ORIGINAL ARTICLE



Clinicopathological and prognostic significance of PD-L1 expression in colorectal cancer: a meta-analysis

Shuxia Wang¹ · Bo Yuan² · Yun Wang¹ · Mingyang Li¹ · Xibo Liu¹ · Jing Cao¹ · Changtian Li² · Jihong Hu³

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Abstract

Purpose To systematically evaluate the correlation between PD-L1 expression and clinicopathological features and prognosis of colorectal cancer (CRC).

Methods Seven databases (PubMed, Cochrane Library, EMBASE, Web of Science, CBM, Wanfang, and CNKI) were searched through May 2020. Risk of bias and quality of evidence were assessed by using the Newcastle–Ottawa scale (NOS), and meta-analysis was carried out by using the Review Manager 5.3 software on the studies with the quality evaluation scores ≥ 6 . Meta-regression analysis was used to determine the independent role of PD-L1 expression on CRC prognosis after adjusting clinico-pathological features and treatment methods.

Results A total of 8823 CRC patients in 32 eligible studies. PD-L1 expression was correlated with lymphatic metastasis (yes/no; OR = 1.24, 95% CI (1.11, 1.38)), diameter of tumor (\geq 5 cm/< 5 cm; OR = 1.34, 95% CI (1.06, 1.70)), differentiation (high-middle/low; OR = 0.68, 95% CI (0.53, 0.87)), and vascular invasion (yes/no; OR = 0.80, 95% CI (0.69, 0.92)). PD-L1 expression shortened the overall survival (hazard ratio (HR) = 1.93, 95% CI (1.66, 2.25)), disease-free survival (HR = 1.76, 95% CI (1.50, 2.07)), and progression-free survival (HR = 1.93, 95% CI (1.55, 2.41)). Meta-regression showed that PD-L1 expression played a significant role on poor CRC OS (HR = 1.95, 95% CI (1.92, 3.98)) and disease-free survival (HR = 2.14, 95% CI (0.73, 4.52)). **Conclusion** PD-L1 expression independently predicted a poor prognosis of CRC.

Keywords Programmed death ligand-1 (PD-L1) \cdot Colorectal cancer (CRC) \cdot Prognosis \cdot Clinicopathological features \cdot Meta-analysis

Introduction

Colorectal cancer (CRC) is one of the most common malignant tumors of the digestive system all around the world [1]. Its incidence and mortality rate ranked third and

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second in the world, respectively [2]. In 2018, both new cases and deaths were close to 30% of the total number of CRC cases in the world [3, 4]. China's cancer statistics indicated that the incidence and mortality of CRC ranked fifth among all malignant tumors in China, bringing about 380,000 new cases and 190,000 deaths annually [5]. Furthermore, most patients have already been in the severe stage when they were seeking the medical examination [6, 7]. Thus, it has become a major public health problem in many countries [8, 9].

Surgery, chemotherapy, and radiation therapy are the main treatments for cancer; unfortunately, the recurrence rate and metastasis rate (approximately 30% and 10%) in advanced CRC patients still remain high [10, 11]. In addition, some treatments showed only mild effects in reducing tumor load, such as cytokine therapy, toll-like receptors, and autologous cell therapy [12]. In recent years, immune card control point drugs have provided a new therapy for CRC, especially the programmed death 1 (PD-1)/programmed death ligand-1(PD-

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L1) monoclonal antibody as an immunodetection point inhibitor and an antibody-type tumor immune drug [13, 14]. PD-L1, also known as CD274 or B7-H1, is the ligand PD-1 and a sort of immune checkpoint inhibitors and belongs to the CD28 family and is expressed on the surface of activated T cells to regulate proliferation and activation [15]. The binding of PD-L1 on tumor cells to PD-1 on lymphocytes can lead to immune escape of tumor cells and ultimately promote the generation and development of tumors by inhibiting the release of cytokines, restricting lymphocyte function, and inducing lymphocyte apoptosis [16]. It was reported that PD-L1 correlated with the clinicopathological features and affected the prognosis of cancers (such as breast, gastric, and ovarian cancers) [17–19].

The correlation between PD-L1 expression and clinicopathological features of CRC was inconsistent, and the independent impacts of PD-L1 expression on CRC prognosis were unclear in the previous meta-analyses [20–23]. Additionally, some limitations reduced the reliability because of small sample sizes [21, 23] or the high heterogeneity [21, 23] or incorrect model selection [21, 23]. Thus, we aimed to update a meta-analysis of cohort studies to confirm the correlation between PD-L1 expression and clinicopathological features, and perform a meta-regression analysis to determine the independent role of PD-L1 on CRC prognosis after adjusting confounders.

Materials and method

Search strategy

Seven databases (PubMed, Cochrane Library, EMBASE, Web of Science, CBM, Wanfang, and CNKI) were searched through May 2020, and the search strategies were ("PD-L1" OR" B7-H1" OR "Programmed Cell Death Ligand 1" OR "CD274" OR "PD-1" OR "Programmed death 1") AND ("Colorectal Cancer" OR "Colorectal Neoplasm" OR "Colorectal Tumor" OR "Colorectal Carcinoma" OR "Colorectal Cancer" OR "Rectal Cancer" OR "Colon Cancer" OR "Rectal Neoplasm" OR "Colon Neoplasm"). Furthermore, we reviewed the reference list of original and review articles to search for more studies. Only studies that were published as full articles and in Chinese and English were considered.

