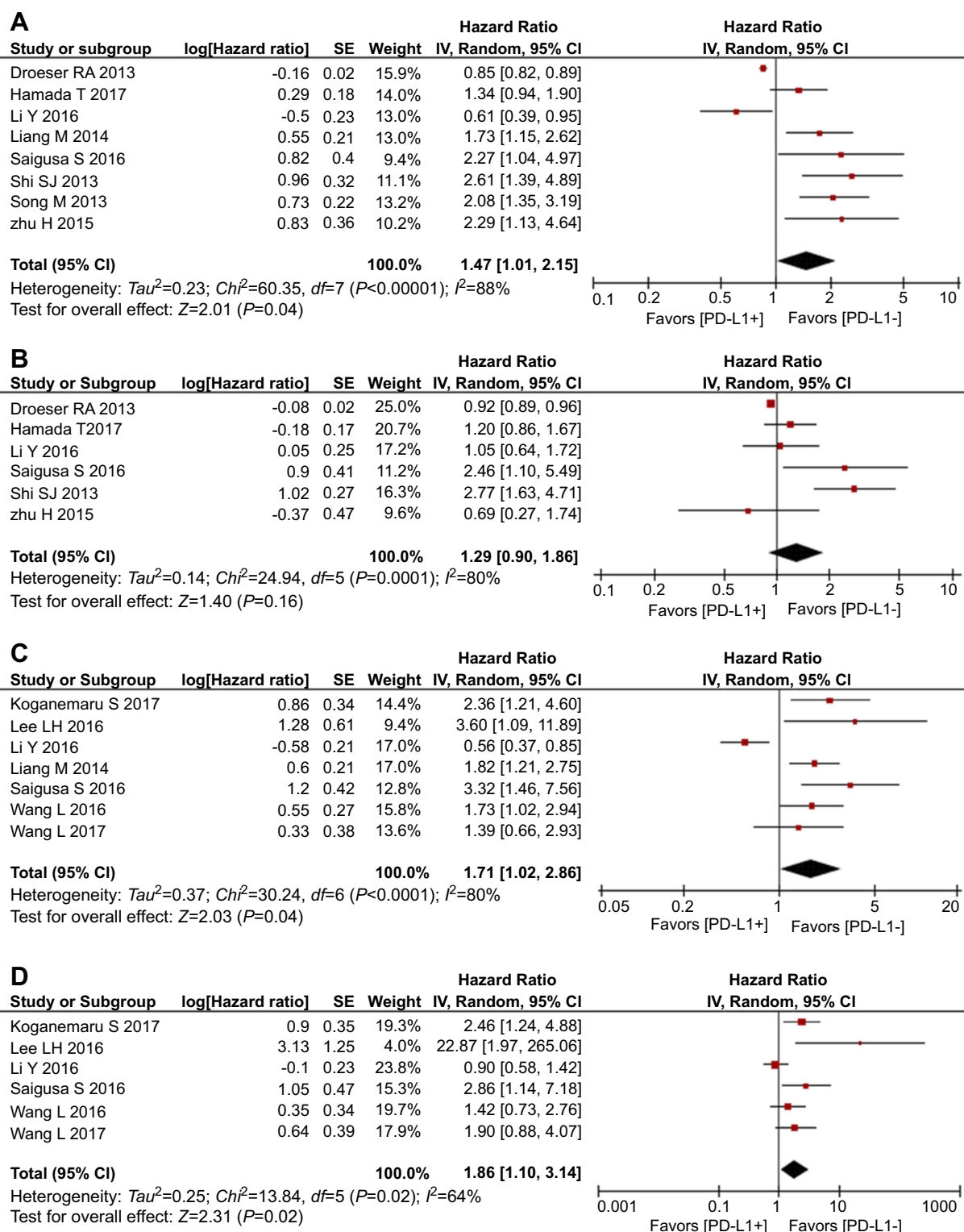
Figure 2 Forest plot describing the association between PD-L1 expression and prognosis of patients with CRC patient. (**A**) OS; (**B**) OS by multivariate analysis; (**C**) RFS/DFS; (**D**) RFS/DFS by multivariate analysis.

melanoma, non-small-cell lung cancer, head and neck cancer, Hodgkin's lymphoma, gastric cancer, and urothelial cancer. Some clinical trials have shown that PD-1/PD-L1 blockage could benefit prognosis.[35–39]

