Original Article

Clinicopathological and prognostic significance of programmed death ligant-1 expression in gastric cancer: a meta-analysis

Zhebing Qiu, Yinguo Du

Department of Gastrointestinal Tumor Surgery, Shengzhou People's Hospital (the First Affiliated Hospital of Zhejiang University Shengzhou Branch), Shengzhou, China

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Correspondence to: Prof. Yinguo Du. Department of Gastrointestinal tumor surgery, Shengzhou People's Hospital (the First Affiliated Hospital of Zhejiang University Shengzhou Branch), No. 666, Dangui Road, Shengzhou 312400, China. Email: duyinguo2000@126.com.

Background: Gastric cancer (GC) is a common malignant tumor with a high incidence in China. The use of immune checkpoint inhibitors has become the focus of tumor immunotherapy in recent years. This study was to investigate the clinicopathological and prognostic significance of programmed death ligant-1 (PD-L1) expression in GC.

Methods: We searched the PubMed, ScienceNet, EMbase, CNKI, and Wanfang databases for retrospective cohort studies on the clinicopathology and prognosis of PD-L1 expression in GC published between January 2010 and April 2020. The literature was first selected to extract data according to the inclusion and exclusion criteria, then a meta-analysis performed using Stata15.0 software. Publication bias and sensitivity analysis were carried out for the included studies.

Results: A total of 3,218 patients in 15 studies were included in the meta-analysis. The positive expression of PD-L1 was related to a decrease in the 3-year survival rate (HR =1.32, 95% CI: 1.02–1.49, P=0.028) and 5-year survival rate (HR =1.39, 95% CI: 1.14–1.69, P=0.001). The difference in PD-L1 expression was related to lymph node metastasis (OR =1.73, 95% CI: 1.18–2.54, P<0.001), but not to tumor stage (OR =1.28, 95% CI: 0.81–2.02, P=0.292).

Conclusions: The results show that PD-L1 is related to the prognosis of GC. Its high expression decreases the 3- and 5-year survival rates and promotes lymph node metastasis, but does not reflect tumor stage. The results may provide a theoretical basis for the choice of clinical immunotherapy in GC patients.

Keywords: Gastric cancer (GC); programmed death ligant-1 (PD-L1); clinicopathological characteristics; prognosis; meta-analysis

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Introduction

Gastric cancer (GC) is a common and life-threatening malignant tumor of the digestive system with a high incidence in China. Most patients are in the middle or advanced stage of the disease when they commence treatment and the 5-year survival rate is only 20–50% (1), placing GC as the second highest mortality cancer in the world. The molecular mechanisms underpinning the occurrence and development of GC are complex and the role played by immune escape and the design of therapies to address it are of increasing interest (2). The use of immune checkpoint inhibitors in particular has become the focus of tumor immunotherapy in recent years.

Programmed death 1 (PD-1) is an important immunosuppressive molecule that regulates tumor growth,

prevents excessive inflammatory responses, and maintains the survival of transplanted donors. The ligand of PD-1, programmed death ligand-1 (PD-L1/B7-H1), is widely expressed in various types of tumor and immune cells (3), and has the effect of immune surveillance (4). PD-L1 is expressed in the anti-tumor T cell response of various solid tumors including renal cell carcinoma and breast, pancreatic, colorectal, and esophageal cancer (5,6). It inhibits the proliferation and activity of T cells and plays a significant role in the negative regulation of the immune response (7). In addition, PD-L1 expression is associated with poor prognosis in patients with various malignant solid tumors including GC (8,9) and is valuable in predicting prognosis and clinicopathological characteristics and as a biomarker in the tumor microenvironment (10-12). Its targeted immunoregulation is of great significance in the treatment of infection, tumors and autoimmune diseases, and the corresponding antibodies have the same effect (13). At present, there are many studies on the clinicopathological and prognostic significance of PD-L1 expression in GC, but the results are not consistent. We performed a meta-analysis to clarify the correlation of PD-L1 expression with clinicopathology and prognosis in GC.

We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/jgo-20-568).

