Prognostic value of PD–L1 expression in patients with primary solid tumors

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ABSTRACT

Programmed death-ligand 1 (PD-L1) is thought to play a critical role in immune escape by cancer, but whether PD-L1 expression can influence prognosis of patients with solid tumors is controversial. Therefore, we meta-analyzed available data on whether PD-L1 expression correlates with overall survival (OS) in such patients. PubMed, EMBASE and other databases were systematically searched for cohort or case-control studies examining the possible correlation between PD-L1 expression and OS of patients with solid tumors. OS was compared between patients positive or negative for PD-L1 expression using scatter plots, and subgroup analyses were performed based on tumor type and patient characteristics. Data from 59 studies involving 20,044 patients with solid tumors were meta-analyzed. The median percentage of tumors positive for PD-L1 was 30.1%. OS was significantly lower in PD-L1-positive patients than in PD-L1-negative patients at 1 year (P = 0.039), 3 years (P < 0.001) and 5 years (P < 0.001). The risk ratios of OS (and associated 95% confidence intervals) were 2.02 (1.56-2.60) at 1 year, 1.57 (1.34-1.83) at 3 years and 1.43 (1.24-1.64) at 5 years. Similar results were obtained in subgroup analyses based on patient ethnicity or tumor type. The available evidence suggests that PD-L1 expression negatively affects the prognosis of patients with solid tumors. PD-L1 might serve as an efficient prognostic indicator in solid tumor and may represent the important new therapeutic target.

INTRODUCTION

Immune co-stimulatory and co-inhibitory receptors determined the functional outcome of T cell receptor (TCR) signaling and immune surveillance [1]. Tumors can modulate the interactions between inhibitory receptors and ligands to escape immune responses [2, 3]. For example, the co-inhibitory receptor programmed cell death 1 (PD-1) plays a key role in cancer immune, especially in the immune escape phase [4]. PD-1 can be expressed in activated CD4+ and CD8+ T cells, but also in some natural killer cells and B cells [5]. When PD-1 binds to the ligand PD-L1 (B7-H1) expressed on the surface of tumors, it strongly inhibits the production of T cells and cytokines [6, 7], promoting tumor cell growth and immune escape [8, 9].

PD-L1 also plays a key role in binding to PD-1 receptors expressed on activated T cells in T cell co-suppression and depletion [9–11]. PD-L1 expressed on tumor cells promotes tumor cell-specific T cell inactivation or apoptosis, leading to tumor cell growth and exacerbation of tumor immune escape [12]. PD-L1 is expressed in many types of human cancers, including in esophageal, gastrointestinal, pancreatic, breast, lung...
and kidney cancers [10–14]. Clinical trials suggest that blocking the PD-1/PD-L1 interaction using anti-PD-1 antibodies can be effective against several different malignancies, including melanoma, lung cancer, kidney cancer and bladder cancer [15–19].

In addition to serving as a therapeutic target, PD-L1 may also be useful as a prognostic biomarker [22]. However, whether PD-L1 expression is associated with worse prognosis for patients with primary solid tumors remains controversial [20–22]. Therefore we meta-analyzed all available evidence to address this question comprehensively.

RESULTS

A total of 1,258 records were retrieved from PUBMED, EMBASE, Web of Science and EBSCO (Figure 1). After excluding 825 duplicate publications, we reviewed the abstracts and titles of the remaining 433 articles. This led to the exclusion of another 288 records that were not original research articles published in English. The remaining articles were read in full, leading to the exclusion of 86 records because they did not deal with human patients or solid tumors, or because they failed to report adequate outcomes data. In the end, 59 articles were included in the meta-analysis.

Key features of the 59 studies are summarized in Table 1; 35 studies involved Asian populations and 24 involved non-Asian populations. The studies analyzed 20,004 patients from China [23–41], France [42], New Zealand [43, 44], Brazil [45], Australia [46], Canada [47, 48], Italy [49], Germany [50, 51], United States [52–65], Japan [66–74], South Korea [75–78], Switzerland [79] and Taiwan [80, 81]. PD-L1 expression, which was analyzed in similar ways across all studies, was characterized as positive in 6,028 patients and negative in the remaining 13,976. One third of the studies (19) involved gastrointestinal tumors, while the remaining 40 involved other types of tumors. Altogether 11 malignancies were represented in the patient population: breast cancer (5 studies), renal cell carcinoma (7), colorectal cancer (3), esophageal cancer (3), gastric cancer (7), hepatocellular carcinoma (7), Merkel cell carcinoma (3), small cell lung cancer (11), oral squamous cell carcinoma (5), pancreatic cancer (3), and urinary tract epithelial cell carcinoma (4).