Nonetheless, there are no consistent results for the prognostic value of PD-L1 in colorectal cancer patients. Lots researches have indicated that the expression of PD-L1 is correlated with an obviously poor survival,[19,10–24] while

A

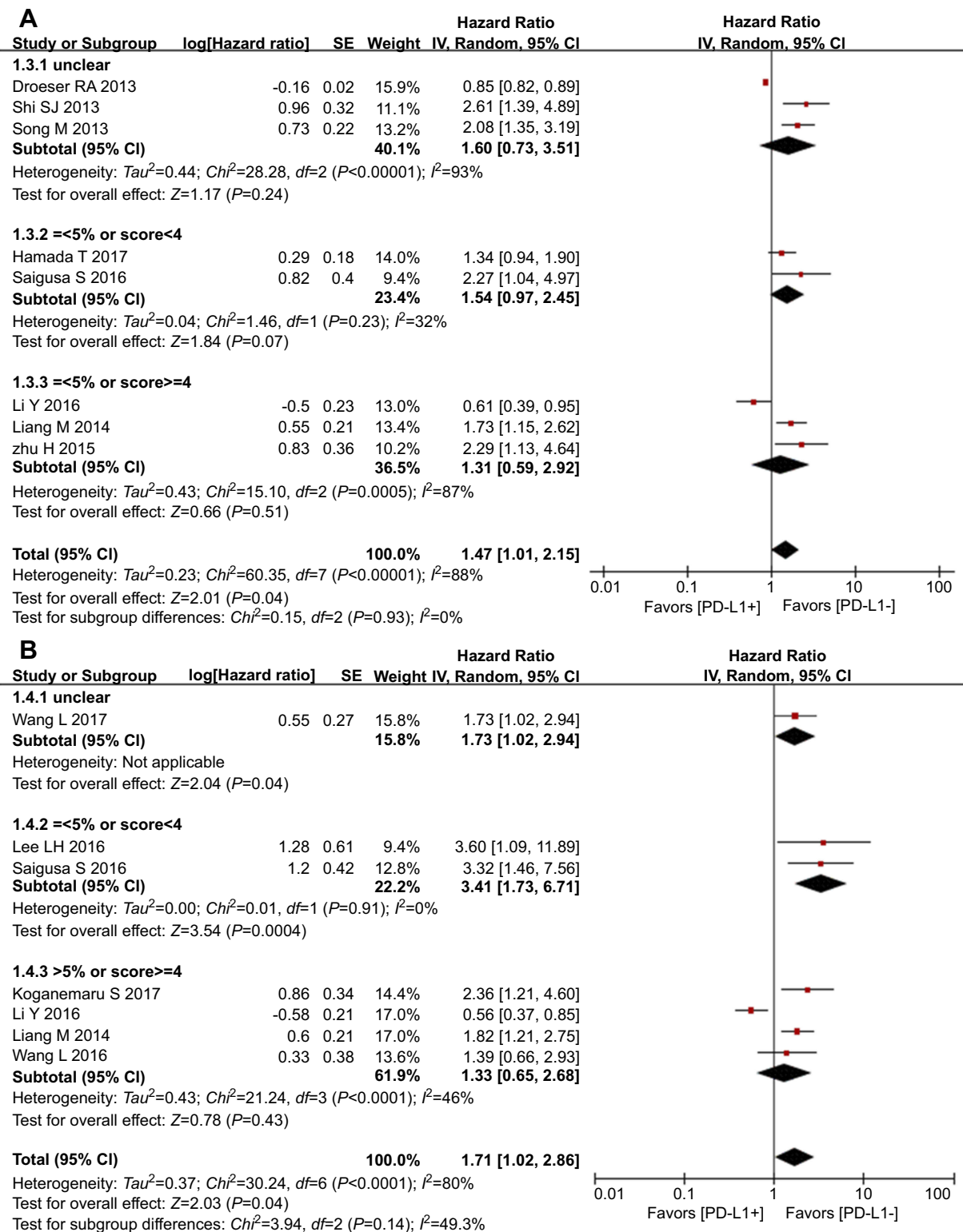| Study or Subgroup	log[Hazard ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
1.3.1 unclear				
Droeser RA 2013	-0.16	0.02	15.9%	0.85 [0.82, 0.89]
Shi SJ 2013	0.96	0.32	11.1%	2.61 [1.39, 4.89]
Song M 2013	0.73	0.22	13.2%	2.08 [1.35, 3.19]
Subtotal (95% CI)			**40.1%**	**1.60 [0.73, 3.51]**
Heterogeneity: Tau^2=0.44; Chi^2=28.28, df=2 (P<0.00001); I^2=93%				
Test for overall effect: Z=1.17 (P=0.24)				
1.3.2 =<5% or score<4				
Hamada T 2017	0.29	0.18	14.0%	1.34 [0.94, 1.90]
Saigusa S 2016	0.82	0.4	9.4%	2.27 [1.04, 4.97]
Subtotal (95% CI)			**23.4%**	**1.54 [0.97, 2.45]**
Heterogeneity: Tau^2=0.04; Chi^2=1.46, df=1 (P=0.23); I^2=32%				
Test for overall effect: Z=1.84 (P=0.07)				
1.3.3 =<5% or score>=4				
Li Y 2016	-0.5	0.23	13.0%	0.61 [0.39, 0.95]
Liang M 2014	0.55	0.21	13.4%	1.73 [1.15, 2.62]
zhu H 2015	0.83	0.36	10.2%	2.29 [1.13, 4.64]
Subtotal (95% CI)			**36.5%**	**1.31 [0.59, 2.92]**
Heterogeneity: Tau^2=0.43; Chi^2=15.10, df=2 (P=0.0005); I^2=87%				
Test for overall effect: Z=0.66 (P=0.51)				
Total (95% CI)			**100.0%**	**1.47 [1.01, 2.15]**
Heterogeneity: Tau^2=0.23; Chi^2=60.35, df=7 (P<0.00001); I^2=88%				
Test for overall effect: Z=2.01 (P=0.04)				
Test for subgroup differences: Chi^2=0.15, df=2 (P=0.93); I^2=0%				