Inclusion and exclusion criteria

Inclusion criteria for study enrollment were (1) cohort studies; (2) patients had confirmed colorectal cancer; (3) PD-L1 expression detected method: immunohistochemistry (IHC); (4) the literature provides the relationship between PD-L1 expression and clinicopathological features, such as sex, age, lymphatic metastasis, differentiation, TNM stage, and tumor location; (5) studies that provided detailed pathological parameters and survival





Cutoff	Score ≥ 2 (intensity)	>50% positive cells	≥1% TC staining	≥5% TC staining	NA	Score > 3 (area and intensity)	NA	Score > 4 (area and intensity)	NA	NA	NA	≥5% TC staining	NA	NA	NA	NA	NA	Score ≥ 2 (intensity)	≥5% TC staining	NA	NA	NA
HR and 95% CI	1.999 (0.846, 4.725)	1.274 (0.852, 1.904), 1.586 (1.069, 2.353)	$0.530\ (0.390,\ 0.720)$	$1.370 \ (1.080, \ 1.740)$	$0.920\ (0.880,\ 0.960)$	$\begin{array}{c} 1.913 \; (0.811, 4.516), 3.873 \\ (1.193, 12.571) \end{array}$	3.180 (1.642, 6.156)	0.692 (0.277, 1.729)	2.914 (1.307, 4.697), 4.267 (1.144, 15.917)	1.645 (0.809, 3.346)	0.863 (0.333, 2.235), 1.095 (0.382, 3.143)	2.450 (1.239, 4.847)	NA	3.504 (1.461, 8.406), 3.785 (1.447, 9.898)	3.600 (1.080, 12.000)	$0.325\ (0.108,\ 0.794)$	$1.830 \ (1.090, \ 3.050)$	$1.200\ (0.350, 4.040), 1.180\ (0.630, 2.230)$	2.070 (1.342, 3.193)	1.831 (1.214, 2.806), 1.740	(1.195, 2.713) 2.771 (1.048, 2.994)	3.311 (1.444, 7.591), 2.278 (1.034, 5.016)
Outcome	DFS	DFS, OS	SO	DFS	SO	DFS, OS	SO	SO	DFS, OS	PFS	PFS, OS	DFS	PFS	DFS, OS	DFS	DFS	PFS	DFS, OS	SO	DFS, OS	PFS, OS	PFS, OS
Follow-up duration (months)	NA	88	60	NA	NA	60	NA	NA	35	60	36	72	24	52	55	60	60	60	30	60	60	6-12
Detection methods for PD-L1 expression	IHC	IHC	IHC	IHC	IHC	IHC	IHC	IHC	IHC	IHC	IHC	IHC	IHC	IHC	IHC	IHC	IHC	IHC	IHC	IHC	IHC	IHC
Treatment	Surgery + CRT	Surgery + CRT	Surgery	Surgery	Surgery	Surgery + CRT	Surgery	Surgery	Surgery	Surgery	Surgery + CRT	Surgery + CRT	Surgery	Surgery + CRT	Surgery + CRT	Surgery	Surgery	Surgery	Surgery	Surgery	surgery	Surgery + CRT
Type TNM stage	RC LIV	CRC I-IV	CRC I-IV	CC II–III	CRC I-IV	CRC II–III	CRC I-IV	SAC I-IV	CRC HIV	RC I-IV	CRC I-IV	CRC II–III	CRC I-IV	CC I-III	CRC I-IV	CC I-IV	CRC II–III	CRC HIV	CRC I-IV	CRC I-IV	CRC HIV	RC LIV
Sex (male/female)	195/92	105/70	247/279	463/401	673/741	77/37	47/43	71/49	37/28	52/45	81/39	140/95	72/38	201/135	201/194	58/31	166/96	62/132	160/187	87/98	61/82	64/26
Age (years)	61 (27–81)	68 (35.5–93)	50-85	NA	69.9 (30–96)	69.7 (41–93)	70 (24–90)	NA	60 (23–79)	NA	54 (22–87)	63 (32–84)	55 (26–85)	63.1 ± 12.5	55 ± 15	73 (26–89)	28-75	NA	NA	52 (29–72)	59.8 ± 12.4	64 (33–80)
Sample	287	175	526	864	1420	116	90	120	65	76	120	235	110	336	395	89	262	242	247	185	143	90
Year Country	2018 Japan	2018 Korea	2018 Sweden	2018 China	2013 Switzerland	2018 China	2017 China	2015 China	2020 China	2016 China	2017 China	2017 Japan	2019 China	2018 Korea	2016 USA	2018 Korea	2016 China	2019 Finland	2013 China	2014 China	2013 China	2016 Japan
First author	A Ogura	Bae SU	Berntsson J	CY Huang	Droeser RA	Enkhbat T	HQ Li	H Zhu	Hao Jiang	J Xu	JY He	Koganemaru S	L Wang	Lee KS	Lee LH	Lee SJ	LS Wang	M Ahtiainen	M Song	M Liang	SJ Shi	S Saigusa

 Table 1
 Basic study characteristics

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First author	Year Country	Sample	Age (years)	Sex (male/female)	Type TNM stage	Treatment	Detection methods for PD-L1 expression	Follow-up duration (months)	Outcome	HR and 95% CI	Cutoff
ShuFen Chiang	2018 USA	104	59.3 ± 12.5	33/71	RC I–IV	Surgery + CRT	IHC	46	DFS, OS	2.550 (1.050, 6.200), 2.370 (0.760, 7.3800	NA
Takato Yomoda.	2018 Japan	132	NA	67/65	CRC I-IV	Surgery + CRT	IHC	60	DFS, OS	3.320 (1.170, 11.800), 2.710 (2.720, 2.820)	NA
X Lei	2018 China	80	52.5 (32-77)	40/40	CRC I-IV	Surgery	IHC	20	PFS	1.587 (1.050, 2.988)	NA
X Gao	2017 China	85	58.6 (23-90)	39/46	CC I–IV	Surgery	IHC	48	PFS	0.503 (0.254, 0.997)	NA
XL Wei	2018 China	422	56 (24–83)	249/173	CRC I-IV	Surgery	IHC	72	DFS, OS	0.420 (0.250, 0.720), 0.810 (0.530, 1.230)	$\geq 1\%$ IC and/or $\geq 5\%$ TC staining
Yohei Masugi	2016 USA	823	69.1 ± 9.0	365/458	CRC I-IV	Surgery + CRT	IHC	24	SO	1.020 (0.720, 1.430)	> 50% positive cells
Y Li	2016 China	356	57 (27–85)	199/157	CRC NA	Surgery	IHC	13	DFS, OS	1.048 (0.639, 1.719), 0.626 (0.332, 1.181)	> 50% positive cells
ZF Xiong	2018 China	250	52 (18–88)	143/107	CRC 1-IV	Surgery	IHC	18	PFS	1.587 (1.050, 2.988)	NA
Z Li	2018 China	153	63 (26–89)	77/76	CRC I-IV	Surgery	IHC	60	DFS, PFS	3.180 (1.642, 6.156)	≥5% TC staining
Zhaoying Wu	2019 China	204	65.5 (25–89)	124/80	CRC I-IV	Surgery + CRT	IHC	22	SO	1.914 (1.031, 3.553)	NA
CRC, colorec free survival;	tal cancer; SAC, se PFS, progression-	strated adence free surviva	ocarcinoma; <i>CC</i> l; <i>HR</i> , hazard r	, colon cancer; <i>K</i> atio; <i>CI</i> , confider	C, rectal canc	er; <i>CRT</i> , chemo	oradiotherapy;	IHC, immunohi	stochemistr	y; NA, not available; OS, overall	l survival; DFS, disease-