Figure 1: Flow chart of study selection.
| Study      | Country | Tumor type | Characteristic | Age       | Gender male / female | No. patients positive/ negative for PD-L1 | PD-L1-positive OS (%) | PD-L1-negative OS (%) | P       |
|------------|---------|------------|----------------|-----------|----------------------|------------------------------------------|------------------------|------------------------|---------|
| Qin 2015   | China   | Breast cancer | Primary        | 47 (21-84) | -                    | 189/681                                  | 81%                    | 92%                    | <0.001  |
| Sabatier 2015 | France | Breast cancer | Primary        | ≤50: 1288  | 1021 (28%) 267 (31%) 3207 | 1076/4378                                | 90%                    | 91%                    | 0.070   |
| Muenst 2014 | Switzerland | Breast cancer | Primary        | 63.8 ± 14.2 | -                    | 152/498                                  | 37%                    | 37%                    | <0.001  |
| Baptista 2016 | Brazil | Breast cancer | Primary        | ≤50: 176   | 1021 (28%) 267 (31%) 204 | 107/82                                   | 85%                    | 85%                    | 0.030   |
| Beckers 2016 | Australia | Breast cancer | Primary        | -                              | -                                    | 123/38                                  | 65%                    | 65%                    | 0.035   |
| Droeser 2013 | Italy | Colorectal cancer | Primary        | 69.9 (30-96) | -                    | 741/673                                  | 61%                    | 61%                    | <0.001  |
| Shi SJ 2013 | China  | Colorectal cancer | Primary        | 59.8 ± 12.5 | -                    | 91/116                                   | 42%                    | 42%                    | 0.017   |
| Zhu 2014   | China   | Colorectal cancer | Primary        | ≤50: 54    | 1021 (28%) 267 (31%) 47 | 53/48                                   | 47%                    | 47%                    | 0.051   |
| Krambeck 2007 | USA | Renal cell carcinoma | Primary        | ≤65: 54    | 1021 (28%) 267 (31%) 47 | 150/148                                  | 47%                    | 47%                    | <0.005  |
| Thompson 2005 | Canada | Renal cell carcinoma | Primary        | -                              | -                                    | 103/196                                  | 52%                    | 52%                    | <0.001  |
| Thompson 2007 | Canada | Renal cell carcinoma | Primary        | ≤65: 138   | 1021 (28%) 267 (31%) 129 | 177/90                                  | 52%                    | 52%                    | 0.004   |
| Abbas 2016 | Germany | Renal cell carcinoma | Primary        | 63 (31-88) | -                    | 116/61                                   | 47%                    | 47%                    | 0.005   |
| Choueiri 2014 | USA | Renal cell carcinoma | Primary        | 59 (24-81) | -                    | 55/46                                    | 48%                    | 48%                    | <0.001  |
| Thompson 2004 | USA | Renal cell carcinoma | Primary        | -                              | -                                    | 87/109                                   | 25%                    | 25%                    | <0.001  |
| Thompson 2006 | USA | Renal cell carcinoma | Primary        | -                              | -                                    | 73/233                                   | 42%                    | 42%                    | <0.001  |
| Ohigashi 2005 | Japan | Esophageal cancer | Primary        | ≤65: 24    | 1021 (28%) 267 (31%) 17 | 32/9                                    | 18%                    | 18%                    | 0.001   |
| Tanaka 2016 | Japan   | Esophageal cancer | Primary        | 62.6 ± 10.0 | -                    | 157/33                                   | 25%                    | 25%                    | 0.001   |
| Chen 2014   | China   | Esophageal cancer | Primary        | ≤65: 51    | 1021 (28%) 267 (31%) 48 | 76/23                                    | 17%                    | 17%                    | 0.675   |