Methods

Retrieval strategy

We searched the PubMed, ScienceNet, EMbase, CNKI, and Wanfang databases for publications appearing between January 2010 and April 2020 using the key terms PD-L1, PD-1, programmed death cell 1, programmed death 1 ligand, and gastric cancer or GC. The literature was collected by the combination of subject words and free words according to the characteristics of different databases.

Inclusion and exclusion criteria

The following inclusion criteria were used: (I) all patients were pathologically diagnosed with GC; (II) PD-L1 expression was obtained by immunohistochemical (IHC) method; (III) the relationship between PD-L1 expression and the prognosis of GC was clarified; (IV) all GC patients had been followed up and the results were reported; (V) treatises, not reviews, case reports, conference abstract, and others were included; (VI) articles contained complete research data; (VII) the full text was in English; (VIII) the Newcastle-Ottawa Quality Assessment Scale (NOS) score was ≥6 points.

Data extraction and quality evaluation

The following data were extracted: name of the first author, year of publication, country, total cases, survival rate, number of PD-L1 positive cases, number of PD-L1 negative cases, tumor stage, and presence of lymph node metastasis. If a clear survival report was not available, the Kaplan-Meier curve was read for survival information through Engauge Digitizer 4.1.

The quality of the articles was evaluated by NOS, with the highest score being 9. A score ≥6 was rated as high quality.

Statistical analysis

Meta-analysis was performed by Stata15.0 software (StataCorp., College Station, TX). The data were analyzed by hazard ratio (HR), odds ratio (OR), and 95% confidence interval (CI). Heterogeneity between studies was judged with I^2 and Q tests. If there was no heterogeneity (P>0.10, I^2<50%), the fixed effect model (FEM) was used for analysis and the random effect model (REM) then used for analysis. Sensitivity analysis was performed to evaluate the stability of the results by eliminating the study results one by one, that is, removing the effect of each study on the overall results to explore the source of heterogeneity. Publication bias was analyzed by funnel plot.

Results

Results of literature screening

A total of 761 related studies were obtained and after reading the title, abstract and full text, 704 articles were excluded. A further 42 articles with other intervention measures and low quality but without a control group were also excluded. Finally, 15 articles (14-28) were included in the meta-analysis, with a total of 3,218 patients. The screening procedure is shown in *Figure 1*.

Research characteristics

Basic research characteristics of the 15 included studies

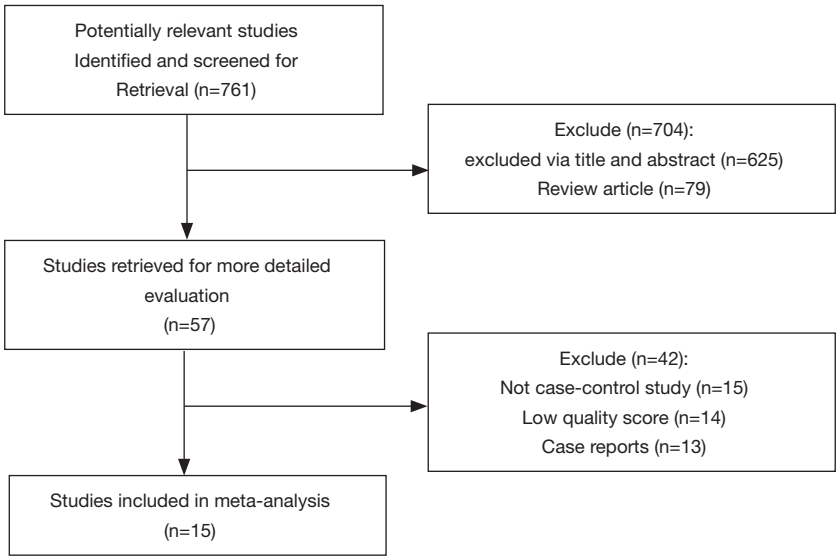

Figure 1 Literature screening procedure.

are shown in *Table 1*. The NOS score ranged from 7 to 8, indicating that all were high-quality studies.

