Prognostic significance of circulating soluble programmed death ligand-1 in patients with solid tumors

A meta-analysis

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Abstract

Background: The prognostic significance of circulating soluble programmed death ligand-1 (sPD-L1) in patients with solid tumors remains unclear. We performed a meta-analysis to address this issue.

Methods: Several electronic databases were searched from January 1970 to May 2017. The hazard ratios (HRs) and 95% confidence interval (95% CI) were calculated to determine the relationship between the level of soluble PD-L1 in peripheral blood and patient overall survival.

Results: A total of 1040 patients with solid tumors from 8 eligible studies were included in the present meta-analysis. The pooled HR suggested that a high level of soluble PD-L1 (sPD-L1) in peripheral blood was significantly correlated with a worse overall survival (HR = 2.26, 95% CI 1.83–2.80, Z = 7.51, P < .001).

Conclusion: The present meta-analysis demonstrated that a high level of soluble PD-L1 in peripheral blood significantly predicts poor prognosis in patients with solid tumors, suggesting that high level of sPD-L1 may serve as a predictive biomarker for poor prognosis.

Abbreviations: CI = confidence interval, ELISA = enzyme-linked immunosorbent assay, HCC = hepatocellular carcinoma, HR = hazard ratio, IV = inverse variance, mPD-L1 = membrane-bound programmed death ligand-1, NM = not mentioned, NOS = Newcastle–Ottawa Quality Assessment Scale, NSCLC = nonsmall cell lung cancer, PD-1 = programmed death 1, PD-L1 = programmed death ligand-1, SE = standard error, sPD-L1 = soluble programmed death ligand-1, VEGF = vascular endothelial growth factor.

Keywords: prognosis, solid tumor, soluble programmed death ligand-1

1. Introduction

Human cancer cells generate cancer-specific antigens that are theoretically recognizable as targets to be eliminated for the immune system. However, the immune system is held in check by immune checkpoints pathways, which normally maintain self-tolerance and limit collateral tissue damage during inflammation.[1,2] The binding of programmed death 1 (PD-1) and its ligand (PD-L1), usually upregulated in the tumor microenvironment, activates a typical immune checkpoint pathway, suppressing T-cell related antitumor activity.[3,4] Major breakthroughs were made over the past decade concerning cancer immunotherapy directed against such checkpoints.[5] Recent clinical trials involving the usage of PD-1/PD-L1 blockade in cancer patients gained inspiring results, leading to the widespread clinical application of PD-1/PD-L1 antibodies, benefiting numerous cancer patients.[6-7]

PD-L1 is presented in 2 forms, the membrane-bound (mPD-L1) form that is detected mostly on the membrane of tumor cells, and the soluble (sPD-L1) form that is found in the peripheral blood of patients with cancers and other chronic diseases such as rheumatoid arthritis.[8,9] Previous studies mainly focused on the expression of mPD-L1 in tumor tissues and established that high expression of mPD-L1 inside the tumor microenvironment was related with worse survival in cancer patients.[10-13] Likewise, it is presumed that the soluble form of PD-L1 in peripheral blood is also able to bind to its PD-1 receptor on T cells, consequently dampening T cell related immune activity.[16,17] The theory was validated by several studies that explored the prognostic role of sPD-L1 in patients with solid tumors.[18-25] from which we performed a meta-analysis using the studies that met our criteria to determine the prognostic significance of sPD-L1 in patients with solid tumors.
2. Materials and methods

2.1. Search strategy
A systematic search was performed from January 1970 to May 2017 through several major medicine-related electronic databases, including PubMed, EMBASE, Cochrane Library, CKM, Wang fang Database, and CNKI. In order to identify studies concerning the clinicopathologic and prognostic significance of soluble PD-L1 in patients with solid tumors, we conducted literature search by a comprehensive strategy combining text word and MeSH (Emtree for EMBASE database accordingly) with the terms “prognosis” or “prognostic” or “clinical” or “clinicopathological” and “soluble” or “serum” or “peripheral blood” or “sPD-L1” and “neoplasms” or “neoplasias” or “neoplasm” or “tumors’ or “tumor” or “malignancy” or “malignancies” or “cancer” or “cancers” or “carcinoma” and “PD-1” or “PD-L1” or “programmed death 1” or “B7H1” or “B7-H1” or “CD274” or “B7 homolog 1” or “cluster of differentiation 274.” The strategy was respectively adjusted in each database. Only human studies were included. In addition, we carried out a manual search according to the references of the eligible studies. We also attempted to contact the corresponding author for detailed information when necessary. The entire screening process was conducted according to the PRISMA 2009 statement.