(Continued)
| Study       | Country     | Tumor type            | Characteristic | Age       | Gender male / female | No. patients positive/negative for PD-L1 | PD-L1-positive OS (%) | PD-L1-negative OS (%) | P         |
|------------|-------------|-----------------------|----------------|-----------|----------------------|---------------------------------------|------------------------|------------------------|-----------|
| Loos 2011  | Germany     | Esophageal cancer     | Primary        | -         | -                    | 37/64                                 | 79 51 32               | 96 82 69               | <0.001    |
| Shohei 2016| Japan       | Gastric carcinoma     | Primary        | 67 ± 14   | -                    | 75/30 28/105                         | 84 41 10               | 91 63 51               | 0.022     |
| Geng 2015  | China       | Gastric carcinoma     | Primary        | ≤65: 65   | 1021 (28%) 267 (31%) | 61/39 65/100                         | 72 41 29               | 87 61 37               | 0.026     |
|            |             |                       |                | >65: 65   |                       |                                       |                        |                        |           |
| Hou 2014   | China       | Gastric carcinoma     | Primary        | ≤58: 55   | 1021 (28%) 267 (31%) | 75/36 70/111                         | 78 46 32               | 93 77 68               | <0.001    |
|            |             |                       |                | >58: 56   |                       |                                       |                        |                        |           |
| Wu 2006    | Sweden      | Gastric carcinoma     | Primary        | ≤65: 64   | 1021 (28%) 267 (31%) | 75/27 43/102                         | 75 38 30               | 98 71 64               | 0.001     |
| Tamura 2015| Japan       | Gastric carcinoma     | Primary        | 66.1 (17-89) | 305/126 128/303 | 90 65 49 | 94 78 64               | 0.001     |
| Zheng 2014 | China       | Gastric carcinoma     | Primary        | ≤60: 42   | 1021 (28%) 267 (31%) | 62/18 33/47                         | 86 65 52 | 91 69 53 | 0.636     |
| Qing 2015  | USA         | Gastric carcinoma     | Primary        | ≤60: 42   | 1021 (28%) 267 (31%) | 72/35 54/107                         | 81 28 18 | 93 47 27 | 0.004     |
| Gao 2009   | China       | Hepatocellular carcinoma | Primary        | 52 (18-81) | 204/36 60/180 70 42 39 | 83 57 49 | 0.029     |
| Jung 2016  | South Korea | Hepatocellular carcinoma | Primary        | ≤53: 44   | 1021 (28%) 267 (31%) | 69/16 23/62                         | 43 19 17 | 90 69 59 | <0.001    |
| Kan 2015   | China       | Hepatocellular carcinoma | Primary        | ≤50: 56   | 1021 (28%) 267 (31%) | 108/20 105/23                      | 30 5 0 | 50 15 10 | 0.001     |
| Umemoto 2015| Japan      | Hepatocellular carcinoma | Primary        | 64 ± 10   | 71/9 37/43 74 51 40 | 80 73 71 | 0.051     |
| Zeng 2011  | China       | Hepatocellular carcinoma | Primary        | 53.1(35–68)| 109/32 31/32 | 38 - - | 85 - - | 0.000     |
| Gabrielson 2016| USA     | Hepatocellular carcinoma | Primary        | 61 (30–86)| 50/15 30/35 | 85 85 - | 53 45 - | 0.029     |
| Wu 2009    | China       | Hepatocellular carcinoma | Primary        | 48, 23–75 | 65/6 35/36 81 54 40 | 97 83 71 | 0.014     |
| Azuma 2014 | Japan       | Lung cancer           | Primary        | ≤54: 23   | 1021 (28%) 267 (31%) | 26/14 69/120                      | 71 11 - | 85 48 - | <0.001    |