Hazard Ratio IV, Random, 95% CI
0.01 0.1 1 10 100
Favors [PD-L1+] Favors [PD-L1-]

B

Study or Subgroup	log[Hazard ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
1.4.1 unclear				
Wang L 2017	0.55	0.27	15.8%	1.73 [1.02, 2.94]
Subtotal (95% CI)			**15.8%**	**1.73 [1.02, 2.94]**
Heterogeneity: Not applicable				
Test for overall effect: Z=2.04 (P=0.04)				
1.4.2 =<5% or score<4				
Lee LH 2016	1.28	0.61	9.4%	3.60 [1.09, 11.89]
Saigusa S 2016	1.2	0.42	12.8%	3.32 [1.46, 7.56]
Subtotal (95% CI)			**22.2%**	**3.41 [1.73, 6.71]**
Heterogeneity: Tau^2=0.00; Chi^2=0.01, df=1 (P=0.91); I^2=0%				
Test for overall effect: Z=3.54 (P=0.0004)				
1.4.3 >5% or score>=4				
Koganemaru S 2017	0.86	0.34	14.4%	2.36 [1.21, 4.60]
Li Y 2016	-0.58	0.21	17.0%	0.56 [0.37, 0.85]
Liang M 2014	0.6	0.21	17.0%	1.82 [1.21, 2.75]
Wang L 2016	0.33	0.38	13.6%	1.39 [0.66, 2.93]
Subtotal (95% CI)			**61.9%**	**1.33 [0.65, 2.68]**
Heterogeneity: Tau^2=0.43; Chi^2=21.24, df=3 (P<0.0001); I^2=46%				
Test for overall effect: Z=0.78 (P=0.43)				
Total (95% CI)			**100.0%**	**1.71 [1.02, 2.86]**
Heterogeneity: Tau^2=0.37; Chi^2=30.24, df=6 (P<0.0001); I^2=80%				
Test for overall effect: Z=2.03 (P=0.04)				
Test for subgroup differences: Chi^2=3.94, df=2 (P=0.14); I^2=49.3%				

Hazard Ratio IV, Random, 95% CI
0.01 0.1 1 10 100
Favors [PD-L1+] Favors [PD-L1-]

Figure 3 (**A**) Subgroup analysis based on a different cut-off of association between PD-L1 expression and OS. (**B**) Subgroup analysis based on a different cut-off of association between PD-L1 expression and RFS/DFS.