2.2. Criteria for inclusion and exclusion
Studies were deemed eligible when meeting the inclusion criteria as follows: the patients were pathologically diagnosed of a certain kind of solid tumors; soluble PD-L1 level was measured by enzyme-linked immunosorbent assay (ELISA); the study provided information concerning hematological malignancies such as lymphoma and multiple myeloma; nonhuman experiments; laboratory studies; and studies without sufficient data.

2.3. Quality assessment and data extraction
The Newcastle–Ottawa Quality Assessment Scale (NOS) was applied by 2 reviewers (WW and YW) to independently determine the quality of each included study in this meta-analysis. The third reviewer (BX) would join to reach consensus if disagreements occurred during assessment. Two investigators (WW and YW) independently extracted the following data from the included studies: surname of the first author, year of publication, country, study time, tumor kind, sample source, cut-off values, positivity and number of patients, follow-up period, and survival data (HR and 95% CI). A standardized information form was applied in which each study was given the code name of its first author + publication year. Disagreements during the data extraction process were resolved by consensus with the third reviewer (BX). All analyses were based on previously published studies; thus, no ethical approval was required.

2.4. Statistical analysis
This meta-analysis was performed by Cochrane Revman 5.3.0 (the Cochrane Collaboration, Copenhagen, Denmark). The HRs for overall survival (OS) with 95% CI were pooled. If the study did not offer direct HR and 95% CI, the survival data were extracted from the Kaplan–Meier curves and HR was estimated using the methods established by Tierney et al.\textsuperscript{[26]} Heterogeneity was assessed using the Cochrane Q and I\textsuperscript{2} statistics, which was defined by the Cochrane Handbook Version 5.1.0 retrieved from http://handbook.cochrane.org/. 0% to 40%, negligible heterogeneity; 30% to 60%, moderate heterogeneity; 50% to 90%, substantial heterogeneity; 75% to 100%, considerable heterogeneity. A fixed effects model was applied unless significant heterogeneity occurred, in which case a random effects model was applied. A funnel plot was drawn to assess the potential publication bias.

3. Results

3.1. Search results
The initial search returned 770 studies with additional 4 studies identified by manual search. After 31 duplicated studies were removed by Endnote Software (Version X7; Thompson Reuters, CA), 743 studies were screened and 730 studies were excluded for irrelevant title or abstract. The remaining 13 potential studies were scanned through full-text and 5 studies were eliminated for incomplete data. Eventually, 8 studies with a total of 1040 patients were included in the current meta-analysis. The detailed selection process is shown in Figure 1.

3.2. Study characteristics
The characteristics of the included studies are listed in Table 1. The publication time varied from 2014 to 2017. Studies were from Germany, Japan, Korea, and China with different kinds of solid tumors, including lung cancer, gastric cancer, biliary tract cancer, hepatocellular carcinoma, and renal cancer. The exclusion criteria were as follows: reviews, letters, case reports, and conference abstracts without original data; studies concerning hematological malignancies such as lymphoma and multiple myeloma; nonhuman experiments; laboratory studies; and studies without sufficient data.

Figure 1. Flow diagram of study selection in the present meta-analysis.
cell carcinoma. The subject number of studies varied from 75 to 215, with a mean size of 130. Patient age ranged from 18 to 86 years. The samples tested for soluble PD-L1 were serum or plasma retrieved from peripheral blood of cancer patients. All the studies adopted an ELISA kit obtained from different manufacturers as listed to measure the levels of soluble PD-L1. The cut-off values ranged from 0.0183 to 7.32 ng/mL and positivity rate varied from 29.8% to 56.0%. The follow-up period ranged from 1 month to 100 months. All the studies reached a NOS score above 5 and the mean score was 7.25.

