Effect of proton pump inhibitors on the clinical outcomes of PD-1/PD-L1 inhibitor in solid cancer patients

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Abstract

Background: Some concomitant drugs may affect the efficacy of programmed death protein-1/ ligand-1 (PD-1/L1) inhibitors. Among the various concomitant drugs, proton–pump inhibitors (PPI) have attracted some attention but have not reached a conclusion. We conducted a meta-analysis to evaluate the impact of PPIs on the survival of cancer patients treated with PD-1/ L1 inhibitors.

Material/methods: Related databases and conferences reports were searched. Studies that reported the relationship between PPI use and clinical outcomes of PD-1/L1 inhibitors were included. Meta-analysis was conducted to obtain pooled hazard ratios (HR)s with 95% confidence interval (CI).

Results: Eight studies involving 4869 cancer patients were included. Meta-analysis showed that PPI use was associated with worse overall survival (OS) (HR = 1.43, 95% CI 1.32–1.56), worse progression free survival (PFS) (HR = 1.30, 95% CI 1.20–1.40), and decreased objective response (odds ratio = 0.71, 95% CI 0.58–0.87) in cancer patients receiving PD-1/L1 inhibitors. Neither cancer type nor therapy type affected the effect of concomitant PPIs on the OS and PFS. In the subgroup of studies with a population size <500, PPIs did not reduce the OS, but the PFS. Only 1 single-center study was conducted, showing that PPI use did not affect the OS and PFS. There was no evidence of publication bias among included studies.

Conclusion: Concomitant PPI use was correlated with worse clinical outcomes in cancer patients treated by PD-1/L1 inhibitors. Further prospective clinical and experimental studies are needed to confirm the effect and mechanism of PPI in worsening the clinical outcome of PD-1/L1 inhibitors.

Abbreviations: CI = confidence interval, NSCLC = non-small cell lung cancer, ORR = objective response rate, OS = overall survival, PD-1 = programmed death protein-1, PD-L1 = programmed death ligand-1, PFS = progression free survival, PPI = proton–pump inhibitor.

Keywords: clinical outcome, meta-analysis, programmed death ligand-1 (PD-L1) inhibitor, programmed death protein-1 (PD-1), proton–pump inhibitor (PPI)

1. Introduction

Immunotherapy has made astounding advances in the treatment of cancer.[1] Programmed death protein-1/ligand-1 (PD-1/ PD-L1) inhibitors, representative immune checkpoint inhibitors used in immunotherapy,[1,2] have been approved to treat a variety of tumors, such as non-small cell lung cancer (NSCLC), urothelial cancer, melanoma, head and neck squamous cell cancer, lymphoma.[3]

As the spectrum of PD-1/PD-L1 inhibitors expands, drug-drug interactions have become a field of particular interest. Some concomitant drugs may enhance or discount the efficacy of immunotherapy,[4] such as antibiotics[5] and corticosteroids.[6,7]

Recently, a body of studies have been conducted to analyze the general impact of proton–pump inhibitors (PPIs) on the efficacy of PD-1/PD-L1 inhibitors.

PPIs can irreversibly inhibit the hydrogen-potassium-AT-Pase. Long-term use of PPIs can change the structure of microbiome.[8,9] Previous studies have proved the that gut microbiota are closely implicated in native immunity. The interaction between PPIs and bPD-1/PD-L1 inhibitors has been explored in some retrospective studies.[6,7,10–16] Unfortunately, no consensus has arrived. Here, we systematically reviewed the literature and made a meta-analysis to explore the impact of PPI use on the outcomes of PD-1/PD-L1 inhibitors in advanced cancer patients.

2. Materials and Methods

2.1. Search strategy

This study was registered in PROSPERO with registration number CRD42021273673. Relevant literature published before June 1, 2021 were searched by 2 researchers independently from databases and conference proceedings such as EMBASE, PubMed, Cochrane, European Society for Medical Oncology, American or Chinese Society of Clinical Oncology, and American Association for Cancer Research.

We used keywords such as "PD-1 inhibitor," "PD-L1 inhibitor," "avelumab," "atezolizumab," "camrelizumab," "nivolumab," "pembrolizumab," "sintilimab," "durvalumab," "toripalimab," "sintilimab," "proton pump inhibitor," "omeprazole," "pantoprazole," "lansoprazole," "rabeprazole," "esomeprazole," "dexlansoprazole," "esomeprazole." Literature in any language was reviewed.