some study accounted the opposite effect.[25,26] Several studies have revealed the relationship between PD-L1 and Solid Tumors.[27–29] However, those studies differs from our in that their subjects include all solid tumors in which the number of colorectal cancers included too few, and our study provides an in-depth analysis between PD-
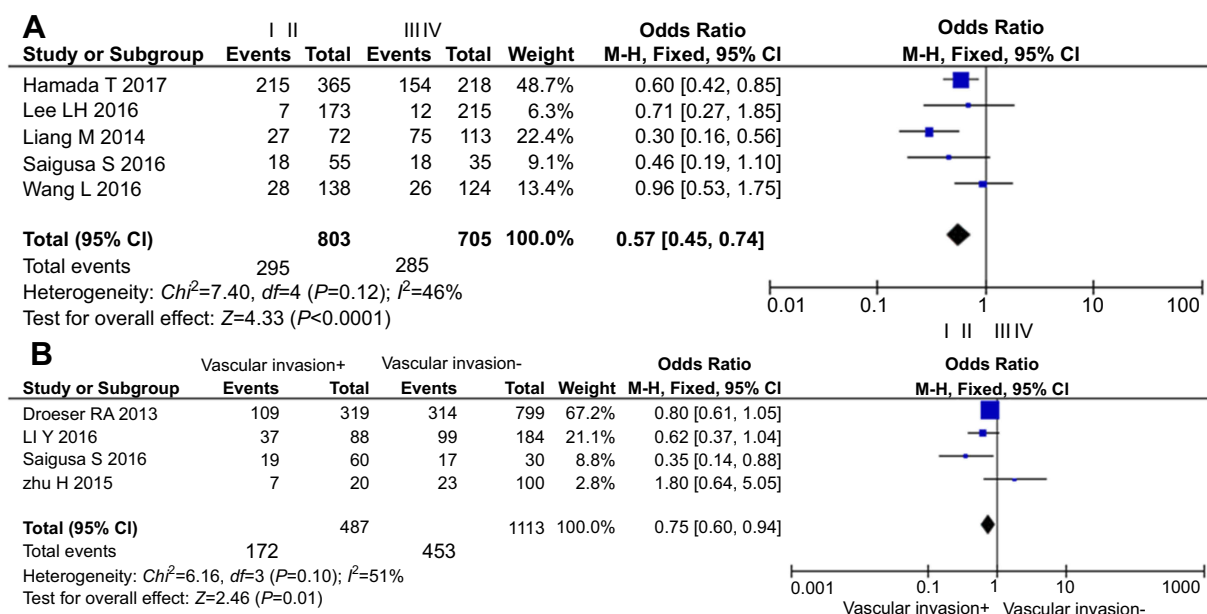
A

Study or Subgroup	I II Events	Total	III IV Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Hamada T 2017	215	365	154	218	48.7%	0.60 [0.42, 0.85]
Lee LH 2016	7	173	12	215	6.3%	0.71 [0.27, 1.85]
Liang M 2014	27	72	75	113	22.4%	0.30 [0.16, 0.56]
Saigusa S 2016	18	55	18	35	9.1%	0.46 [0.19, 1.10]
Wang L 2016	28	138	26	124	13.4%	0.96 [0.53, 1.75]
Total (95% CI)		803		705	100.0%	0.57 [0.45, 0.74]
Total events	295		285			

Heterogeneity: Chi^2=7.40, df=4 (P=0.12); I^2=46%
Test for overall effect: Z=4.33 (P<0.0001)

Odds Ratio M-H, Fixed, 95% CI

I II III IV

B

Study or Subgroup	Vascular invasion+ Events	Total	Vascular invasion- Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Droeser RA 2013	109	319	314	799	67.2%	0.80 [0.61, 1.05]
LI Y 2016	37	88	99	184	21.1%	0.62 [0.37, 1.04]
Saigusa S 2016	19	60	17	30	8.8%	0.35 [0.14, 0.88]
zhu H 2015	7	20	23	100	2.8%	1.80 [0.64, 5.05]
Total (95% CI)		487		1113	100.0%	0.75 [0.60, 0.94]
Total events	172		453			

Heterogeneity: Chi^2=6.16, df=3 (P=0.10); I^2=51%
Test for overall effect: Z=2.46 (P=0.01)

Odds Ratio M-H, Fixed, 95% CI

Vascular invasion+ Vascular invasion-

Figure 4 Forest plots for the association between PD-L1 expression and clinicopathological parameters. (**A**) Tumor stage; (**B**) vascular invasion-negativity.
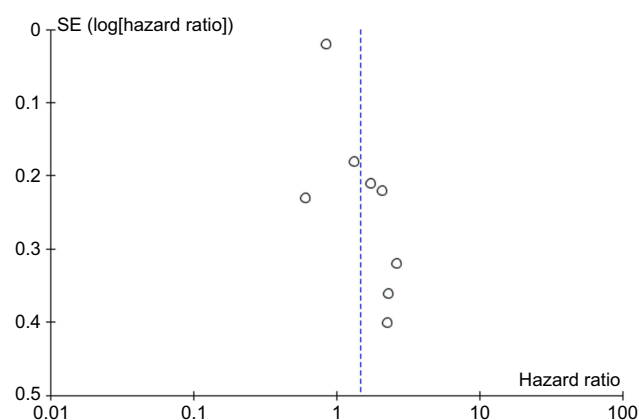
Figure 5 Funnel plot of publication bias for overall survival.