The total sample size was 3,218 cases, with individual sample sizes ranging from 56 to 478. The studies were from four countries, including nine from China (14,15,17-19,23,24,26,27), three from South Korea (22,25,28), two from Japan (16,21), and one from Germany (20). The relationship between PD-L1 and 3-year survival was provided in 15 studies (14-28) and 12 (14,16,19-28) reported the relationship between PD-L1 and 5-year survival. The correlation between PD-L1 and lymphatic metastasis was reported in 12 studies (14,16,19-28) and among these, 10 studies recruited patients in stage I–IV in GC (14,15,17,18,20,21,23,25,26,28), and four recruited GC patients in stage I–III (16,19,22,24).

Relationship between PD-L1 expression and 3-year survival rate in GC patients

The 3-year survival rate was reported in all 15 studies. There was significant heterogeneity between the studies (I^2=78.1%, P<0.001), so the REM was used. The results show that positive expression of PD-L1 was related to a decrease in the 3-year survival rate (HR =1.23, 95% CI: 1.02–1.49, P=0.028) and in the subgroup analysis of ethnicity, the positive expression of PD-L1 in Asians was also related to a decrease in the 3-year survival rate (HR =1.29, 95% CI: 1.06–1.57, P=0.010) (*Figure 2*).

Relationship between PD-L1 expression and 5-year survival rate in GC patients

The 5-year survival rate was reported in 12 studies (14,16,19-28). There was significant heterogeneity between the studies (I^2=88.7%, P<0.001) (*Figure 3*), so the REM was used. The result showed that the positive expression of PD-L1 was related to a decrease in the 5-year survival rate (HR =1.39, 95% CI: 1.14–1.69, P=0.001). In the subgroup analysis of ethnicity, the positive expression of PD-L1 in Asians was also related to a decrease in the 5-year survival rate (HR =1.48, 95% CI: 1.18–1.86, P=0.001) (*Figure 3*).

Relationship between PD-L1 expression and clinicopathological characteristics in GC patients

To further understand the role of PD-L1 as a biomarker, we investigated the relationship between PD-L1 expression and the clinicopathological features of GC using REM. The correlation between PD-L1 expression and lymphatic metastasis was reported in 12 studies (14,16,19-28) and there was significant heterogeneity among them (I^2=73.9%, P<0.001). The positive expression of PD-L1 in the group with lymph node metastasis was 1.73 times higher than that in the group without lymph node metastasis, and the difference was statistically significant (OR =1.73, 95% CI: 1.18–2.54, P<0.01) (*Figure 4A*). The result showed that patients with higher expressions of PD-L1 are more prone to lymph node metastasis.

Table 1 Basic characteristics of included literature

First author	Year	Country	No.	Cases (PD-L1–)	Cases (PD-L1+)	Tumor stage	NOS score
Geng (14)	2015	China	100	35	65	I–IV	8
Hou (15)	2014	China	111	41	70	I–IV	8
Eto (16)	2016	Japan	105	79	26	II–III	8
Qing (17)	2015	China	107	53	54	I–IV	7
Wang (18)	2016	China	56	36	20	I–IV	7
Zhang (19)	2015	China	132	65	67	II–III	8
Böger (20)	2016	Germany	465	354	111	I–IV	8
Kawazoe (21)	2017	Japan	478	376	111	I–IV	8
Kim (22)	2016	Korea	243	137	106	I–IIIC	8
Li (23)	2016	China	137	81	56	I–IV	8
Wu (24)	2006	China	102	59	43	I–III	7
Kwon (25)	2017	Korea	394	271	123	I–IV	7
Wu (26)	2017	China	340	263	77	I–IV	8
Yan (27)	2019	China	278	22	256	NR	7
Kim (28)	2019	Korea	170	67	103	I–IV	8

