Clinicopathological and prognostic significance of programmed cell death ligand 1 (PD-L1) expression in patients with esophageal squamous cell carcinoma: a meta-analysis

Hai-Xia Qu[1], Li-Ping Zhao[2], Shu-Hui Zhan[2], Chang-Xin Geng[2], Lin Xu[2], Yong-Ning Xin[1], Xiang-Jun Jiang[1]

[1]Department of Gastroenterology, Qingdao Municipal Hospital, School of Medicine, Qingdao University, Qingdao 266071, China; [2]Department of Gastroenterology, Qingdao Municipal Hospital, Qingdao 266071, China

Contributions: (I) Conception and design: HX Qu, XJ Jiang; (II) Administrative support: XJ Jiang; (III) Provision of study materials or patients: HX Qu, LP Zhao; (IV) Collection and assembly of data: SH Zhan, CX Geng; (V) Data analysis and interpretation: HX Qu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Xiang-Jun Jiang. Department of Gastroenterology, Qingdao Municipal Hospital, School of Medicine, Qingdao University, Qingdao 266071, China. Email: xiangjunjiang@outlook.com.

Background: The clinicopathological and prognostic significance of programmed cell death ligand 1 (PD-L1) expression in patients with esophageal squamous cell carcinoma (ESCC) remains controversial. To investigate this question, we conducted a meta-analysis.

Methods: A comprehensive literature search of electronic databases (up to July 10, 2016) was performed for relevant studies using multiple search strategies. Correlation between PD-L1 expression and clinicopathological features/overall survival (OS) was analyzed.

Results: A total of 1,350 ESCC patients from eight studies were included. The pooled odds ratios (ORs) indicated that none of the clinicopathological characteristics was correlated with PD-L1 expression, including gender [OR =0.84; 95% confidence interval (CI): 0.59–1.18; P=0.31], histological differentiation (OR =1.33; 95% CI: 0.95–1.85; P=0.09), tumor depth (OR =0.66; 95% CI: 0.33–1.35; P=0.26), status of lymph node metastasis (OR =0.67; 95% CI: 0.30–1.52; P=0.34), distal metastasis (OR =0.66; 95% CI: 0.40–1.09; P=0.10) and tumor node metastasis (TNM) stage (OR =0.93; 95% CI: 0.49–1.75; P=0.82). The combined hazard ratio (HR) for OS showed a trend that overexpression of PD-L1 might be associated with the survival outcome of ESCC, though the difference was not statistically significant (HR =1.65; 95% CI 0.95–2.85; P=0.07).

Conclusions: Based on the published studies, PD-L1 overexpression in ESCC was not associated with common clinicopathological characteristics. PD-L1 might be a poor prognostic biomarker for ESCC. Further large-scale research should be performed to reveal the precise clinicopathological and prognostic significance of PD-L1 in ESCC by unified testing standard.

Keywords: Meta-analysis; esophageal squamous cell carcinoma (ESCC); programmed cell death ligand 1 (PD-L1); prognosis

Introduction

Esophageal squamous cell carcinoma (ESCC), which is most common in Asia, Southern and Eastern Africa, is one of the predominant histological types of esophageal cancer

(1,2). Though the advances in multidisciplinary therapeutic strategies have improved the prognosis of ESCC, overall outcome is still dismal and novel approaches of treatment are needed.

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Programmed cell death ligand 1 (PD-L1) and its receptor, programmed cell death 1 (PD-1), are key immune checkpoint proteins and play crucial roles in tumor immune escape (3). PD-L1 expressed on cancer cells can inhibit T-cell activation, maintain the exhaustion of T cell, impairing cytokine production, and induce the apoptosis of effector T cells which eventually result in the growth of tumor (4,5). The overexpression of PD-L1 was reported to be associated with poor prognosis and the resistance to anticancer therapies (6-8). Recent clinical studies have shown promising clinical activity of PD-1- or PD-L1-targeting antibodies in certain malignancies, including esophageal cancer (9-11). Researches also demonstrated that PD-L1 protein expression on cancer cells may predict favorable response to anti-PD-1/PD-L1 therapy (10,12-14).

Several studies have investigated the expression of PD-L1 in esophageal cancer, whereas some conflicting results on the prevalence and the prognostic role of PD-L1 were present (15-26). Whether diversity in these data has been due to limited sample size or genuine heterogeneity is still confused. Therefore, we carry out a meta-analysis to clarify this issue.