Table 1 (continued)

Juin Case definition adequate? Representativeness of the cases? Ascertainment of exposure Comparability? Assessment of outcome? Was follow-up long enough for outcomes to oc- cur? Description A Ogun 2018 + + + + + + + + + + + + 7 Bac SU 2018 + + + + + + + 7 Berntson J 2018 + + + + + + 7 Brentson J 2018 + + + + + + + 7 Procest RA 2013 + + + + + + 7 Procest RA 2013 + + + + + 7 7 Nu 2016 + + + + + 7 7 Ver Mag 2016 + + + + 7 <th>First author</th> <th>Published year</th> <th>Sample sel</th> <th>ection</th> <th></th> <th>Comparability?</th> <th>Outcome</th> <th></th> <th></th> <th>NOS</th>	First author	Published year	Sample sel	ection		Comparability?	Outcome			NOS
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Droser \mathbf{R} 2013+++++++++7Enkhbar T2018++++++++6HQ Li2017++++++++6HZhu2015++++++++-6Hao Jiang2020++++++++7JY Lu2016+++++++7Logamemaru S2017+++++++7Le Mang2019+++++++7Lee KS2018++++++7Lee KS2018++++++7Lee SJ2018++++++7Lee SJ2013++++++7M Abriane2019++++++7Siguas2016++++++7S Saiguas2016++++++7S Gao2017++++++7Yomod+++++7Yomod+ <td< td=""><td>CY Huang</td><td>2018</td><td>+</td><td>+</td><td>+</td><td>+</td><td>+</td><td>+</td><td>+</td><td>7</td></td<>	CY Huang	2018	+	+	+	+	+	+	+	7
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	ZLi	2018	+	+	+	+	+	+	+	7
	Zhaoving Wu	2019	+	+	+	+	+	+	+	7

 Table 2
 Methodological quality evaluation of included studies by using the NOS

outcomes; and (6) studies that provided hazard ratios and 95% confidence interval (CI) to calculate survival outcomes. The exclusion criteria were (1) studies that were case reports, reviews, or conference papers; (2) republished literature, reviews, and case series; and (3) full text not available.

Data extraction

Two researchers (Shuxia Wang and Yun Wang) identified and classified the literature that met the inclusion criteria independently and excluded the study that obviously did not meet the inclusion criteria after reading the full text. For studies with insufficient information, we contacted the primary authors to acquire and verify data when possible. In cases of disagreement, the two researchers can make an attempt to reach a consensus. We extracted these objective data which were analyzed for aims of this study : (1) the basic information of the study including first author, year of publication, country, number of subjects, their demographic features, (2) type of study, (3) treatment method, (4) outcomes including the pathological parameters (sex, age, tumor location, TNM stage, lymphatic metastasis, differentiation, infiltration degree, tumor diameter, distant metastasis, and vascular invasion), and (5) prognostic values including overall survival (OS), diseasefree survival (DFS) and progression-free survival (PFS).

Quality assessment

Study quality was assessed by using the Newcastle–Ottawa score [24], which consists of three factors: patients selection, comparability of study groups, and assessment of outcomes.

a	lymphatic metasta	sis[yes]	lymphatic meta	astasis[no]]	Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
A Ogura 2018	37	86	67	195	5.7%	1.25 [0.92, 1.71]	
Bae SU 2018	47	93	46	82	6.3%	0.90 [0.68, 1.19]	-
Hao Jiang 2020	10	21	34	44	3.6%	0.62 [0.38, 0.99]	
J Berntsson 2018	31	70	58	165	5.4%	1.26 [0.90, 1.76]	+-
J Xu 2016	14	27	28	70	3.7%	1.30 [0.82, 2.06]	
JY He 2017	19	68	16	52	2.9%	0.91 [0.52, 1.59]	
L Wang 2019	14	43	23	67	3.0%	0.95 [0.55, 1.63]	
Lee KS 2018	65	174	49	162	5.9%	1.24 [0.91, 1.67]	+-
Lee LH 2016	9	176	9	178	1.3%	1.01 [0.41, 2.49]	
LS Wang 2016	27	124	27	138	3.6%	1.11 [0.69, 1.79]	
M Liang 2014	76	108	26	77	5.3%	2.08 [1.49, 2.92]	
S Koganemaru 2017	21	70	38	165	3.8%	1.30 [0.83, 2.05]	
S Saigusa 2016	15	31	21	59	3.4%	1.36 [0.82, 2.24]	
Shu-Fen Chiang 2018	17	30	34	74	4.5%	1.23 [0.83, 1.84]	
SJ Shi 2013	31	71	33	72	4.9%	0.95 [0.66, 1.37]	-
Takato Yomoda 2018	15	57	19	75	2.7%	1.04 [0.58, 1.86]	
X Gao 2017	43	51	21	34	6.1%	1.37 [1.02, 1.82]	
X Lei 2018	51	55	19	25	7.1%	1.22 [0.97, 1.54]	-
Y Li 2016	76	108	26	77	5.3%	2.08 [1.49, 2.92]	
ZF Xiong 2018	48	92	80	180	6.7%	1.17 [0.91, 1.51]	
Zhaoying Wu 2019	47	91	37	113	5.4%	1.58 [1.13, 2.20]	
Zhu, H.2015	22	52	19	68	3.4%	1.51 [0.92, 2.49]	
Total (95% CI)		1698		2172	100.0%	1.24 [1.11, 1.38]	•
Total events	735		730				
Heterogeneity: Tau ^a = (0.03; Chi ² = 40.16, df = 3	21 (P = 0.0	07); I ² = 48%				
Test for overall effect 2	z = 3.72 (P = 0.0002)						lymphatic metastasis[yes] lymphatic metastasis[no]

