INPLASY PROTOCOL

To cite: Peng et al. The Clinicopathological and Prognostic Value of Programmed Death-Ligand 1 in Gallbladder cancer: A meta-analysis. Inplasy protocol 2021100078. doi: 10.37766/inplasy2021.10.0078

Received: 20 October 2021

Published: 20 October 2021

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Support: **2018JY0404.**

Review Stage at time of this submission: **Data analysis.**

Conflicts of interest:
None declared.

The Clinicopathological and Prognostic Value of Programmed Death-Ligand 1 in Gallbladder cancer: A meta-analysis

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Review question / Objective: **Gallbladder cancer (GBC) is the most common cancer of the biliary system. Previous studies investigated the prognostic role of programmed death-ligand 1 (PD-L1) expression in patients with GBC, but the results remained controversial. Therefore, we performed the present meta-analysis with the aim of clarifying the association between PD-L1 expression and overall survival as well as with several important clinicopathological features of GBC.**
Condition being studied: **We systematically searched all studies on the correlation between clinicopathology/ prognosis and PD-L1 in patients with GBC using Pubmed, Embase, and Web of Science databases on 5 September 2021. All relevant articles data were extracted independently by two reviewers (XP and XZ), including the first author, year of publication, country, sample size, enrollment period, specimen, detection method, cut-off value for high expression of PD-L1, survival end point. Pooled hazard ratios (HRs), odds ratios and mean difference with 95% confidence intervals (CIs) were calculated to estimate the correlations.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 October 2021 and was last updated on 20 October 2021 (registration number INPLASY2021100078).

INTRODUCTION

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METHODS

Participant or population: GBC patients.

Intervention: Long-term follow up.

Comparator: PD-L1-negative GBC patients.

Study designs to be included: Our study designs include data retrieval, inclusion and exclusion criteria, data extraction, literature Quality assessment and publication bias and do meta-analysis using STATA and Revman5.4 software.

Eligibility criteria: The inclusion criteria for eligible studies were as follows: (1) original articles; (2) patients' GBC diagnoses were pathologically and/or histologically confirmed; (2) immunohistochemistry (IHC) analysis of PD-L1 expression in GBC tissue was conducted; (3) the studies recorded sufficient data to estimate the hazard ratio (HR) with 95% confidence interval (CI) for overall survival (OS); (4) PD-L1 expression was stratified into high and low groups using a definite cut-off value. (5) full-text articles available in English. This analysis excluded articles based on the following standards: (1) duplicate articles, reviews, meta-analysis, abstracts which cannot extract data, case report, correspondences and letters; (2) animal studies and basic research; (3) irrelevant to GBC, PD-L1, or prognosis; (4) studies with insufficient data.

Information sources: PubMed, Web of Science, and EMBASE.

Main outcome(s): The pooled estimate of the prevalence of PD-L1 expression in GBC was 0.37 (95% CI: 0.23-0.53, P=0.00) with significantly heterogeneous (I2 = 96.70, P=0.00). positive PD-L1 expression showed a trend towards shorter OS in GBC patients, but the result was not statistically significant (HR = 2.36, 95% CI:0.95-5.90, P = 0.065). However, based on cut-off value≥10%, and we found high expression of PD-L1 was correlated with poor OS (HR=5.42, 95%CI: 2.16-13.56, P=0.000). PD-L1 expression significantly correlates with histologic grade (p=0.0004) and T stage (P=0.005).

Quality assessment / Risk of bias analysis: The quality of the retrieved articles was evaluated with the Newcastle-Ottawa Scale (NOS) criteria. The NOS contains three domains: selection (0–4 stars), comparability (0–2 stars), and outcome assessment (0–3 stars). The NOS scores ranged from 0 to 9. Researches with NOS scores≥6 were considered to be high-quality. Two reviewers (XP and CJ) independently assessed the quality of the selected papers. Any disagreements were discussed by all the researchers, to reach a consensus. Publication bias was examined visually using funnel plots and statistically assessed using Egger's test.

Strategy of data synthesis: All statistical analyses were performed using Stata version 16.0. and Revman5.4. The pooled estimates of the prevalence of PD-L1 expression were calculated. The prognostic value of PD-L1 for GBC was assessed by using the hazard ratio (HR) and 95% CI values. An HR >1 with a p-value <0.05 indicated a poor prognosis in patients with PD-L1 overexpression. The merged odds ratios (ORs), mean difference (MD) and 95% CIs were utilized to quantitatively evaluate the relationship between PD-L1 expression and clinicopathological

characteristics of GBC. The heterogeneity among the studies was examined using Cochran's Q test and the I2 test. If the heterogeneity was significant (p50%), a random-effects model was implemented; otherwise, a fixed-effects model was applied. P-values <0.05 were considered statistically significant.

Subgroup analysis: We carried out a subgroup analysis of the prevalence of PD-L1 expression in Tumor cells. The pooled estimate of the prevalence of PD-L1 expression in GBC was 0.37 (95% CI: 0.23-0.53, P=0.00) with significantly heterogeneous (I2 = 96.70, P=0.00). Studies using cut-off values ≥1% (0.43, 95% CI :0.20-0.67, P=0.00, I2=97.17%) documented higher prevalence of PD-L1 expression compared to those using cut-off values ≥5% (0.30, 95% CI :0.06-0.63, P=0.00, I2=97.97%). In addition, we carried out a subgroup analysis of OS based on cut-off value≥10%, and found high expression of PD-L1 was correlated with poor OS (HR=5.42, 95%CI: 2.16-13.56, P=0.000).

Sensitivity analysis: Sensitivity analysis was conducted to assess the reliability of the results.

Country(ies) involved: China.

Keywords: PD-L1, gallbladder cancer, meta-analysis.

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