L1 expression and tumor stage, vascular invasion, MSI/MMR mutation, etc. In our meta-analysis, we concentrate on the clinicopathological characteristics of patients with colorectal cancer and the prognostic validity of PD-L1 in colorectal cancer.

The interaction between PD-L1 and PD-1 can lead to exhausted phenotype and dysfunction of T-cells which protected tumor cells escape from the host immune surveillance.[40] Immune-checkpoint blockades become a new way in immunotherapy for cancer and it gradually changes the standard treatment of advanced-stage cancers. According to reports, overexpression of PD-1 and PD-L1 on tumor-infiltrating lymphocytes (TIL) and tumor cells (TC) correlates with poor prognosis in several cancers.[41]

Such as breast cancer,[42] renal cell cancer,[43] lung cancer,[44] glioma.[45] In colorectal cancer, this is in agreement with the study by Hamada et al,[19] which indicated the association of PD-L1 overexpression and poor OS in CRCs (HR 1.33, 95% CI 0.94–1.89). Additionally, Song et al,[23] using tissue microarray immunohistochemistry to detect 404 CRC patient samples, univariate analysis disclosed that patients overexpression of PD-L1 had poorer overall survival (p<0.001; HR =2.07 (1.342–3.193). But, multivariate analysis did not support PD-L1 as an independent prognostic factor (p=0.548). Otherwise, some similar studies have revealed similar results. In contrast, a study of Droeser et al,[25] which involved 1420 CRCs patients, found the patients with MMR-proficient with PD-L1 overexpression correlated with better OS (p=0.003; HR =0.84 (0.79–0.88); In univariate analysis, PD-L1 overexpression in MMR-proficient CRC was significantly correlated with early T stage, absence of lymph node metastases, lower tumor grade, absence of vascular invasion. Moreover, in the study by Li et al,[26] this involved two cohorts; In the TCGA cohort, higher PD-L1 expressions indicated a better OS (p=0.002). In FUSCC cohort, expressions of PD-L1 on tumor cells were associated with better OS (p=0.002) and DFS (p=0.004) of CRC patients. Therefore, a meta-analysis of available data on the prognostic significance of PD-L1 will be useful and imperatively needed.

In this meta-analysis, we synthesized twelve pieces of research relevant to prognosis and clinicopathological of PD-

L1 expression in colorectal cancer. As we know, this is the first meta-analysis focus on the prognosis and clinicopathological characteristics of patients with colorectal cancer. Our data indicated that PD-L1 overexpression was associated with shorter OS (HR 1.47, 95% CI =1.01–2.15, p=0.04) and shorter RFS/DFS (HR 1.47, 95% CI =1.01–2.15, p=0.04), suggesting that PD-L1 expression could serve as an important prognostic factor for colorectal cancer. Related research shows that immune evasion caused by PD-1/PD-L1 pathway may be related to poor infiltration of T cells into tumors and lack activation of cancer-specific T cells in the tumor microenvironment.[46] Moreover, PD-L1 overexpression was increased in patients with inferior tumor stage (OR=0.57, 95%CI: 0.45, 0.74, p<0.0001) and Vascular invasion-negativity (OR=0.75, 95%CI: 0.6, 0.94, p=0.01). For the present study, we didn't find relationship between PD-L1 expression and age, gender, tumor location, tumor differentiation, pT stage, pN stage, MSI/MMR status.

There were several limitations to our study. Some significant heterogeneity can be observed in our study. These heterogeneities may have different sources. Firstly, only articles published in English were included in this meta-analysis. Secondly, the sample sizes of the studies enrolled in our analysis were comparatively small. Third, PD-L1 positivity was evaluated by using different antibody and dilution which affect the sensitivity of IHC. Fourth, the cut-off value where PD-L1 expressed was varied among the studies. So, future researches should make efforts in the standardization of PDL1 expression detection. Additionally, because not all study hasa distinction about MSI/MMR status and not provide sufficient information which may bring heterogeneity to the meta-analysis. Based on our observations, we believe that the results of our meta-analysis should be noticed and should be validated by additional studies with appropriate multivariate analyses.