b	>=50	m	< 5 ci	m		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Hao Jiang 2020	31	44	6	21	2.0%	5.96 [1.89, 18.77]	· · · · · · · · · · · · · · · · · · ·
HQ Li 2017	22	40	22	50	7.3%	1.56 [0.67, 3.59]	- +-
JY He 2017	2	26	13	94	4.3%	0.52 [0.11, 2.46]	
LS Wang 2016	22	89	32	173	13.6%	1.45 [0.78, 2.68]	+
T Enkhbat 2018	37	52	37	64	8.0%	1.80 [0.83, 3.92]	+
X Lei 2018	6	8	64	72	2.7%	0.38 [0.06, 2.18]	
Y Li 2016	72	85	111	144	10.5%	1.65 [0.81, 3.34]	+
ZF Xiong 2018	57	99	93	151	26.0%	0.85 [0.51, 1.42]	
Zhaoying Wu 2019	46	100	38	104	16.7%	1.48 [0.84, 2.59]	+
Zhu, H.2015	14	54	16	66	8.9%	1.09 [0.48, 2.51]	
Total (95% CI)		597		939	100.0%	1.34 [1.06, 1.70]	◆
Total events	309		432				
Heterogeneity: Chi ² =	14.39, df:	= 9 (P =	= 0.11); l ²	= 37%			
Test for overall effect:	Z=2.46 (P = 0.0	11)				Favours [> = 5 cm] Favours [

Fig. 2 Meta-analysis between PD-L1 expression and lymphatic metastasis (a) and tumor diameter (b)

A score of 0 to 9 was assigned to each study, and studies achieving a score of 6 or higher were considered high quality.

Statistical analysis

If the numbers of included studies were less than 3, the metaanalysis could not be used. All statistical analyses were conducted by using Review Manager 5.3. Odds ratios (OR) and 95% CI were analyzed for the relationship between PD-L1 expression and basic clinicopathological features including sex (male/female), age (\geq 60/< 60 years old), tumor location (right + rectum/left + colon), TNM stage (III–IV/I–II), lymphatic metastasis (yes/no), differentiation (high–middle/low), tumor diameter (\geq 5 cm/< 5 cm), vascular invasion (yes/no), infiltration degree (3–4/1–2), and distant metastasis (yes/no). Hazard ratio (HR) and its 95% CI were presented for PD-L1 on CRC prognosis. Subgroup analysis was used to find the source of heterogeneity according to treatment methods (surgery or surgery combined with chemoradio-therapy (CRT)). Moreover, meta-regression analysis was used to analyze the independent role of PD-L1 on the prognosis of CRC

а	high-mi	ddle	low			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total I	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% CI
A Ogura 2018	4	17	85	264	3.3%	0.65 [0.21, 2.05	5]
Bae SU 2018	88	159	5	16	3.5%	2.73 [0.91, 8.21	i +
CY Huang 2018	313	732	65	120	9.0%	0.63 (0.43, 0.93	a
Droeser RA 2013	29	123	394	994	8.5%	0.47 [0.30, 0.73	a
Hao Jiang 2020	24	44	12	21	3.7%	0.90 (0.32, 2.57	n
J Xu 2016	24	65	18	32	4.8%	0.46 (0.19, 1.08	
JY He 2017	11	99	4	21	2.9%	0.53 (0.15, 1.87	ń <u> </u>
L Wang 2019	28	80	15	30	4.9%	0.54 (0.23, 1.28	
Lee KS 2018	145	319	6	17	3.9%	1.53 (0.55, 4.23	
Lee LH 2016	12	336	7	54	4.1%	0.25 (0.09, 0.66	
Lee SJ 2018	42	71	14	18	3.1%	0.41 [0.12, 1.38	
M Liang 2014	29	60	73	125	6.7%	0.67 [0.36, 1.24	i
S Saigusa 2016	31	80	5	10	2.7%	0.63 [0.17, 2.37	
SJ Shi 2013	53	127	11	16	3.4%	0.33 [0.11, 0.99	
T Enkhbat 2018	20	52	26	64	5.6%	0.91 [0.43, 1.93	
Takato Yomoda 2018	23	110	11	22	4.2%	0.26 [0.10, 0.69	
X Gao 2017	36	53	28	32	3.1%	0.30 (0.09, 1.00	
XI. Wei 2018	162	308	26	54	7 1 %	1 19 10 67 2 13	
ZE Xiong 2018	73	154	37	96	7.6%	1.44 [0.86, 2.41	í +
Zhaoving Wu 2019	74	182	10	22	4.6%	0.82 [0.34, 2.00	i
Zhu H 2015	27	102	5	18	3 4 %	0.94 (0.31, 2.87	n
2110,11.2010	2.	102	0		0.470	0.04 [0.01, 2.01	,
Total (95% CI)		3273		2046	100.0%	0.68 [0.53, 0.87	ı ◆
Total events	1248		857				
Heterogeneity: Tau ² =	0.14; Chi ² =	: 37.60, d	f = 20 (P	= 0.01	0); l ² = 41	7%	
Test for overall effect:	Z = 3.10 (P =	= 0.002)					Eavours [high-middle] Eavours [low]
L.							
D,	/ascular invas	ion [ves]	Vascula	ar invas	ion [no]	Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Eve	ents	Total	Weight M-H, Fixed, 95%	CI M-H, Fixed, 95% CI
A Ogura 2018	40	145		49	136	8.7% 0.68 (0.41, 1.1	2]
Bae SU 2018	64	93		61	82	4.8% 0.76 [0.39, 1.4	7]
CY Huang 2018	188	480		194	419	29.8% 0.75 [0.57, 0.9	7
Droeser RA 2013	109	319		314	799	27.9% 0.80 [0.61, 1.0	[5]
Hau Jiang 2020	24	44		12	21	0.7% 3.84 [1.20, 12.3	
Lee KS 2018	14	45		111	291	4.8% 0.73[0.37,1.4	41
HAR A THE REAL AND A							