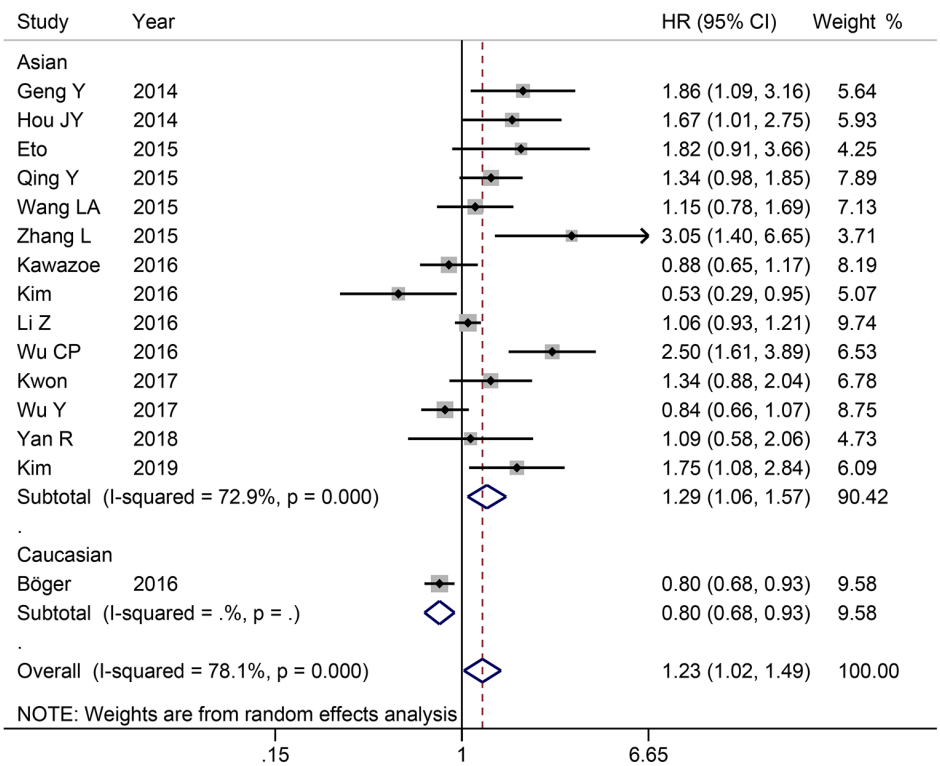

Figure 2 Forest plot of the correlation between PD-L1 expression and 3-year survival rate. PD-L1, programmed death ligant-1.

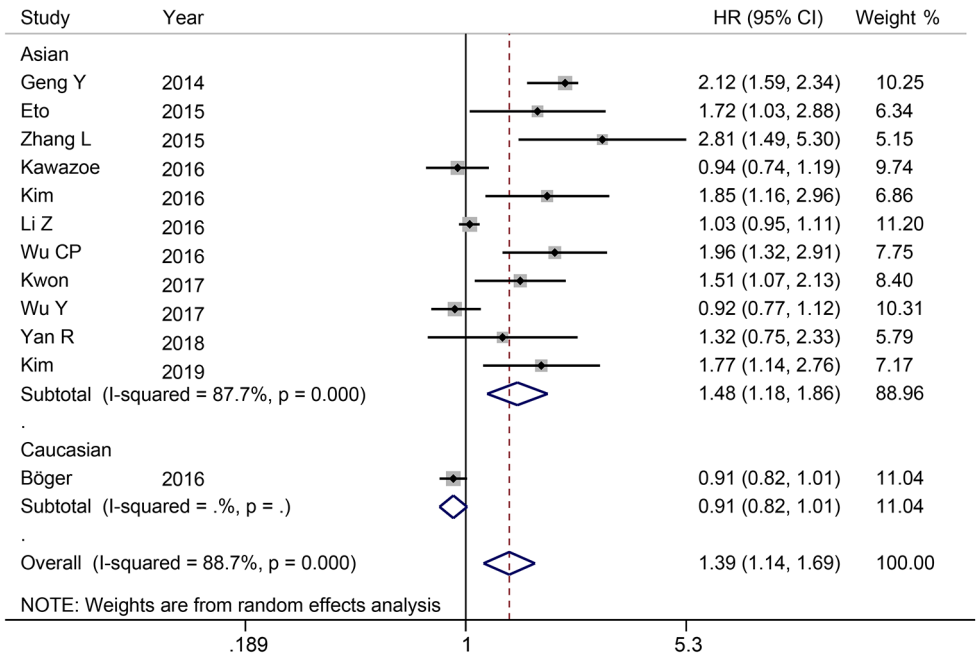

Figure 3 Forest plot of the correlation between PD-L1 expression and 5-year survival rate. PD-L1, programmed death ligant-1.