3.3. Prognostic significance of soluble PD-L1 in patients with solid tumors

As is depicted in Figure 2, a total of 1040 patients with solid tumors from 8 eligible studies were collected and the HRs for OS were analyzed. In each study, patients with a sPD-L1 level higher than the cut-off value were deemed sPD-L1-positive, and the rest sPD-L1-negative. The pooled HR was 2.26 (95% CI 1.83–2.80, Z = 7.51, P < .001). The result indicated that solid tumor patients with high levels of soluble PD-L1 had significantly poor prognosis compared with patients with low levels of soluble PD-L1. A fixed effects model was applied because no significant heterogeneity was found among the studies ($I^2 = 0\%$).

3.4. Sensitivity analysis

The HRs and 95% CI of all the included studies are listed in Table 2. Each study was successively removed to determine whether any one of the 8 studies had a significant impact on the pooled HR. The results of sensitivity analysis showed that the pooled HR was not significantly affected by any specific study.

3.5. Publication bias

A funnel plot was drawn to determine the potential publication bias. As is demonstrated in Figure 3, the plot was symmetric, suggesting that there was no significant publication bias.

4. Discussion

In the present meta-analysis, we searched through several major databases to identify studies exploring the relationship between sPD-L1 and prognosis in patients with solid tumors. Here, we selected 8 eligible studies involving 1040 patients to assess the prognostic value of sPD-L1. Patients from Japan, Germany, Korea, and China were diagnosed of different types of solid tumors, including nonsmall cell lung cancer, gastric cancer, hepatocellular carcinoma, biliary tract cancer, and renal cancer. We found a consistent negative effect of an elevated sPD-L1 on OS with a pooled HR of 2.26 (95% CI 1.83–2.80, Z = 7.51, P < .001). No significant heterogeneity was discovered. We conducted a sensitivity analysis and were convinced that the result of this meta-analysis was not significantly affected by any specific study. A funnel plot was drawn and no apparent publication bias was found.

Immunotherapy has taken the battle between human versus cancer into a new era. Scientists successfully harnessed

| Table 1  | Characteristics of studies included in the present meta-analysis. |
|-----------------|---------------------------------------------------------------|
| **References**  | **Country** | **Tumor** | **Study time** | **Median age, y** | **Female number** | **Follow-up period, mo** |
| Finkelmeier et al[18] | Germany | Hepatocellular carcinoma | 2009–2015 | 64 (38–86) | 44/215 | 9.9 (1–48.8) |
| Fukuda et al[19] | Japan | Renal cell carcinoma (post VEGF-targeted therapy) | 2007–2015 | NM | 72/181 | 31 (3–100) |
| Okuma et al[20] | Japan | Advanced lung cancer | 2014–2016 | 68.5 (20–86) | 42/96 | NM |
| Takahashi et al[21] | Japan | Metastatic/recurrent gastric cancer | 2011–2015 | 67 (39–79) | 17/75 | NM |
| Zhang et al[22] | China | advanced NSCLC | 2012–2014 | 57 (15–76) | 44/109 | 27.6 (6.5–38.3) |
| Zhao et al[23] | China | Advanced gastric adenocarcinoma | 2009–2013 | NM | 31/126 | 25 |
| Zheng et al[24] | Korea | Advanced biliary tract cancer (post palliative chemotherapy) | 2006–2009 | NM | 18/80 | 39.6 (1.5–76.6) |
| Ha et al[25] | Korea | | 2004–2009 | 59.6 (51.3–76.2) | 59/158 | 95.3 |

ELISA = enzyme-linked immunosorbent assay, HCC = hepatocellular carcinoma, NM = not mentioned, NSCLC = nonsmall cell lung cancer, VEGF = vascular endothelial growth factor

Figure 2. Forest plot of studies evaluating the hazard ratios of sPD-L1 for overall survival in solid tumor patients.

Figure 3. Funnel plot of studies evaluating the hazard ratios of sPD-L1 for overall survival in solid tumor patients.
tumor-infiltrating T cells for adoptive cell therapy. Tumor vaccines were developed to boost active antitumor immunity. The discovery of immune checkpoint molecules mediating T cell functions opened the new chapter of checkpoint blockade therapy. Unlike hematological malignancies, solid tumors were not universally acknowledged to be systemic diseases, yet the attempt to undertake human cancer from the scope of immunology should never be restricted to a single cell or organ. Although many studies explored the expression of PD-L1 inside the tumor microenvironment, it is reasonable to postulate that the soluble form of PD-L1 outside the tumor microenvironment is of no less importance, not to mention the fact that a blood test is far less invasive than a tissue biopsy.