2.2. Selection and inclusion of studies

We included randomized controlled trials and retrospective trials that met inclusion criteria. Inclusion criteria included: Patients were definitely diagnosed with solid cancer and received PD-1/PD-L1 inhibitor alone or in combination with other anti-cancer drugs; PPIs were prescribed before, during, or after PD-1/PD-L1 inhibitor treatment in the experimental group, but did not prescribe in the control group; Articles reported the clinical outcomes, such as overall survival (OS), progression-free survival (PFS), or objective response rate (ORR). The eligible studies were screened and included by 2 independent investigators.

2.3. Data extraction

The following information was extracted from the eligible articles: authors, year of publication, region/country, number of centers, inclusion period, study size, cancer type, treatment line, name of PD-1/PD-L1 inhibitor, treatment type, PPI type, duration of PPI treatment, hazard ratio (HR) (odds ratio) and 95% confidence interval (CI) of OS, PFS, and ORR. Cutoffs in every study was listed in Table 1.

2.4. Quality assessment

The quality of included retrospective studies was evaluated by the Newcastle-Ottawa quality assessment scale.[17] Newcastle-Ottawa quality assessment scale scores were graded by 2 reviewers separately and discussed by all authors of the present study. A score 7 or 8, indicated a high quality.[18]

2.5. Statistics

Overall HRs with 95% CI for PFS or OS were used to compare the impact of concomitant PPIs on the efficacies of PD-1/PD-L1 inhibitors. The results favor the PPI-using group when the pooled HR <1. Conversely, the results favor the no PPI-using group when the pooled HR >1. I^2 statistics were used to evaluate the heterogeneity, and $I^2 > 50\%$ and/or $P < .10$ were judged as heterogeneously. The random effects model was used for pooling heterogeneous studies, and the fixed effects model was adopted for pooling homogeneous studies. Subgroup analysis was made to investigate the influence of cancer type, therapy type, study size, and center number. Publication bias was evaluated by Egger test. Sensitivity analysis was conducted by using the "one-study removed" method. All statistics were made by Stata software (Version 13.0, Stata Corporation, College Station, TX).

3. Results

3.1. Study selection

A flowchart demonstrating how studies were selected and included is shown in Figure 1. A total of 8 articles were included in this meta-analysis (Figure S1, Supplemental Digital Content 1, http://links.lww.com/MD/H297), including 7 were conducted in multi-centers, 5 studies in NSCLC patients, 3 studies using PD-L1 inhibitor Atezolizumab, 6 studies using PD-1/PD-L1 inhibitors monotherapy. All these retrospective studies were graded as 7 or 8 (Table S1, Supplemental Digital Content 2, http://links.lww.com/MD/H298), indicating their high quality. Table 1 shows the characteristics of included studies. The study size ranged from 109 to 1012 patients. Immunotherapy was performed as first-line, second-line, or beyond treatment

Finally, eight studies involving 4869 patients were included. PPIs were given to 1933 patients (39.70%). PPI type was reported in 4 studies, time window of PPI use in 6 studies, PFS and OS in 8 studies, and ORR in 3 studies.

3.2. OS and subtype analysis

All the 8 studies reported the impact of PPI use on the OS and PFS of patients receiving PD-1/PD-L1 inhibitors. The meta-analysis showed that PPI use was associated with a shorter OS. PPI use increased the risk of death by 43% (HR = 1.43, 95% CI 1.32–1.56) in solid cancer patients receiving PD-1/PD-L1 inhibitors (Fig. 1). There was no significant heterogeneity among these studies (I^2 = 11.8%, Q test P = .338).

Subgroup analyses were performed based on cancer type, study size, therapy type, and center number. Neither cancer type (Fig. 2A) nor therapy type (Fig. 2B) impacted the effect of concomitant PPIs on OS. The OS of NSCLC patients (HR = 1.45, 95%CI: 1.30–1.61) or others (HR = 1.41, 95%CI: 1.24–1.61) were reduced by concomitant PPI use (Fig. 2A). The OS in either monotherapy (HR = 1.44, 95%CI: 1.31–1.57) or combination therapy (HR = 1.42, 95%CI: 1.13–1.78) subgroup was affected by concomitant PPI use (Fig. 2B). In the subgroup of studies with a size >500, PPI-users had worse OS than non-PPI users (HR = 1.44, 95%CI: 1.33–1.57, Fig. 2C). But in the subgroup of studies with a size <500, PPI-users had similar OS as those of non-PPI users (HR = 1.29, 95%CI: 0.93–1.78, Fig. 2C). In the study of Zhao in 2019, which was conducted in a single center, PPI use did not affect the OS (HR = 0.68, 95%CI: 0.33–1.42, Fig. 2D). The other 7 studies were conducted in multiple centers, and PPI use was associated with a shorter OS (HR = 1.45, 95%CI: 1.33–1.57, Fig. 2D).