Methods

Search strategy

A comprehensive literature search of electronic databases PubMed, Embase, Web of Science and China National Knowledge Infrastructure (CNKI) was performed up to July 10, 2016. Studies were selected using the following search terms: 'esophageal or oesophageal' and 'cancer or neoplasm or carcinoma' and 'PD-L1 or programmed cell death ligand 1'. The references of articles and reviews were also manually searched for additional studies. The eligible reports were identified by two reviewers (HX Qu and LP Zhao), and controversial studies were adjudicated by a third reviewer (XJ Jiang).

Selection criteria

We collected all eligible articles about relationship between PD-L1 expression and clinicopathological features or clinic outcome of ESCC in this meta-analysis. Studies meeting the following inclusion criteria were included: (I) PD-L1 protein expression evaluated in the primary ESCC tissues; (II) research that revealed the relationship between PD-L1 expression and clinicopathological parameters or prognosis

of ESCC; (III) studies regarding the prognosis provided sufficient information to estimate hazard ratio (HR) about overall survival (OS) and 95% confidence interval (CI); (IV) if there were multiple articles based on similar populations, only the largest or the most recent article was included. The exclusion criteria included the following: (I) letters, reviews, case reports, conference abstracts, editorials and expert opinion; (II) patients had received previous chemotherapy or radiotherapy.
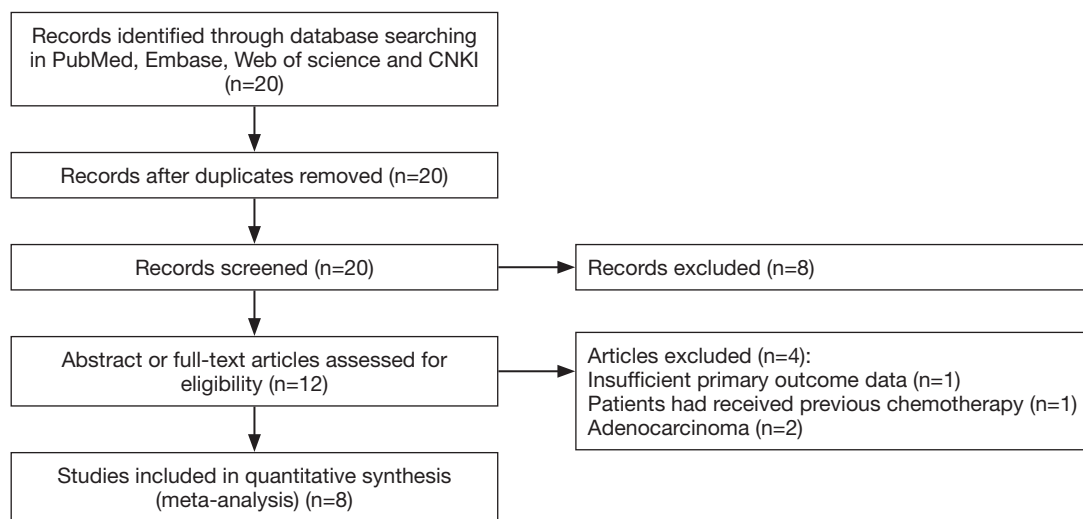
Data extraction

Two investigators (SH Zhan and CX Geng) independently extracted data from eligible studies. Disagreements were resolved by discussion and consensus. Two investigators reviewed all of researches that met inclusion and exclusion criteria. The following information was recorded for each study: name of the first author, year of publication, sample source, number of cases, detection methods, clinicopathological parameters, tumor node metastasis (TNM) stage, definition of PD-L1 positive and survival of patients. If the HR or standard errors (SEs) were not reported in included studies, we calculate or estimate the HR from available data or Kaplan-Meier curves using the methods reported by Tierney *et al.* (27).

Assessment of study quality

Two authors (HX Qu and LP Zhao) independently assessed the quality of all studies on the basis of a 9-scores system of the Newcastle-Ottawa Scale (NOS) (28). Discrepancies in the score were resolved through discussion between the authors. Each study included in the meta-analysis was judged on three broad perspectives: (I) the selection of the groups of study (four items, one score each); (II) the comparability (one item, up to two scores); and (III) the ascertainment of either the exposure or outcome of interest (three items, one score each). A score presents a high quality choice of individual study.