С	Right + recta	Left+	colon		c	odds Ratio		Odds Ratio	
Test for overall effect: Z = 3.11	(P = 0.002)						0.01	Vascular invasion [yes] Vascular invasion [no]	100
Heterogeneity: Chi# = 18.42, d	If = 13 (P = 0.14);	I ^z = 29%					h		100
Total events	598	,	1194						
Total (95% CI)		1514		2687	100.0%	0.80 [0.69, 0.92]		•	
Zhu, H.2015	7	20	23	100	1.2%	1.80 [0.64, 5.05]			
ZF Xiong 2018	25	63	85	187	6.1%	0.79 [0.44, 1.41]			
Y Li 2016	56	70	207	235	4.5%	0.54 [0.27, 1.10]			
Takato Yomoda 2018	15	98	9	34	2.7%	0.50 [0.20, 1.28]			
T Enkhbat 2018	27	52	35	64	3.6%	0.89 [0.43, 1.86]			
S Saigusa 2016	22	47	14	43	1.8%	1.82 [0.77, 4.30]			
M Ahtiainen 2019	4	19	75	175	2.7%	0.36 [0.11, 1.11]			
Lee KS 2018	14	45	111	291	4.8%	0.73 [0.37, 1.44]			
JY He 2017	3	19	12	101	0.8%	1.39 [0.35, 5.49]			

•	Right + H	ectar	Leit + C	01011		Ouus Rauo		Odds Ralio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Random, 95% CI	
Bae SU 2018	21	31	72	144	6.4%	2.10 [0.92, 4.77]		—	
CY Huang 2018	185	384	238	480	10.9%	0.95 [0.72, 1.24]		-	
J Berntsson 2018	3	63	16	172	3.9%	0.49 [0.14, 1.73]			
Lee KS 2018	9	96	6	240	4.8%	4.03 [1.40, 11.67]			
Lee LH 2016	12	142	7	232	5.5%	2.97 [1.14, 7.72]			
LS Wang 2016	25	121	29	141	8.1%	1.01 [0.55, 1.83]		-+	
M Ahtiainen 2019	1	19	78	175	1.9%	0.07 [0.01, 0.53]	•		
S Koganemaru 2017	3	63	16	172	3.9%	0.49 [0.14, 1.73]			
S Saigusa 2016	11	28	2	8	2.4%	1.94 [0.33, 11.41]			
T Enkhbat 2018	24	52	13	64	6.4%	3.36 [1.48, 7.61]			
Takato Yomoda 2018	11	35	13	97	5.7%	2.96 [1.18, 7.45]			
XL Wei 2018	133	303	103	229	10.3%	0.96 [0.68, 1.35]		-	
Y Li 2016	78	87	223	269	6.8%	1.79 [0.84, 3.82]			
ZF Xiong 2018	36	80	73	170	8.7%	1.09 [0.64, 1.86]		_ _ _	
Zhaoying Wu 2019	34	72	50	132	8.3%	1.47 [0.82, 2.62]		+	
Zhu, H.2015	16	79	14	41	6.2%	0.49 [0.21, 1.14]			
Total (95% CI)		1655		2766	100.0%	1.28 [0.95, 1.74]		-	
Total events	602		953					. .	
Heterogeneity: Tau ² = 0.1	20; Chi ² =	42.40, 0	df = 15 (P	= 0.000	12); I ² = 65	5%	0.01	01 1 10 10	ທີ
Test for overall effect: Z =	= 1.60 (P =	0.11)					0.01	Right + rectal Left + colon	~

 $\label{eq:Fig.3} Fig. 3 \ \ \mbox{Meta-analysis between PD-L1 expression and differentiation (a) and vascular invasion (b) and tumor location (c) \\$

after adjusting for above clinicopathological features and treatment methods. If the numbers of included studies were less than 10, the meta-regression could not be used. Depending on the results from the tests of heterogeneity, a fixed effect model or a