PD-L1 is found on the surface of various antigen-presenting cells. Human tumor cells express PD-L1 as a mechanism to suppress host antitumor immunity. It is believed that sPD-L1 can be released or shed from PD-L1-positive tumor cells or immune cells, but the accurate source of soluble form of PD-L1 remains unclear. However, it has been proved that sPD-L1 still retains its biological activity and is able to specifically bind to PD-1 receptor in peripheral blood, thus activating the PD-1/PD-L1 pathway and theoretically establishing a systematic immunosuppressive effect.

The result of this meta-analysis illustrated that cancer patients with high levels of sPD-L1 had a shorter OS than those with low levels of sPD-L1, indicating that high sPD-L1 level may serve as a prognostic biomarker to identify patients with worse prognosis. Our conclusion could be rationalized from the following 2 perspectives. First, sPD-L1 can be released from PD-L1 positive tumor cells, which means that there could exist a certain correlation between sPD-L1 levels and PD-L1 tissue expression. Provided that previous studies already agreed high expression of PD-L1 on tumor cells was related with a worse prognosis, it is only logical to assume that sPD-L1 may also serve as a prognostic biomarker for worse survival. It was found that sPD-L1 level is elevated in cancer patients compared with healthy people, and higher sPD-L1 levels in cancer patients are usually found in more severe cases with earlier disease progression and later clinical stage. Second, it has been proved that the soluble form of PD-L1 still retains its biological activity, which means that sPD-L1, when binding to its receptor, can still activate the PD-1/PD-L1 pathway and function as an immune-suppressive regulator. On the basis of such assumptions, we can further speculate that sPD-L1 in peripheral blood might be able to specifically bind to PD-1 on the tumoricidal cell toxic lymphocytes (CTLs) before they reach the tumor site, thereby suppressing T cell activity and hampering antitumor response on a systemic scale.

While searching through the databases for eligible studies, we noticed that several studies focusing on hematological malignancies achieved similar conclusions. It was reported that elevated sPD-L1 was associated with a poorer prognosis in patients with aggressive diffuse large B-cell lymphoma and the result was validated through a replication study with a large cohort.

Similar results were gained in several other studies concerning natural killer/T-cell lymphoma and multiple myeloma.

There are several limitations in this meta-analysis. We intended to explore the prognostic value of sPD-L1 in all patients with solid tumors, but only 8 studies with a total of 1040 patients met our criteria. The studies focused on nonsmall cell lung cancer, gastric cancer, hepatocellular carcinoma, biliary tract cancer, and renal cancer, and our conclusion is yet to be validated in patients with other tumors. The sample size is rather small and sampling error may render our conclusion less reliable. More relative studies involving different solid tumor types are required to further strengthen our conclusion. In addition, although we did not set a criterion for a specific patient nationality or area, patients included in this meta-analysis were mainly from Asian areas, which may influence the results with population bias. More studies with a larger sample size from around the globe are needed to resolve such problems. Another obvious problem is the largely varied cut-off values of sPD-L1 in each individual study listed in Table 3. We believe that this can be explained by the following reasons: Different types of cancer have different sPD-L1 basic levels, as we included patients with different tumor types. In a recent meta-analysis focusing on the protein expression of PD-L1 in malignant solid tumors, similar differences were also observed, as positive rates evaluated by immunohischemistry also varied among different tumor kinds. Moreover, some studies measured sPD-L1 levels before treatment, while others following certain kinds of treatment such as chemotherapy or radiotherapy. It remains to be elucidated how those treatments might affect the levels of sPD-L1. The studies used different sample sources such as serum or plasma to measure sPD-L1, and different antibodies manufactured by different companies were used during ELISA. We believe that these differences are potentially responsible for the varied results even among the same tumor types as listed in Table 3. Taking account of these listed limitations, we think the final conclusion that high sPD-L1 predicts worse survival remains reliable, yet needs to be solidified with more data.