Statistical analysis

Analysis was performed using the Stata 12.0 (Stata Corporation, Texas, US) and Review Manager 5.2 (Cochrane Collaboration, Oxford, UK). Comparisons of dichotomous measures were performed by pooled estimates of odds ratios (ORs), as well as their 95% CI. A P value <0.05 was considered as statistical significance. Heterogeneity was

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┌─────────────────────────────────────────┐
│ Records identified through database      │
│ searching in PubMed, Embase, Web of      │
│ science and CNKI (n=20)                  │
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│ Abstract or full-text articles assessed  │────────▶│ Articles excluded (n=4):                 │
│ for eligibility (n=12)                   │         │ Insufficient primary outcome data (n=1)  │
└─────────────────────────────────────────┘         │ Patients had received previous           │
                    │                                │ chemotherapy (n=1)                       │
                    ▼                                │ Adenocarcinoma (n=2)                     │
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│ Studies included in quantitative         │
│ synthesis (meta-analysis) (n=8)          │
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Figure 1 Flow chart for selection of studies. CNKI, China National Knowledge Infrastructure.

tested using the chi-square test with significance being set at P<0.10, the total variation among studies was estimated by I-Square. If there was heterogeneity among studies, we used a random effect model to pool the ORs; otherwise, a fixed effect model was selected. The potential for publication bias was assessed using the Begg's rank correlation method and the Egger's weighted regression method.

Results

Search results

Twenty articles were identified using the search strategy above. Twelve of those were excluded due to laboratory studies, insufficient primary outcome data, non-original articles (review), irrelevant study to the current analysis, or research of patients that received previous chemotherapy or radiotherapy. Finally, there were eight studies (15-22) included in final meta-analysis (*Figure 1*).

Study characteristics

Eight studies published from 2014 to 2016 were eligible for meta-analysis. Their characteristics were summarized in *Table 1*. A total of 1,350 patients from China and Japan were enrolled. PD-L1 overexpression was found in 559 patients (41.4%). Immunohistochemistry (IHC) was the only method used to evaluate the expression of PD-L1 in ESCC specimens. The definition of PD-L1 positive staining varied among the studies.

Qualitative assessment

The study quality was assessed using the Newcastle-Ottawa quality assessment scale, generating scores ranging from 6 to 8 (with a mean of 6.63), with a higher value indicating better methodology. The results of quality assessment are shown in *Table 1*.

Quantitative synthesis

PD-L1 expression and clinicopathological features

The association between PD-L1 and gender was investigated in six studies. It is found that PD-L1 expression was not different in male and female with ESCC (male *vs.* female, OR =0.84; 95% CI: 0.59–1.18; P=0.31) (*Table 2*).

Five studies described PD-L1 expression according to histological differentiation. The combined OR revealed PD-L1 expression was not related to tumor differentiation (well/moderate *vs.* poor differentiation, OR =1.33; 95% CI: 0.95–1.85; P=0.09) (*Table 2*).

Five, six, five and five out of seven studies showed the relationship of PD-L1 expression to invasive depth of tumor, status of lymph node metastasis, distal metastasis and TNM stage respectively. The result of meta-analysis demonstrated PD-L1 expression was associated with none of these clinicopathological factors (tumor depth, OR =0.66, 95% CI: 0.33–1.35, P=0.26; status of lymph node, OR =0.67, 95% CI: 0.30–1.52, P=0.34; distal metastasis, OR =0.66, 95% CI: 0.40–1.09, P=0.10; TNM stage, OR =0.93, 95% CI: 0.49–1.75, P=0.82) (*Table 2*).

Table 1 Characteristics of eligible studies

First author	Year	Origin	Study period	Cases	Method	Antibody source	Dilution	PD-L1 distribution	Counting method	Definition of PD-L1 positive	Scores of study quality
Chen	2014	China	2005–2006	99	IHC	NBP1-03220; Novus Biologicals, Littleton, CO, USA	1:200	Cytoplasm and membrane	Staining intensity score and percentage of positive cells	H-score >0	7
Ma	2015	China	2010–2014	92	IHC	17952-1-AP, ProteinTech, IL, USA	1:100	Cytoplasm	Staining intensity score and percentage of positive cells	Score ≥2.0	6
Chen	2016	China	2008–2012	536	IHC	Clone SAB2900365, rabbit immunoglobulin G1, Sigma-Aldrich, Saint Louis, USA	1:400	Cytoplasm and membrane	Staining intensity score and percentage of positive cells	5% of the tumor cells displayed at least moderate staining	8
Chen	2016	China (Taiwan)	–	162	IHC	–	–	Cytoplasm and membrane	Staining intensity score and percentage of positive cells	IRS ≥2.0	5
Hatogai	2016	Japan	2000–2011	196	IHC	Clone E1L3N, Cell Signaling Technology, Cambridge, UK	–	Membrane	Percentage of positive cells	≥1%	7
Ito	2016	Japan	1994–2007	90	IHC	Cat. No. LS-B480, Lifespan Biosciences, Seattle, WA, USA	–	Cytoplasm and membrane	Staining intensity score and percentage of positive cells	Score ≥7.0	7
Leng	2016	China	2008–2009	106	IHC	No. ab58810; Abcam, Cambridge, MA, USA	1:40	Cytoplasm and membrane	Staining intensity score and percentage of positive cells	Score ≥4.0	6
Tanaka	2016	Japan	1999–2012	69	IHC	Clone 27A2; MBL, Woburn, MA, USA	–	Cytoplasm	Staining intensity score and percentage of positive cells	IRS ≥4.0	7