а				Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Bae SU 2018	0.4612151	0.2012672	7.2%	1.59 [1.07, 2.35]	-
Droeser RA 2013	0.833816	0.221968	6.6%	2.30 [1.49, 3.56]	
Hao Jiang 2020	1.450911	0.6716471	1.2%	4.27 [1.14, 15.92]	
HQ LI 2017	1.156881	0.3371205	3.9%	3.18 [1.64, 6.16]	
J Berntsson 2018	0.6348783	0.1564042	9.0%	1.89 [1.39, 2.56]	
JY He 2017	0.0907544	0.5376307	1.8%	1.10 [0.38, 3.14]	
Lee KS 2018	1.331046	0.4905205	2.1%	3.79 [1.45, 9.90]	
M Ahtiainen 2019	0.1655144	0.3224584	4.1%	1.18 [0.63, 2.22]	
M Liang 2014	0.5538851	0.2091604	7.0%	1.74 [1.15, 2.62]	
M Song 2013	0.7275486	0.2211224	6.6%	2.07 [1.34, 3.19]	
S Koganemaru 2017	0.8960881	0.3479733	3.7%	2.45 [1.24, 4.85]	
S Salgusa 2016 Shu Eon Chiong 2011	0.8232979	0.4028500	3.0%	2.28 [1.03, 5.02]	
Shu-Fen Chiang 2010	1 01020099	0.5799000	5.2%	2.37 [0.76, 7.39]	
T Enkhhat 2018	1 354029	0.2077874	1.5%	3 87 [1 19 12 57]	
Takato Yomoda 2018	0 9969487	0.0007400	9.8%	2 71 [2 07 3 54]	+
XL Wei 2018	0.210721	0.2147685	6.8%	1.23 [0.81, 1.88]	+
Y LI 2016	0.4684049	0.3237199	4.1%	1.60 (0.85, 3.01)	+
Yohei Masugi 2016	0.198026	0.1750455	8.2%	1.22 [0.86, 1.72]	+-
Zhaoying Wu 2019	0.6491953	0.3156283	4.3%	1.91 [1.03, 3.55]	⊢ •−
Zhu, H.2015	0.3681694	0.4671635	2.3%	1.45 [0.58, 3.61]	
Total (95% CI)			100.0%	1.93 [1.66, 2.25]	
Heterogeneity: Tau ² =	0.04; Chi ² = 32.88, df	= 20 (P = 0.0	(3); I ² = 39	3%	
Test for overall effect:	Z = 8.46 (P < 0.00001)			Favors [PD-L1+] Favors [PD-L1-]
_					
b				Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
2.2.1 DFS					
A Ogura 2018	0.692647	0.4388019	2.3%	2.00 [0.85, 4.72]	
Bae SU 2018	0.2421616	0.2051341	10.4%	1.27 [0.85, 1.90]	
CY Huang 2018	0.3148108	0.2216643	8.9%	1.37 [0.89, 2.12]	+
Hao Jiang 2020	1.069527	0.4090832	2.6%	2.91 [1.31, 6.50]	
Lee KS 2018	1.253905	0.4463838	2.2%	3.50 [1.46, 8.40]	
Lee LH 2016	1.280934	0.6142718	1.2%	3.60 [1.08, 12.00]	
Lee SJ 2018	1.12393	0.5089104	1.7%	3.08 [1.13, 8.34]	
M Ahtiainen 2019	0.0198026	0.6239966	1.1%	1.02 [0.30, 3.47]	
M Liang 2014	0.6048623	0.2137345	9.5%	1.83 [1.20, 2.78]	
S Koganemaru 2017	0.8960881	0.3479733	3.6%	2.45 [1.24, 4.85]	
Shu-Fen Chiang 201	8 0.9360933	0.4529998	2.1%	2.55 [1.05, 6.20]	
TENKNDAT 2018	0.6486727	0.4380392	2.3%	1.91 [0.81, 4.51]	
Takato Yomoda 2018	1.199900	0.0890003	1.3%	3.32 [1.05, 10.54]	
XL WEI 2016	0.0070000	0.2096440	6.0%	2.30 [1.40, 4.04]	
71;2010	0.0400030	0.2024473	4.0%	1.00 [0.04, 1.72]	
Subtotal (95% CI)	0.5242407	0.5501740	65.8%	1.76 [1.50, 2.07]	•
Heterogeneity: Chi ² =	19.36. df = 15 (P = 0.	20): I ² = 23%	00.07		
Test for overall effect:	Z = 6.97 (P < 0.0000)	1)			
C		.,			
2.2.2 PFS					
J Xu 2016	0.4977404	0.362174	3.3%	1.65 [0.81, 3.35]	+
JY He 2017	0.1473406	0.485677	1.8%	1.16 [0.45, 3.00]	
LS Wang 2016	0.604316	0.2624908	6.3%	1.83 [1.09, 3.06]	
S Saigusa 2016	1.19725	0.4233536	2.4%	3.31 [1.44, 7.59]	
SJ Shi 2013	1.019208	0.2677874	6.1%	2.77 [1.64, 4.68]	
X Gao 2017	0.6871651	0.3488307	3.6%	1.99 [1.00, 3.94]	—
X Lei 2018	0.8064759	0.403573	2.7%	2.24 [1.02, 4.94]	
Z Li 2018	0.1450258	0.4929485	1.8%	1.16 [0.44, 3.04]	
ZF Xiong 2018	0.4618455	0.2667893	6.1%	1.59 [0.94, 2.68]	
Subtotal (95% CI)			34.2%	1.93 [1.55, 2.41]	•
Heterogeneity: Chi ² =	6.55, df = 8 (P = 0.59); I ² = 0%			
Test for overall effect	Z = 5.85 (P < 0.0000)	1)			
Total (05% CI)			100.0*	1 0 2 [1 60 2 07]	▲
Hotorogonoity Chi2-	26.25 df = 24/0 = 0	24):12 - 00/	100.0%	1.02 [1.00, 2.07]	
Test for overall effect	20.35 , $a_1 = 24$ ($P = 0$. 7 = 9.08 ($P < 0.0000$	34), F = 9% 1)			0.02 0.1 i 10 50
Test for subaroun dif	ferences: $Chi^2 = 0.0000$., df=1 (P=0	51) I ² = I	0%	Favors [PD-L1+] Favors [PD-L1-]

Fig. 4 Meta-analysis of PD-L1 expression on OS (a), DFS (b), and PFS (c)

Fig. 5 Subgroup analysis of PD-L1 expression on OS by using different treatment methods