We believe that our findings, once further supported by more prospective, multicenter, randomized controlled trials with larger

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**Table 2**

| References            | HR (95% CI)      | P     | NOS Score |
|-----------------------|------------------|-------|-----------|
| Finkelmeier et al.    | 3.307 (1.477–7.559) | 0.046 | 7         |
| Fukuda et al.         | 4.96 (2.01–12.33)  | 0.005 | 7         |
| Okuma et al.          | 3.69 (1.86–7.30)   | 0.014 | 8         |
| Takahashi et al.      | 1.99 (1.02–3.98)   | 0.041 | 8         |
| Takahashi et al.      | 3.307 (1.477–7.559) | 0.046 | 7         |
| Zhang et al.          | 1.39 (0.41–4.68)   | 0.597 | 7         |
| Zhao et al.           | 2.28 (1.48–3.52)   | 0.002 | 7         |
| Zheng et al.          | 1.80 (0.30–12.77)  | 0.520 | 7         |
| Ha et al.             | 1.891 (1.320–2.650) | 0.001 | 8         |

CI = confidence interval; HR = hazard ratio; NOS = Newcastle–Ottawa Quality Assessment Scale.
Sample sizes, may be granted a promising future of widespread clinical application aiming to predict patient prognosis, as peripheral blood is conveniently accessible and much less invasive than a tissue biopsy under clinical circumstance.

In conclusion, the current meta-analysis presented a significant relationship between high sPD-L1 level and a worse OS in patients with solid tumors, indicating that high sPD-L1 may serve as a predictive biomarker for poor prognosis.

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Table 3

Various levels and cut-off values of soluble PD-L1 in studies included in the present meta-analysis.

| References            | Tumor                          | Sample       | sPD-L1 levels | Cut-off value | Cut-off criteria | Positive rate | ELISA kit manufacturers; and product numbers                        |
|-----------------------|--------------------------------|--------------|---------------|---------------|------------------|---------------|---------------------------------------------------------------------|
| Okuma et al[20]       | Advanced lung cancer           | Plasma       | 0.95 ± 2.30 ng/mL (mean level) | 7.32 ng/mL    | NM               | 41.7% (40/96)   | Cloud-Clone Corp., Houston, TX; WEA788Hu                              |
| Takahashi et al[21]   | Metastatic/recurrent gastric cancer | Serum       | 0.704 ng/mL (median level) | 1.081 ng/mL   | ROC curve for the best disease control rate | 36.0% (27/75)  | USCN Life Science, Wuhan, China; SEA788Hu                           |
| Ha et al[22]          | Advanced biliary tract cancer (post palliative chemotherapy) | Serum       | 1.12 ng/mL (median level) | 0.94 ng/mL    | Minimum P value to separate different prognostic groups | 38.6% (61/158) | USCN Life Science, Wuhan, China; SEA788Hu                           |
| Finkelmeier et al[18] | Hepatocellular carcinoma       | Serum        | 0.73 ± 0.82 ng/mL (mean level) | 0.8 ng/mL     | Median level found in the healthy cohort | 29.8% (64/215) | USCN Life Science, Wuhan, China; SEA788Hu                           |
| Zhang et al[22]       | Advanced NSCLC                 | Serum        | 0.723 ± 0.081 ng/mL (mean level) | 0.636 ng/mL   | ROC curve for NSCLC patients, AUC value 0.956 | 56.0% (61/109) | Beijing Keygenmi Science and Technology Ltd., Beijing, China; ab156361|
| Zheng et al[24]       | Advanced gastric adenocarcinoma | Serum        | 0.8928 ± 0.0900 ng/mL (mean level) | 0.5993 ng/mL  | ROC curve for lymph node metastasis, AUC value 0.613 | 41.3% (33/80)  | USCN Life Science, Wuhan, China; SEA788Hu                           |
| Zhao et al[23]        | NSCLC (postradiotherapy)       | Plasma       | NM            | 0.0065 ng/mL  | Log-rank statistic for maximum hazard ratio | 41.3% (52/126) | USCN Life Science, Wuhan, China; SEA788Hu                           |
| Fukuda et al[19]      | Renal cell carcinoma (post VEGF-targeted therapy) | Serum       | 0.0183 ng/mL (mean level) | 0.0183 ng/mL  | Median serum level | 50.3% (91/181) | Cusabio Biotech, Wuhan, China; CSB-E13644h                          |

AUC = area under the roc curve, ELISA = enzyme-linked immunosorbent assay, HCC = hepatocellular carcinoma, NM = not mentioned, NSCLC = nonsmall cell lung cancer, ROC = receiver operating characteristic, VEGF = vascular endothelial growth factor.
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