(Continued)
| Study       | Country | Tumor type       | Characteristic | Age       | Gender male / female              | No. patients positive/negative for PD-L1 | PD-L1-positive OS (%) | PD-L1-negative OS (%) | P     |
|------------|---------|------------------|----------------|-----------|-----------------------------------|----------------------------------------|----------------------|-----------------------|-------|
| Cooper 2015 | USA     | Lung cancer      | Primary        | ≤60: 15   | 477/201                           | 628/678                                | 95/73/62             | 84/54/44              | 0.023 |
| Jiang 2015  | China   | Lung cancer      | Primary        | 1021 (28%) | 39/40                             | 50/79                                  | 83/74/70             | 0.042                 |
| Kim 2015    | South Korea | Lung cancer  | Primary        | 267 (31%) | 1021 (28%) | 628/678                   | 95                     | 73                     | 62 | 0.570 |
| Mu 2011     | China   | Lung cancer      | Primary        | >60: 64   | -                                 | 58/109                                | 87/20/ -              | 95/38/ -              | <0.005 |
| Velcheti 2014 | USA     | Lung cancer      | Primary        | ≤70: 232  | 260/37                            | 56/155                                | 78/43/27             | 87/61/51              | 0.028 |
| Yang 2014   | Taiwan  | Lung cancer      | Primary        | ≤70: 132  | 54/109                            | 65/163                                | 98/93/91             | 98/87/83              | 0.027 |
| Zhang 2014  | China   | Lung cancer      | Primary        | ≤58: 73   | 84/59                             | 70/143                                | 84/71/53             | 97/89/77              | 0.002 |
| Song 2016   | China   | Lung cancer      | Primary        | <60: 207  | 198/187                           | 186/199                               | 99/71/40             | 99/79/52              | 0.069 |
| Inamura 2016 | Japan  | Lung cancer      | Primary        | ≤60: 96   | 142/126                           | 43/225                                | 85/69/55             | 95/81/71              | 0.019 |
| Chen 2009   | China   | Pancreatic cancer| Primary        | <60: 61   | 76/23                             | 18/40                                 | 32/8/ -              | 84/58/17              | 0.001 |
| Nomi 2007   | Japan   | Pancreatic cancer| Primary        | ≤60: 55   | -                                 | 20/51                                 | 48/12/ -             | 78/24/ -              | 0.016 |
| Wang 2010   | China   | Pancreatic cancer| Primary        | 40/10     | 40/10                             | 23/40                                 | 87/8/ -              | 100/33/ -             | <0.001 |
| Gadiot 2011 | Netherlands | Merkel cell carcinoma | Primary  | -                                   | 36/27                                | 16/63/ -              | - 51/37/ -             | - 68/52/ -             | 0.200 |
| Hino 2010   | Japan   | Merkel cell carcinoma | Primary   | 68.84 ± 2.85 | 38/21                             | 34/59                                | - - 52/ -             | - - 81/ -             | 0.040 |
| Taube 2012  | USA     | Merkel cell carcinoma | Primary | -                                   | 76/74                                | 57/150/ -              | - - 84/ -             | - - 61/ -             | 0.330 |
| Boorjian 2008 | USA     | Urinary tract epithelial cell carcinoma | Primary | -                                   | 259/59                               | 39/314/ -              | 58/51/43              | 91/82/67              | 0.005 |
| Nakanishi 2006 | Japan  | Urinary tract epithelial cell carcinoma | Primary | -                                   | 47/18                                | 46/65/57              | 86/68/57              | 100/100/100            | 0.021 |
| Wang 2009   | China   | Urinary tract epithelial cell carcinoma | Primary | -                                   | 31/5                                 | 36/50                  | 91/68/ -              | 100/100/ -             | 0.020 |
| Xylinas 2014 | USA     | Urinary tract epithelial cell carcinoma | Primary | 65.9 (60.5e72.2)                     | 244/58                               | 76/226                  | 83/66/63             | 95/82/69              | 0.020 |

(Continued)
PD-L1 expression and OS across all studies

Meta-analysis of data from all 59 studies showed that the median OS rate was significantly lower in PD-L1-positive patients than in PD-L1-negative patients at 1 year (P = 0.039), 3 years (P < 0.001) and 5 years (P < 0.001; Figure 2). The RR for OS at the three time points (and associated 95% confidence intervals [CIs]) were 2.02 (1.56-2.60), 1.57 (1.34-1.83) and 1.43 (1.24-1.64) (Table 2 and Figure 2).

Subgroup analysis by tumor type

Given the significant heterogeneity in the meta-analysis involving all 59 studies, we performed a series of subgroup analyses to examine the possible correlation between PD-L1 expression and OS. PD-L1 expression was associated with worse 1-year OS for the following types of solid tumor (Table 2): gastric cancer, 2.48 (1.80-3.41); renal cell carcinoma, 3.38 (2.13-5.39); and hepatocellular carcinoma, 1.87 (1.01-3.46). PD-L1 expression was associated with worse 3-year OS for the following cancers: esophageal cancer, 2.77 (1.78-4.30); gastric cancer, 1.63 (1.43-1.87); pancreatic cancer, 1.48 (1.06-2.06); and renal cell carcinoma, 4.14 (2.07-8.26). PD-L1 expression was associated with worse 5-year OS for esophageal cancer, 3.55 (2.63-5.65); gastric cancer, 1.45 (1.18-1.79); hepatocellular carcinoma, 1.58 (1.11-2.25); and renal cell carcinoma, 2.57 (1.46-4.52).