Study or Subaroup	loo[Hazard Ratio]	\$F	Woight	Hazard Ratio	Hazard Ratio
2.4.1 Surgery		JL	Wolqiit	14,1160,35% 01	14,11,000,35,401
Droeser RA 2013	0.833816	0.221968	7.3%	2.30 [1.49. 3.56]	
Hao Jiang 2020	1.450911	0.6716471	0.8%	4.27 [1.14, 15.92]	
HQ Li 2017	1.156881	0.3371205	3.2%	3.18 [1.64, 6.16]	
J Berntsson 2018	0.6348783	0.1564042	14.7%	1.89 [1.39, 2.56]	+
M Ahtiainen 2019	0.1655144	0.3224584	3.4%	1.18 [0.63, 2.22]	
M Liang 2014	0.5538851	0.2091604	8.2%	1.74 [1.15, 2.62]	
M Song 2013	0.7275486	0.2211224	7.3%	2.07 [1.34, 3.19]	
S Koganemaru 2017	0.8960881	0.3479733	3.0%	2.45 [1.24, 4.85]	
SJ Shi 2013	1.019208	0.2677874	5.0%	2.77 [1.64, 4.68]	
XL Wei 2018	0.210721	0.2147685	7.8%	1.23 [0.81, 1.88]	+
Y Li 2016	0.4684049	0.3237199	3.4%	1.60 [0.85, 3.01]	
Zhu, H.2015	0.3681694	0.4671635	1.6%	1.45 [0.58, 3.61]	
Subtotal (95% CI)			65.7%	1.90 [1.65, 2.20]	•
Heterogeneity: Chi ² =	14.22, df = 11 (P = 0.1	22); I² = 23%			
Test for overall effect:	Z = 8.70 (P < 0.00001)			
2.4.2 Surgery+CRT					
Bae SU 2018	0.4621151	0.2012672	8.9%	1.59 [1.07, 2.36]	
JY He 2017	0.0907544	0.5376307	1.2%	1.10 [0.38, 3.14]	
Lee KS 2018	1.331046	0.4905205	1.5%	3.79 [1.45, 9.90]	
S Saigusa 2016	0.8232979	0.4028566	2.2%	2.28 [1.03, 5.02]	
Shu-Fen Chiang 2018	0.8628899	0.5799006	1.1%	2.37 [0.76, 7.39]	
T Enkhbat 2018	1.354029	0.6007435	1.0%	3.87 [1.19, 12.57]	
Takato Yomoda 2018	0.9969487	0.336939	3.2%	2.71 [1.40, 5.25]	
Yohei Masugi 2016	0.198026	0.1750455	11.7%	1.22 [0.86, 1.72]	+-
Zhaoying Wu 2019	0.6491953	0.3156283	3.6%	1.91 [1.03, 3.55]	-
Subtotal (95% CI)			34.3%	1.69 [1.39, 2.07]	•
Heterogeneity: Chi ² =	11.85, df = 8 (P = 0.1)	6); I² = 32%			
Test for overall effect:	Z = 5.15 (P < 0.00001)			
Total (95% CI)			100.0%	1.83 [1.63, 2.06]	•
Heterogeneity: Chi ² =	26.92, df = 20 (P = 0.1	14); I² = 26%			
Test for overall effect:	Z = 10.07 (P < 0.0000	01)			U.UI U.T 1 10 100
Test for subaroup diff	erences: Chi ² = 0.85.	df = 1 (P = 0.	36), ² = 0	%	ravois (PD-LI+) ravois (PD-L1-)

random effect model was chosen. The chi-square test and l^2 were used to evaluate the heterogeneity of the included studies. Begg's test was used to analyze publication bias by using the software Stata, version 15.1.

Results

Description of studies and quality assessment

Thirty-two eligible studies [25–56] with Newcastle–Ottawa scale (NOS) score ≥ 6 were included in meta-analysis, including five in Chinese and twenty-seven in English, with a total of 8823 CRC patients. The follow-up duration was from 4 months to 7.3 years, and the sample size was from 65 to 1414. The selection process of literature is detailed in Fig. 1. Basic information and quality evaluation of included studies are presented in Table 1 and Table 2.

Correlation between PD-L1 expression and clinicopathological features

The pooled OR indicated that there were significant positive correlations between PD-L1 expression and lymphatic metastasis (yes/no; *n* = 22; 3870 patients; OR = 1.24, 95% CI (1.11, 1.38), Z = 3.72, P < 0.05; $I^2 = 48\%$, P < 0.1) (Fig. 2a) and tumor diameter (≥ 5 cm/< 5 cm; n = 10; 1536 patients; OR = 1.34, 95% CI (1.06, 1.70), Z = 2.46, P < 0.05; $I^2 = 37\%$, P = 0.11) (Fig. 2b), but negative correlation with differentiation (highmiddle/low; n = 21; 5319 patients; OR = 0.68, 95% CI (0.53, 0.87), Z = 3.10, P < 0.05; $l^2 = 47\%$, P < 0.1) (Fig. 3a) and vascular invasion (yes/no; n = 14; 4201 patients; OR = 0.80, 95% CI (0.69, 0.92), Z = 3.11, P < 0.05; $I^2 = 29\%$, P = 0.14) (Fig. 3b). However, there were no significant correlations found between PD-L1 expression and sex (male/female; n = 29; 8043 patients; OR = 0.94, 95% CI (0.85, 1.04), Z = 1.16, P > 0.05; $l^2 = 11\%$, P = 0.29) (Fig. S1A), age ($\geq 60/<60$ years old; n = 21; 4095 patients; OR = 0.96, 95% CI (0.84, 1.10), Z = 0.54,

Prognosis	Variables	HR	Standard error	Ζ	Р	95% CI
OS	Distant metastasis (no/yes)	3.22	1.11	2.91	< 0.05	[1.05, 5.39]
	Treatment methods (surgery/surgery + CRT)	1.05	0.03	41.57	< 0.05	[1.00, 1.10]
	PD-L1 (negative/positive)	1.95	0.01	3.98	< 0.05	[1.92, 3.98]
DFS	Treatment methods (surgery/surgery + CRT)	0.84	0.30	2.75	< 0.05	[0.24, 1.43]
	PD-L1 (negative/positive)	2.14	0.21	3.77	< 0.05	[0.73, 4.52]

Table 3 HR and 95% CI in meta-regression analysis for CRC prognosis

Sex, age, differentiation, lymphatic metastasis, infiltration degree, distant metastasis, tumor diameter, vascular invasion, TNM stage, tumor type, tumor location, PD-L1 expression, and treatment methods were used as adjustment factors in meta-regression analysis

P>0.05; $l^2 = 24\%$, *P*=0.15) (Fig. S1B), TNM stage (III–IV/I– II; *n*=23; 5108 patients; OR = 1.11, 95% CI (0.86, 1.43), *Z*= 0.81, *P*>0.05; $l^2 = 57\%$, *P*<0.1) (Fig. S2A), tumor location (right + rectal/left + colon; *n*=16; 4421 patients; OR = 1.28, 95% CI (0.95, 1.74), *Z*=1.60, *P*>0.05; $l^2 = 65\%$, *P*<0.1) (Fig. 3c), infiltration degree (3–4/1–2; *n*=10; 1837 patients; OR = 0.82, 95% CI (0.64, 1.06), *Z*=1.52, *P*>0.05; $l^2 = 19\%$, *P*=0.27) (Fig. S2B), and distant metastasis (yes/no; *n*=10; 2486 patients; OR = 1.13, 95% CI (0.87, 1.47), *Z*=0.91, *P*>0.05; $l^2 = 30\%$, *P*=0.18) (Fig. S2C).