3.3. PFS and subtype analysis

The meta-analysis showed that PPI use was also associated with shorter PFS in solid cancer patients receiving PD-1/PD-L1 inhibitors. PPI use increased the risk of death by 32% (HR = 1.32, 95% CI 1.23–1.42) (Fig. 3). No statistically significant heterogeneity was observed across these studies (I^2 = 0.0%, Q test P = .628, Fig. 3).

In the subgroup analysis, concomitant PPIs significantly reduced the PFS in either NSCLC patients (HR = 1.31, 95%CI: 1.19–1.43, Fig. 4A) or other cancer patients (HR = 1.35, 95%CI: 1.21–1.51, Fig. 4A). The OS in either monotherapy (HR = 1.33, 95%CI: 1.23–1.44) or combination therapy (HR = 1.29, 95%CI: 1.08–1.53) subgroup was affected by concomitant PPIs (Fig. 4B). Study size did not impact the effect of concomitant PPIs on PFS (Fig. 4C). In the single-center study "Zhao 2019," PPIs did not affect the PFS (HR = 0.91, 95%CI: 0.54–1.54, Fig. 4D). The meta-analysis of multi-center studies indicated that PPI use was correlated with shorter PFS in solid cancer patients using PD-1/PD-L1 inhibitors (HR = 1.33, 95%CI: 1.24–1.43, Fig. 4D).

Table 1

Baseline characteristics of studies included in this meta-analysis.

Study	Region/country	Center	Cancer	Line	Outcome	Combination	Cutoff of treatment
Chalabi 2020	31 countries in Europe and North America	Multi-center	NSCLC	Second- and higher line	PFS,OS	Monotherapy	July 7, 2016 (OAK trial); May 8, 2015 (POPLAR Trial)
Cortellini 2021	Italy	Multi-center	NSCLC	First line	PFS,OS,ORR	Monotherapy	September 2020;
Cortellini 2021-2	Italy	Multi-center	pan-cancer	First- or higher line	PFS,OS,ORR	Monotherapy	May 2020;
Hopkins 2020	Australia	Multi-center	urothelial cancer	First- or second line	PFS,OS	Monotherapy	July 4 2016 (Imvigor 210); March 13,2017 (Imvigor 211)
Hopkins 2021	26 countries	Multi-center	NSCLC	First line	PFS,OS	Combination	September 15, 2017;
Ruiz-Banobre 2021	Spain	Multi-center	urothelial carcinoma	First- or higher line	PFS,OS,ORR	Monotherapy	February 2020;
Svaton 2020	Czech Republic	Multi-center	NSCLC	First- or higher line	PFS,OS	Monotherapy	December 2020;
Zhao 2019	China	Single-center	NSCLC	Any line	PFS,OS	Monotherapy or combination	May 2018;

Study	Treatment	Size	PPI type	Inclusion period	Period of PPI
Chalabi 2020	Atezolizumab	757	Omeprazole, pantoprazole, lansoprazole, esomeprazole, rabeprazole, and dexlansoprazole	Aug 2013-Nov 2014	30 days prior and 30 days after treatment initiation
Cortellini 2021	Pembrolizumab	950	NA	Jan 2017-May 2020	NA
Cortellini 2021-2	Any PD-1/PD-L1 inhibitor	1012	NA	Jun 2014-Mar 2020	NA
Hopkins 2020	Atezolizumab	896	Omeprazole, pantoprazole, esomeprazole, lansoprazole, rabeprazole, and dexlansoprazole	May 2014-Feb 2016	30 days prior and 30 days after treatment initiation
Hopkins 2021	Atezolizumab	802	Omeprazole, pantoprazole, esomeprazole, lansoprazole, rabeprazole, and dexlansoprazole.	Mar 2015-Dec 2016	30 days prior and 30 days after treatment initiation
Ruiz-Banobre 2021	Atezolizumab, pembrolizumab, nivolumab, durvalumab	119	NA	Jun 2016-Feb 2020	30 days prior and 30 days after treatment initiation
Svaton 2020	Nivolumab	224	Omeprazole, pantoprazole, and lansoprazole	2015 and 2019	1 month before and 1 month after treatment initiation
Zhao 2019	Pembrolizumab, nivolumab, or atezolizumab	109	NA	Jan 2016-Jan 2018	1 month before and 1 month after treatment initiation