Among the subset of 4,984 patients with gastrointestinal tumors, 1,778 (35.6%) were PD-L1-positive and 3,206 (64.4%) were PD-L1-negative. PD-L1 expression was associated with significantly worse OS at 1 year (P = 0.004), 3 years (P = 0.005), and 5 years (P = 0.002; Figures 3 and 7). The corresponding RRs and 95% CIs were 2.12 (1.45-3.09), 1.52 (1.23-1.89), and 1.40 (1.17-1.67) (Table 2).

Subgroup analysis by patient ethnicity

Among the subset of 6,337 Asian patients, 2,211 were PD-L1-positive and 4,126 were PD-L1-negative. PD-L1 expression was associated with significantly lower OS at 1 year (P = 0.039), 3 years (P < 0.001) and 5 years (P < 0.001; Figure 2). The RR for OS at the three time points (and associated 95% confidence intervals [CIs]) were 2.02 (1.56-2.60), 1.57 (1.34-1.83) and 1.43 (1.24-1.64) (Table 2 and Figure 2).

Among the subset of 13,667 non-Asian patients, 3,817 were PD-L1-positive and 9,850 were PD-L1-negative. PD-L1 expression was associated with significantly worse OS at 1 year (P = 0.017), 3 years (P = 0.010) and 5 years (P = 0.003; Figures 4 and 8). The corresponding RRs and 95% CIs were 1.79 (1.33-2.40), 1.61 (1.30-1.98), and 1.47 (1.23-1.75) (Table 2).
Table 2: Meta-analysis of possible associations between PD-L1 expression and overall survival in patients with solid tumors

| Group or subgroup | N     | PD-L1(+/−)  | 1 year OS          | 3 year OS          | 5 year OS          |
|-------------------|-------|-------------|-------------------|-------------------|-------------------|
|                   |       |             | RR (95 % CI)      | P     | F    | RR (95 % CI)      | P     | F    | RR (95 % CI)      | P     | F    |
| All studies       | 59    | 6028/13976  | 2.02 (1.56-2.60)  | <0.001 | 84   | 1.57 (1.34-1.83)  | <0.001 | 91   | 1.43 (1.24-1.64)  | <0.001 | 92   |
| Ethnic subgroups  |       |             |                   |       |      |                   |       |      |                   |       |      |
| Asian             | 35    | 2211/4126   | 1.83 (1.61-2.08)  | <0.001 | 49   | 1.57 (1.39-1.77)  | <0.001 | 74   | 1.44 (1.31-1.58)  | <0.001 | 92   |
| Non-Asian         | 24    | 3817/9850   | 1.98 (1.27-3.09)  | 0.003  | 90   | 1.60 (1.18-2.17)  | 0.003  | 95   | 1.39 (1.08-1.78)  | 0.009  | 95   |
| Tumor origin      |       |             |                   |       |      |                   |       |      |                   |       |      |
| Gastrointestinal tumors | 24    | 1778/3206   | 2.12 (1.45-3.09)  | <0.001 | 86   | 1.52 (1.23-1.89)  | <0.001 | 91   | 1.40 (1.17-1.67)  | <0.001 | 91   |
| Other tumors      | 35    | 4250/10770  | 1.79 (1.33-2.40)  | <0.001 | 86   | 1.61 (1.30-1.98)  | <0.001 | 92   | 1.47 (1.23-1.75)  | <0.001 | 91   |
| Tumor type        |       |             |                   |       |      |                   |       |      |                   |       |      |
| Breast cancer     | 5     | 1647/5677   | 1.80 (0.60-5.42)  | 0.30   | 79   | 1.79 (0.77-4.19)  | <0.18  | 95   | 1.80 (0.68-4.73)  | <0.24  | 96   |
| Esophageal cancer | 4     | 187/252     | 1.90 (0.69-5.21)  | 0.21   | 70   | 2.77 (1.78-4.30)  | <0.001 | 48   | 3.55 (2.63-5.65)  | <0.001 | 0    |
| Gastric carcinoma | 7     | 421/875     | 2.48 (1.80-3.41)  | <0.001 | 18   | 1.63 (1.43-1.87)  | <0.001 | 32   | 1.45 (1.18-1.79)  | <0.001 | 79   |
| Hepatocellular carcinoma | 7    | 321/339     | 1.87 (1.01-3.46)  | 0.04   | 78   | 1.40 (0.92-2.15)  | 0.12   | 84   | 1.58 (1.11-2.25)  | 0.01   | 83   |
| Lung cancer       | 11    | 1396/2366   | 1.39 (0.69-2.81)  | 0.36   | 88   | 1.17 (0.84-1.63)  | 0.35   | 92   | 1.16 (0.86-1.57)  | 0.32   | 93   |
| Pancreatic cancer | 3     | 61/131      | 3.43 (2.06-5.73)  | <0.001 | 15   | 1.48 (1.06-2.06)  | 0.02   | 0    | -                | -      | -    |
| Merkel cell carcinoma | 3    | 107/272     | -                 | -      | -    | -                 | -      | -    | 1.01 (0.41-2.99)  | 0.85   | 89   |
| Urinary tract epithelial cell carcinoma | 4    | 197/655     | 6.24 (3.62-10.74) | <0.001 | 0    | 3.43 (1.50-7.84)  | 0.003  | 75   | 1.79 (0.86-3.70)  | 0.12   | 82   |
| Oral squamous cell cancer | 5    | 380/537     | 1.05 (0.58-1.93)  | 0.87   | 63   | 0.95 (0.72-1.26)  | 0.72   | 55   | 1.07 (0.89-1.29)  | 0.45   | 0    |
| Renal cell carcinoma | 7    | 208/572     | 3.38 (2.13-5.39)  | <0.001 | 24   | 4.14 (2.07-8.26)  | <0.001 | 81   | 2.57 (1.46-4.52)  | <0.001 | 79   |
| Colorectal cancer | 3     | 788/1609    | 1.17 (0.27-5.06)  | 0.84   | 95   | 0.94 (0.33-2.67)  | 0.90   | 96   | 1.16 (0.55-2.45)  | 0.69   | 95   |