IHC, immunohistochemistry; PD-L1, programmed cell death ligand 1.

Table 2 Relationship between PD-L1 protein expression and the clinicopathological feature

Clinicopathological feature	Studies	Heterogeneity		OR (95% CI)	P value
		P value	I² (%)		
Gender	6	0.470	0	0.84 (0.59–1.18)	0.31
Differentiation	5	0.100	48	1.33 (0.95–1.85)	0.09
Tumor depth	5	0.010	70	0.66 (0.33–1.35)	0.26
Status of lymph node	6	<0.00001	85	0.67 (0.30–1.52)	0.34
Metastasis	5	0.940	0	0.66 (0.40–1.09)	0.10
Stage	5	0.005	73	0.93 (0.49–1.75)	0.82

CI, confidence interval; PD-L1, programmed cell death ligand 1.
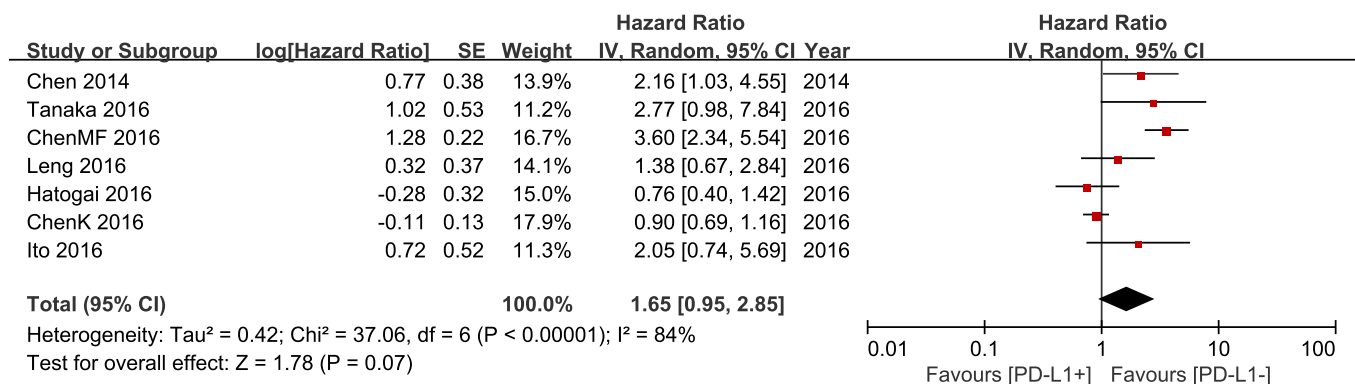
Figure 2 Forest plot of hazard ratio for overall survival of patients with esophageal squamous cell carcinoma. CI, confidence interval; PD-L1, programmed cell death ligand 1.

Heterogeneities were observed in all the analysis except for PD-L1 expression with gender and distal metastasis (*Table 2*), so random-effect models were used.

PD-L1 as a prognostic factor for ESCC

Seven of the eight studies included have estimated the relationship between OS and PD-L1 expression. The pooled HR for OS showed overexpression of PD-L1 tend to reduce the OS in ESCC, but the difference has no statistical significance (HR =1.65; 95% CI: 0.95–2.85; P=0.07) (*Figure 2*). A random-effect model was used in meta-analysis, because of heterogeneity between studies.
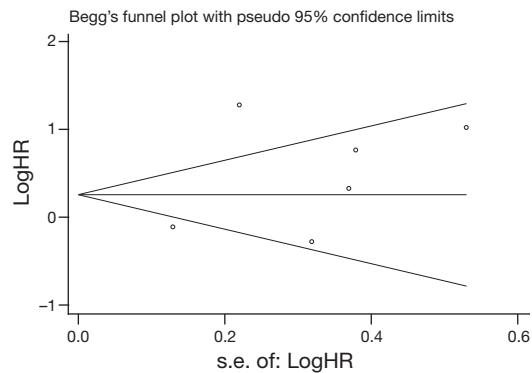
Publication bias

Egger's and Begg's test indicated no publication bias among these studies regarding HR about OS with P values of

0.317 and 0.230 respectively. The funnel plots were largely symmetric (*Figure 3*).