NOS = Newcastle–Ottawa Quality Assessment Scale, NSCLC = non-small cell lung cancer, ORR = objective response rate, OS = overall survival, PD-1 = programmed death protein-1, PD-L1 = programmed death ligand-1, PFS = progression free survival, PPI = proton–pump inhibitor.
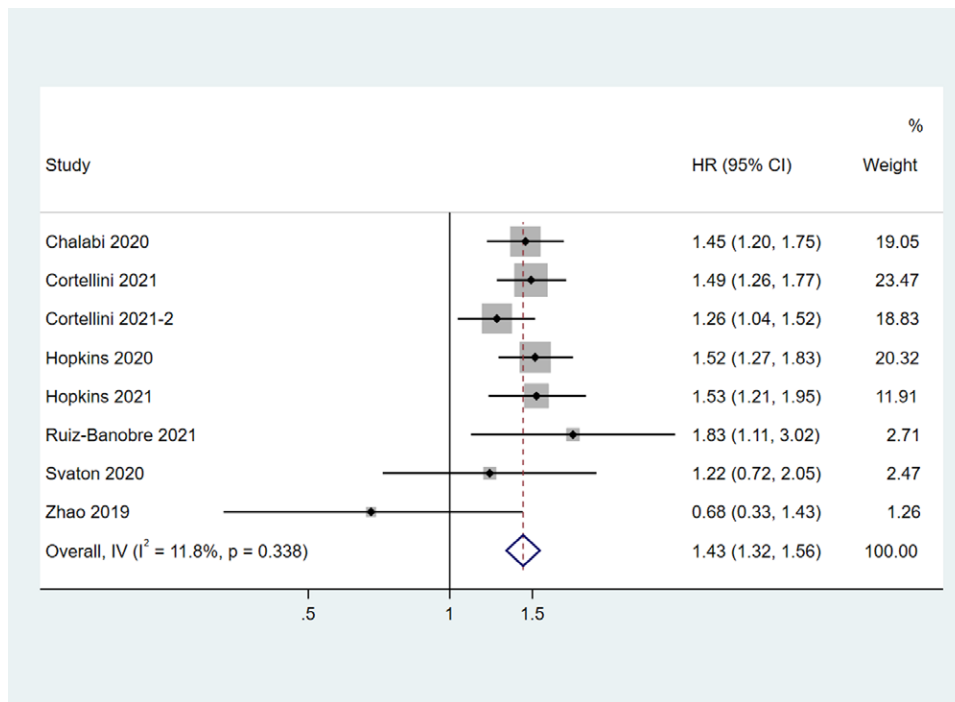
Figure 1. Associations between PPI use and OS in cancer patients treated with PD-1/L1 inhibitors. OS = overall survival, PD-1/L1 = programmed death protein-1/ligand 1, PPI = proton–pump inhibitor.
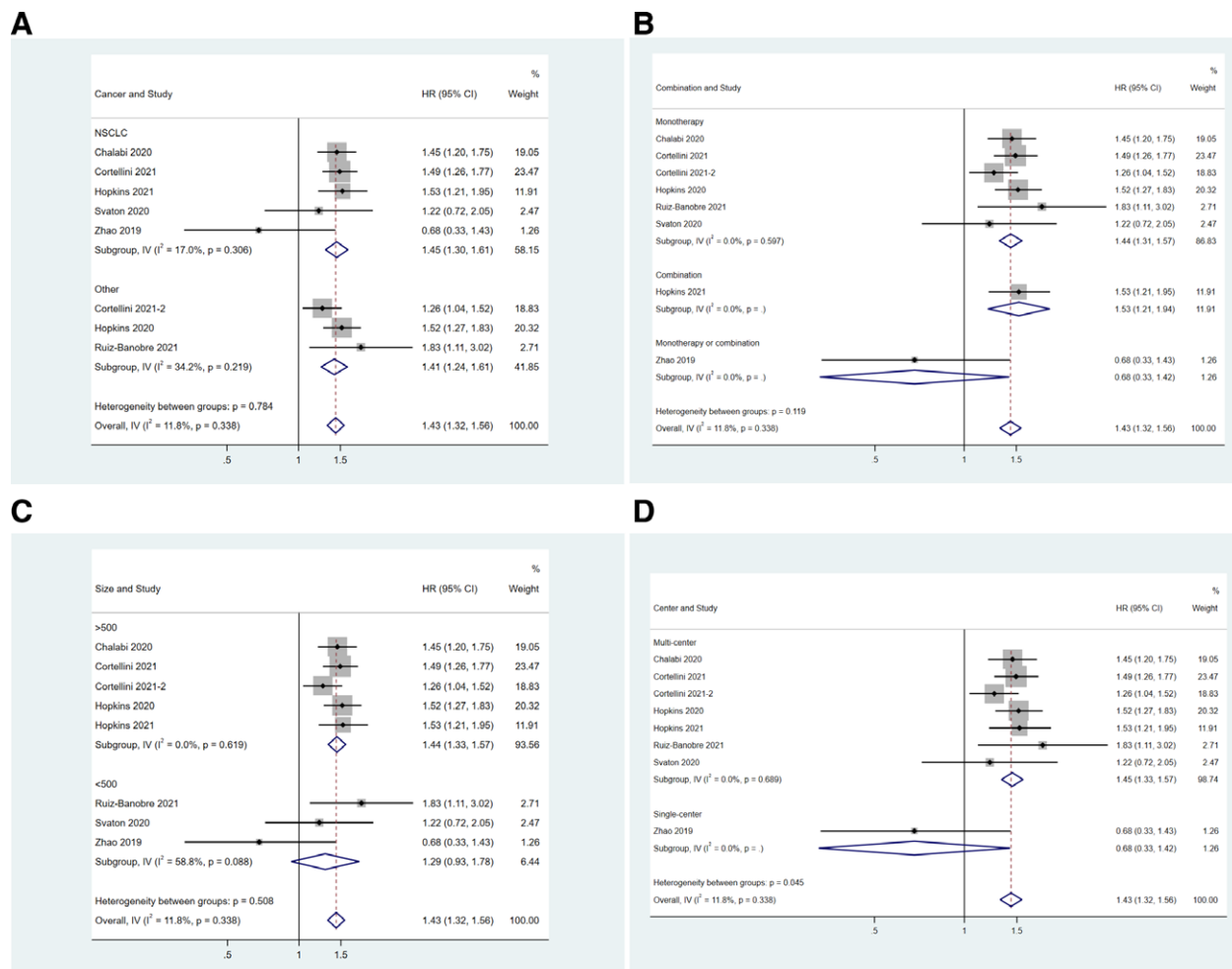