N, number of studies; OS, overall survival; RR, risk ratio; 95% CI, 95% confidence interval
* These meta-analyses were performed using a fixed-effects model. All other meta-analyses were performed using a random-effects model.
DISCUSSION

While studies published more than a decade ago established that PD-L1 promotes cancer immune escape [82, 83] and that blocking PD-L1 can improve the anti-tumor efficacy of anti-tumor responses [84–86], whether PD-L1 expression by solid tumors negatively affects patient prognosis remains unclear. Here we reviewed 59 studies involving 20,004 patients with 11 types of solid tumors and found strong evidence that PD-L1 expression is associated with significantly lower OS at 1, 3 and 5 years. This effect was observed in meta-analyses involving patient survival for 1, 3 and 5 years for patients with gastrointestinal and non-gastrointestinal tumors.

Figure 2: Scatter plot of OS at 1, 3 and 5 years for patients positive or negative for PD-L1 expression. Data come from the entire patient population.

Figure 3: Scatter plot of OS at 1, 3 and 5 years for patients positive or negative for PD-L1 expression. Data come from the subset of patients with gastrointestinal tumors.

Figure 4: Scatter plot of OS at 1, 3 and 5 years for patients positive or negative for PD-L1 expression. Data come from the subset of patients with non-gastrointestinal tumors.
all patients as well as several subgroups of patients stratified by ethnicity and tumor type.

PD-L1 positive expression is associated with viral infection and chronic inflammation [87]. Expression of PD-L1 and/or PD-1 has been described for numerous types of cancers associated with viral infection [88], including polycyclic virus-associated Merkel cell carcinoma [89], hepatitis B virus-associated hepatocellular carcinoma [33], human papillomavirus-associated head and neck cancer, and Epstein-Barr virus-related nasopharyngeal carcinoma [90]. In patients with hepatocellular carcinoma, PD-L1 expression was significantly higher in tumor macrophages than in matched normal tissues, and expression correlated with tumor grade [25].

Our results are consistent with previous reports that PD-L1 expression is associated with worse 5-year outcome in patients with gastrointestinal carcinomas such as esophageal cancer and gastric cancer [70, 79] as well as colorectal cancer [25]. The precise mechanisms whereby PD-L1 expression may worsen prognosis are unknown; When PD-1 binds to the ligand PD-L1 (B7-H1) expressed on the surface of tumors, PD-1 has been shown to promote tumor cell-specific T cell inactivation or apoptosis [12].