Discussion

PD-L1 was reported to play an important role in regulation of T-cell mediated anti-tumor response and impact the biological characteristics of tumor cells. Recent researches had found the expression of PD-L1 was associated with multiple clinicopathological features, prognosis and response to immune check-point targeted therapies in several solid tumors (29-32).

Previous studies have also been conducted to explore the clinicopathological and prognostic significance of PD-L1 expression in patients with esophageal cancer (15-26), some of them showed overexpression of PD-L1 is associated with certain clinicopathological factors and a poor prognosis, but

Figure 3 Funnel plot of publication bias of hazard ratio for overall survival in the meta-analysis.

the results were not confirmed by other studies. Besides, there is no pooled analysis of the data according to the pathological classification of esophageal cancer. The value of PD-L1 overexpression in ESCC is still unclear. For procuring a reasonable conclusion, we combined eight eligible studies including 1,350 cases to perform this meta-analysis.

Clinicopathological features, such as differentiation, tumor depth, status of lymph node metastasis and TNM stage, which were proved to be associated with poor prognosis of esophageal cancer (33-35), have been reported correlated with PD-L1 expression in ESCC by some independent researches. But most of them were not strongly confirmed by other studies. For instance, only one of the eight enrolled researches in our analysis showed PD-L1 expression was correlated with tumor differentiation (17). Two articles identified PD-L1 overexpression was related to deeper tumor invasion (15,21). With regards to status of lymph node metastasis and TNM stage, positive results were reported in four (15,17,19,22) and two (17,22) studies respectively. Interestingly, Chen *et al.* found PD-L1 overexpression was associated with better lymph node status and earlier stage (17), which was completely contrary to other studies. When we pooled the data together, none of the clinicopathological features (gender, differentiation, tumor depth, lymph node status and TNM stage) was associated with PD-L1 expression. The conclusion is not the same as conventional experiences of other tumors (36-39). Differences might be caused by the mechanism of PD-L1 in ESCC, inadequate sample size or variable definitions of PD-L1 expression. Further studied is needed to resolve this conflict.

Two former articles have meta-analyzed the relationship

of expression status of PD-L1 and prognostic significance in esophageal cancer (31,32). Both studies demonstrated positive PD-L1 expression status in tumor cells is a risk factor for prognosis in esophageal cancer. However, none of them have a subgroup analysis according to the pathological classification of esophageal cancer. Two major histological types of esophageal cancer, ESCC and esophageal adenocarcinoma (EAC), have different etiology, origins of tumor cells, biological behaviors, growth pattern and prognosis. Though only one study suggested PD-L1 overexpression was associated with poor prognosis of EAC (25), inconsistent results were found in researches of ESCC. In our study, the pooled HR showed high expression of PD-L1 impaired the OS of ESCC (HR =1.65; 95% CI: 0.95–2.85), whereas the difference has no statistical significance (P=0.07).

Efforts were made to conduct a comprehensive analysis, but some limitations still should be acknowledged. First, unified criteria had not been established for determining the positive expression of PD-L1 in ESCC. Various definitions of PD-L1 positivity and diverse antibodies for detecting PD-L1 expression were used in enrolled researches, which would cause heterogeneity of the overall results. Secondly, some HRs of survival data in current analysis were calculated or estimated from available data or Kaplan-Meier curves, which may have compromised the precision of the data. Thirdly, all included studies were hold in East Asia (five studies in China and three in Japan). The results need to be confirmed in a wider range of population especially in western countries. Fourthly, the number of included studies is relatively small.

Conclusions

Our meta-analysis revealed PD-L1 expression in ESCC was not associated with common clinicopathological features, including gender, histological differentiation, tumor depth, status of lymph node metastasis, distal metastasis and TNM stage. A trend was found that positive PD-L1 expression might impair the survival outcome of ESCC, though the difference was not statistically significant. Further large-scale studies should be performed to have a deeper insight into the precise clinicopathological and prognostic significance of PD-L1 expression in ESCC by unified testing standard.

Acknowledgements

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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