Our investigation exhibited that the overexpression of PD-L1 indicates a poor prognosis and clinicopathological features and that treatment with anti-PD-L1 antibodies should be attempted in patients with CRCs patient in the future.

Disclosure

The authors report no conflicts of interest in this work.

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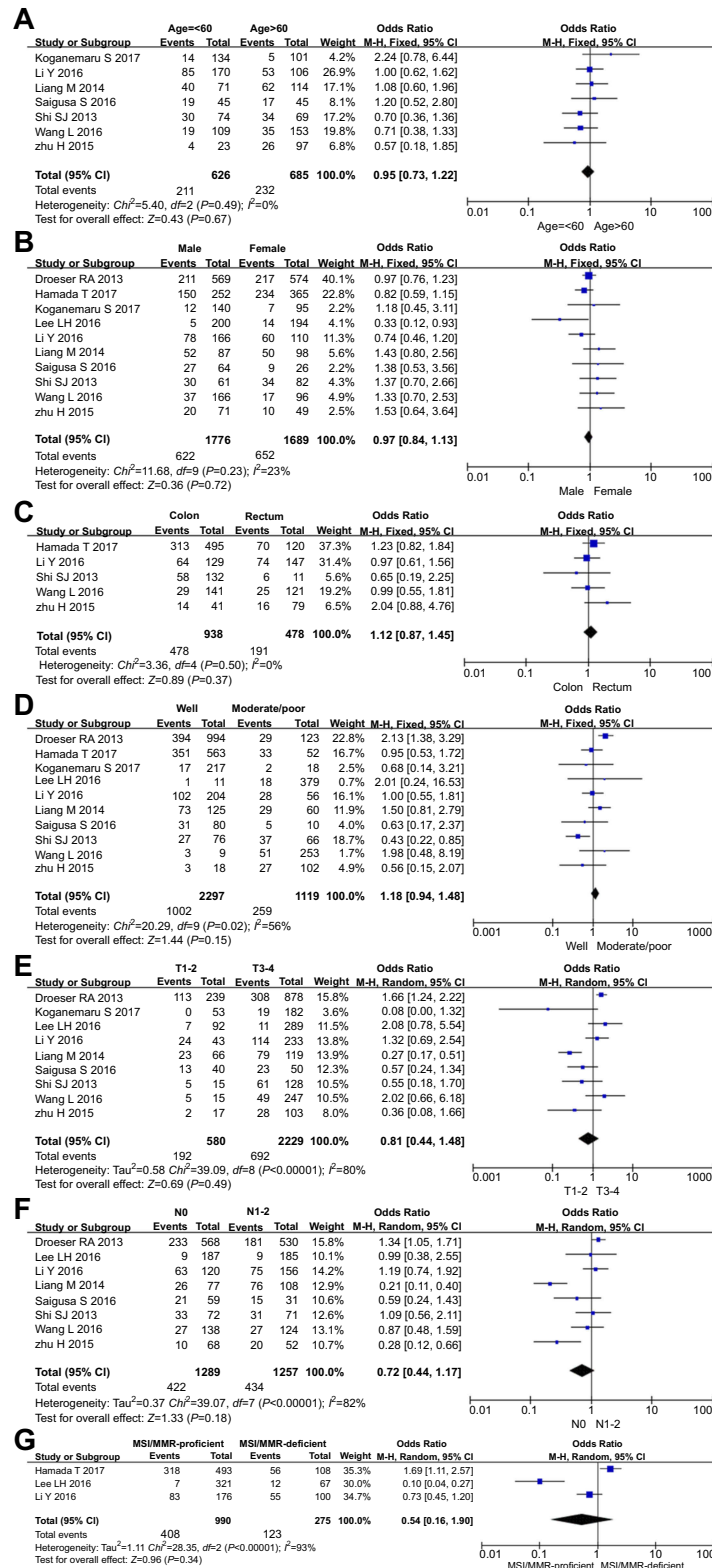
Supplementary material

Figure S1 Forest plots for the association between PD-L1 expression and clinicopathological parameters. (A) Age; (B) sex; (C) tumor location; (D) tumor differentiation; (E) pT stage; (F) pN stage; and (G) MSI/MMR status.

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