The results of this meta-analysis should be interpreted cautiously because of several limitations. One is the lack of a standardized assay and cut-off value for classifying patients as PD-L1-positive. This may help explain the high heterogeneity observed across the included studies. Another limitation is our exclusion of gray literature, which may have increased the risk of publication bias and selection bias.

Despite these limitations, this large meta-analysis provides strong evidence that expression of PD-L1 may be a meaningful index for predicting prognosis in a wide variety of patients with solid tumors. These findings justify more focused prognostic studies in well-defined patient populations in which a panel of clinically relevant outcomes beyond only OS are considered.

Figure 5: Scatter plot of OS at 1, 3 and 5 years for patients positive or negative for PD-L1 expression. Data come from the subset of Asian patients.

Figure 6: Scatter plot of OS at 1, 3 and 5 years for patients positive or negative for PD-L1 expression. Data come from the subset of non-Asian patients.
Figure 7: Forrest plot of OS at 1, 3 and 5 years for patients positive or negative for PD-L1 expression. Data come from the subset of patients with gastrointestinal tumors.

Figure 8: Forrest plot of OS at 1, 3 and 5 years for patients positive or negative for PD-L1 expression. Data come from the subset of patients with non-gastrointestinal tumors.

Figure 9: Forrest plot of OS at 1, 3 and 5 years for patients positive or negative for PD-L1 expression. Data come from the subset of Asian patients.

Figure 10: Forrest plot of OS at 1, 3 and 5 years for patients positive or negative for PD-L1 expression. Data come from the subset of non-Asian patients.
MATERIALS AND METHODS

Literature search

PubMed, EMBASE, Web of Science and EBSCO were searched through 15 January 2017 to identify cohort and case-control studies examining the relationship between PD-L1 expression and prognosis of patients with solid tumors. The following search terms were used: *programmed death-ligand 1, PD-L1, B7-H1, CD274 and solid tumor*.

Inclusion and exclusion criteria

To be included in our meta-analysis, studies had to involve (1) primary solid tumors in human patients; (2) The main content of the articles is to analyze the relationship between the expression of PD-L1 and the prognosis of solid tumors in patients; (3) a hospital-based or population-based case-control or cohort design, regardless of sample size; (4) immunohistochemical assay of PD-L1 expression as high and low PD-L1 expression; (5) all patients underwent surgery; and (6) adequate reporting of overall survival (OS) data. When eligible studies involved overlapping patient populations, only the most recent or complete report was included. Studies were excluded if they were letter, summary of meeting and review; if they were published in a language other than English; or if they failed to report adequate data; or they investigated metastatic tumors. Gray literature (Reports and papers that were not published in PubMed, EMBASE, Web of Science and EBSCO) was not included into this study. Reference lists within identified articles were also searched manually to identify additional articles.

Meta-analysis outcomes

The primary outcome in the meta-analysis was OS. This outcome was compared between patients showing high or positive PD-L1 expression and patients showing low or no expression, as defined within the individual studies.

Data collection

Two researchers (P.-C.Y, X.X) independently screened studies for inclusion. Disagreements were resolved by discussion and, when necessary, consultation with a third author (S.Z). The first author's name, year of publication, country, number of patients, and tumor type were extracted from each study, and OS results for 1, 3 and 5 years were extracted from tables or Kaplan-Meier curves.

Statistical analysis

Forest plots of OS were generated using RevMan 5.3 (Cochrane Collaboration, Copenhagen, Denmark). Weighted risk ratio (RR) estimates were generated from pooled data using Mantel-Haenszel random-effects meta-analysis, unless no statistically heterogeneity, in which case fixed-effects meta-analysis was performed. Statistical heterogeneity in meta-analyses was assessed using Cochrane's Q and I² statistics. Survival results were analyzed using scatter plots generated in Prism 5 (Graphpad Software, San Diego, USA). The results for different patient groups were compared using the log-rank test. The threshold of statistical significance was defined as P < 0.05.

Author contributions

X.X, J.-H.Z and L.L conceived the study; P.-C.Y collected and analyzed the data; X.X drafted the manuscript; all authors have read and approved the final version to be published.

CONFLICTS OF INTEREST

The authors have declared that no competing interests exist.

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