Correlation between PD-L1 expression and the prognostic parameters (OS, DFS, and PFS)

Twenty studies provided the OS parameters. As weak heterogeneity existed ($l^2 = 39\%$, P = 0.03), the random effects model was used. Meta-analysis showed that OS was significantly associated with PD-L1 expression in CRC patients (n = 21; HR = 1.93, 95% CI (1.66, 2.25), Z = 8.46, P < 0.05) (Fig. 4a).

Sixteen studies provided the DFS parameters. Results showed that DFS was significantly associated with PD-L1 expression in CRC patients (n = 16; HR = 1.76, 95% CI (1.50, 2.07), Z = 6.97, P < 0.05; $l^2 = 23\%$, P = 0.20) (Fig. 4b).

Nine studies provided the PFS parameters. Results showed that PFS was significantly associated with PD-L1 expression in CRC patients (n = 9; HR = 1.82, 95% CI (1.60, 2.07), Z = 5.85, P < 0.05; $I^2 = 0\%$, P = 0.59) (Fig. 4c).

Subgroup analysis on OS under different treatment methods

Results were as follows: (1) surgery: PD-L1 expression was significantly associated with OS (n = 12; HR = 1.90, 95% CI (1.65, 2.20), Z = 8.70, P < 0.05; $\bar{I}^2 = 23\%$, P = 0.22); (2) surgery + CRT: PD-L1 expression was significantly associated with OS (n = 9; HR = 1.69, 95% CI (1.39, 2.07), Z = 5.15, P < 0.05; $\bar{I}^2 = 32\%$, P = 0.16) (Fig. 5).

Meta-regression analysis

Meta-regression analysis confirmed that PD-L1 expression was to be correlated with OS (HR = 1.95, 95% CI (1.92, 3.98)) and DFS (HR = 2.14, 95% CI (0.73, 4.52)). And the prognosis of patients with surgery treatment alone was worse than that of surgery combined with CRT. Patients with distant metastasis had a poor prognosis (Table 3).

Sensitivity analysis

Sensitivity analysis on OS, DFS, and PFS indicated that after excluding any single study individually, there was no separate study that significantly affected HR and 95% CI, suggesting that the results of this meta-analysis were stable (Fig. S3).

Publication bias

Results of Begg's test suggested that there may be no publication bias among studies for OS, DFS, and PFS (all P > 0.05) (Fig. 6).

Discussion

Studies reported that the PD-1/PD-L1 pathway has become a promising therapeutic target for various human malignancies [17, 18, 57–60]. Nonetheless, the correlation between PD-L1 expression and clinicopathological features [26, 30] and the prognosis of CRC patients are still controversial [36, 51]. Therefore, this study comprehensively searched the literature to solve the above-existing controversies in order to draw more reliable conclusions.

Data of our meta-analysis from 32 studies (8823 CRC patients), the largest to date, indicated that PD-L1 expression was significantly positively correlated with lymphatic metastasis and tumor diameter, but negatively correlated with differentiation and vascular invasion. However previous meta-analysis found that PD-L1 expression was correlated with tumor stage [21] and gender [22] and tumor location [23], which results were



Fig. 6 Begg's funnel plot for OS (a), DFS (b), and PFS (c) publication bias in the included studies

unreliable due to high heterogeneity (all $l^2 > 70\%$) [21–23] and the incorrect analytical model (all selected the fixed effects model that is available for $l^2 < 50\%$) [21–23]. In this study, the random effects model was selected for TNM stage and tumor location because of mild heterogeneity ($l^2 = 57\%$ for TNM stage and $l^2 = 65\%$ for tumor location).

In univariate analysis, PD-L1 was correlated with poor prognosis of CRC in this study, which was similar to the results of previous meta-analysis [20-23]. However, high heterogeneity existed in our study and those meta-analyses [20-23]. Furthermore, in subgroup analysis based on

treatment, we found that the degree of statistical heterogeneity reduced both in subgroup for OS (Fig. 5). It meant that the treatment method was the source of heterogeneity for OS. In order to control other confounders, meta-analysis should be necessary to analyze the independent role of PD-L1 on CRC prognosis. We found that PD-L1 expression independently predicted a poor prognostic outcome with meta-regression analysis. Previous meta-analysis made a contradictory conclusion by univariate analysis [20–23]. Meta-regression analysis can get a more reliable and accurate outcome after adjusting confounders including clinicopathological features and treatment methods that influence the CRC prognosis.

In our sensitivity analysis, none of the inclusions and exclusions of specific studies one by one materially changed the results of the primary meta-analysis; it suggested that the results of this meta-analysis were stable.

From the perspective of publication bias, Begg's test on OS, DFS, and PFS found that there was no significant publication bias that existed among included studies, and the results of this study were relatively reliable.

Despite some positive findings from this meta-analysis, two limitations still existed to our study. Firstly, although Chinese and English studies were included in this meta-analysis, language bias still existed. Secondly, although the literature screening was carried out with a strict search strategy, a small number of literatures including gray literature and conference literature may still be missing.

Conclusions

In summary, PD-L1 expression was significant correlated with lymphatic metastasis, tumor diameter, differentiation, and vascular invasion, and could act as an independently poor prognostic factor for CRC.

Authors' contributions All authors have read and approved the final manuscript. The corresponding author of this manuscript is Jihong Hu, and contribution of the authors was mentioned below with their responsibility in the research. All authors of this research paper have directly participated in the planning, execution, or analysis and interpretation of data and have read and approved the final version submitted. The contribution of each author is as follows: conceptualization, Jihong Hu; data curation, Shuxia Wang, Xibo Liu, and Mingyang Li; formal analysis, Jing Cao and Bo Yuan; methodology, Changtian Li and Yun Wang; writing—original draft, Shuxia Wang; designed the research and revised, Jihong Hu.

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Data availability The data supporting this meta-analysis are from previously published studies, which have been cited. The processed data are available from the first author (wangshuxialucky@163.com) upon request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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