The correlation between PD-L1 expression and tumor stage was reported in eight (14-16,19,22,23,25,26) studies and there was significant heterogeneity among them (I^2=71.6%, P<0.001). There was no significant difference in PD-L1 expression among different tumor stages (OR =1.28, 95% CI: 0.81–2.02, P=0.292) (*Figure 4B*).

Sensitivity analysis and publication bias

The heterogeneity of 3-year (*Figure 5A*) and 5-year (*Figure 5B*) survival rates was high among the studies. After eliminating the study results one by one, sensitivity analysis revealed no significant change in overall heterogeneity, which indicated that the results were robust. Publication bias was analyzed by funnel plot. The 3-year (*Figure 6A*) and 5-year (*Figure 6B*) survival rates of the included literature were mostly in the funnel plot, indicating that there was a small publication bias.

Discussion

An increasing number of studies show that PD-L1 is highly expressed in a variety of malignant tumors and can be used as a marker in tumor prognosis. However, its relationship with survival in GC patients remains controversial. Statistical analysis of the 15 articles and 3,218 patients assessed in this study showed that the 3- and 5-year overall survival rates of patients with positive expression of PD-L1 were significantly lower than those in whom it was negatively expressed. The positive expression of PD-L1 was more common in patients with positive lymphatic metastasis but had no correlation with tumor stage. Therefore, PD-L1 expression can be used as a reliable indicator for monitoring the clinical prognosis of GC patients.

Studies have shown that PD-L1 is barely expressed in normal gastric tissues, while its expression level is significantly up-regulated in GC tissues (29). In the tumor microenvironment, overexpression of PD-L1 can produce immunosuppressive effects (30) and promote the immune escape of tumor cells. Blocking this signal pathway can induce T cells to activate and kill tumor cells, enhancing the endogenous anti-tumor effect to provide a new approach to the treatment of GC (31). Consistent with the results of this study, many others have shown that patients with high PD-L1 expression have a poor 5-year overall survival rate, indicating PD-L1 is closely related to prognosis (32-34). While a variety of PD-L1 monoclonal antibodies have been applied in the clinical treatment of cancer patients with good clinical efficacy (35,36) there remain few clinical studies on PD-L1 monoclonal antibodies in

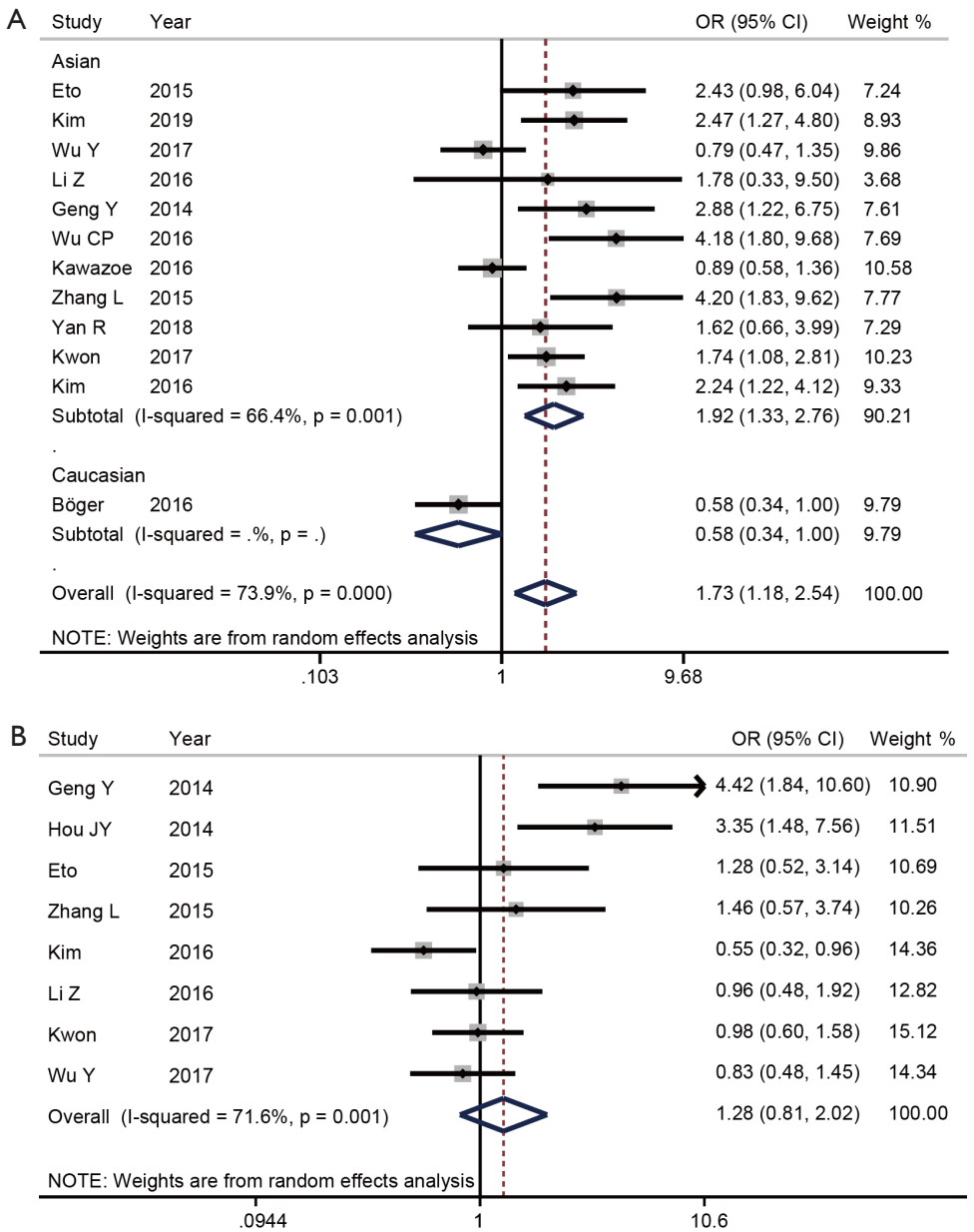

Figure 4 Forest plot of the correlation between PD-L1 expression and clinicopathological characteristics. (A) Forest plot of the correlation between PD-L1 expression and lymphatic metastasis; (B) Forest plot of the correlation between PD-L1 expression and tumor stage. PD-L1, programmed death ligant-1.

GC patients. The present study shows that PD-L1 is more common in GC patients with lymph node metastasis, which may provide a theoretical basis for its use in evaluating the prognosis of GC.

There are several limitations to this study. Firstly, the number of publications in the meta-analysis is small. Secondly, although subgroup analysis was performed, only one publication concerned Caucasian groups. Finally, the heterogeneity of the results is large, which is caused by many factors including technical deviation due to test methods and operators. Larger, multicenter prospective cohort studies of the predictive role of PD-L1 expression in

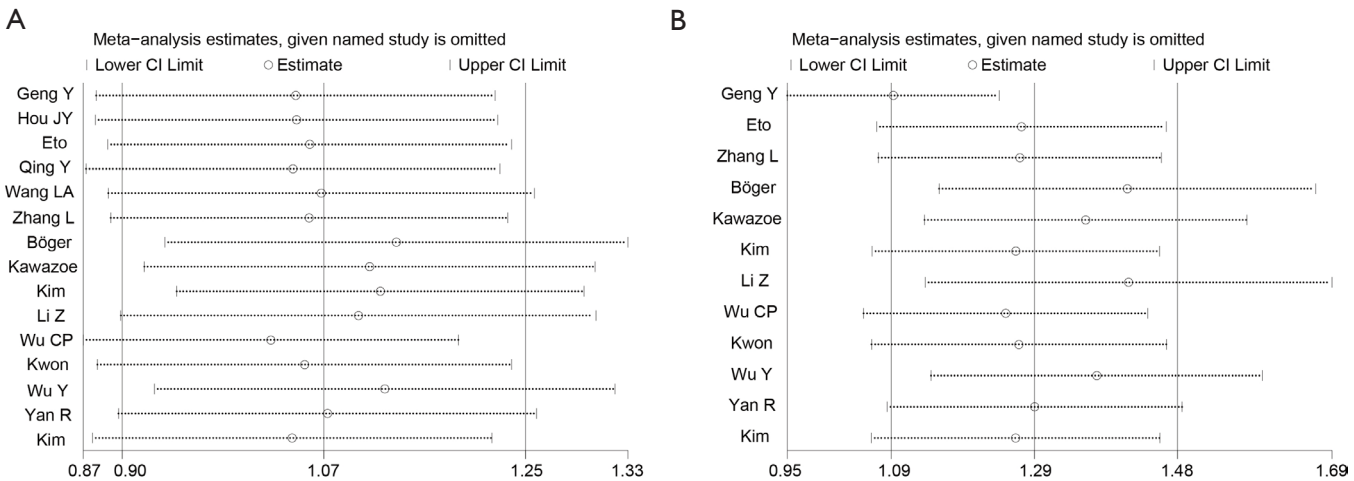

Figure 5 Sensitivity analysis of the correlation between PD-L1 expression and 3- and 5-year survival rates. (A) Sensitivity analysis of correlation between PD-L1 expression and 3-year survival rate; (B) sensitivity analysis of correlation between PD-L1 expression and 5-year survival rate. PD-L1, programmed death ligant-1.

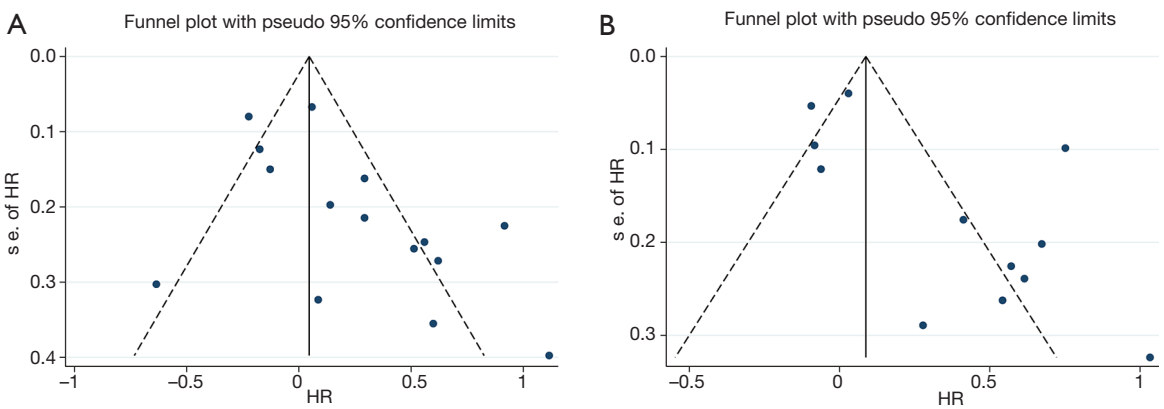

Figure 6 Funnel chart of the correlation between PD-L1 expression and 3- and 5-year survival rates. Funnel chart of the correlation between PD-L1 expression and 3-year survival rate; (B) Funnel chart of the correlation between PD-L1 expression and 5-year survival rate. PD-L1, programmed death ligant-1.

GC are needed to verify our results.

Conclusions

In summary, we found that the high expression of PD-L1 decreases 3- and 5-year survival rates and promotes lymph node metastasis in GC patients although this was not related to tumor stage. PD-L1 is a negative factor in GC prognosis, and whether it can be used as prognostic factor in GC requires verification through high-quality prospective studies with uniform criteria. Further studies on the mechanism of PD-L1 overexpression in GC will also provide more reliable evidence for individualized treatment of GC.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at http://dx.doi.org/10.21037/jgo-20-568

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jgo-20-568). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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