Figure 2. Associations between PPI use and OS in cancer patients stratified by cancer type (A), treatment type (B), study size (C), and center number (D). OS = overall survival, PPI = proton–pump inhibitor
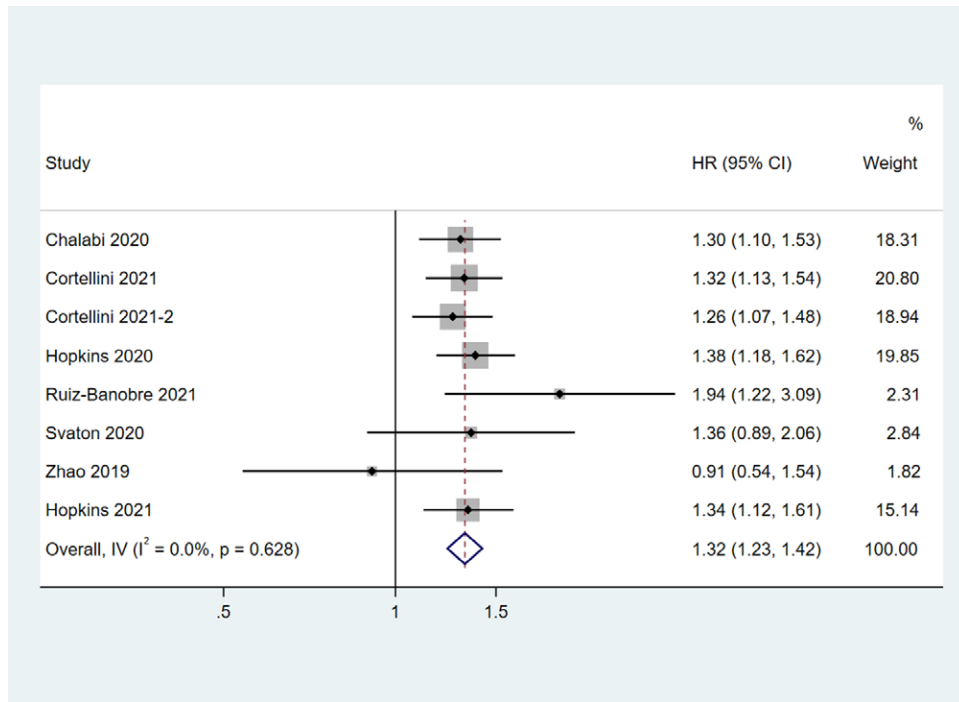
Figure 3. Associations between PPI use and OS in cancer patients treated with PD-1/L1 inhibitors. OS = overall survival, PD-1/L1 = programmed death protein-1/ligand 1, PPI = proton–pump inhibitor.
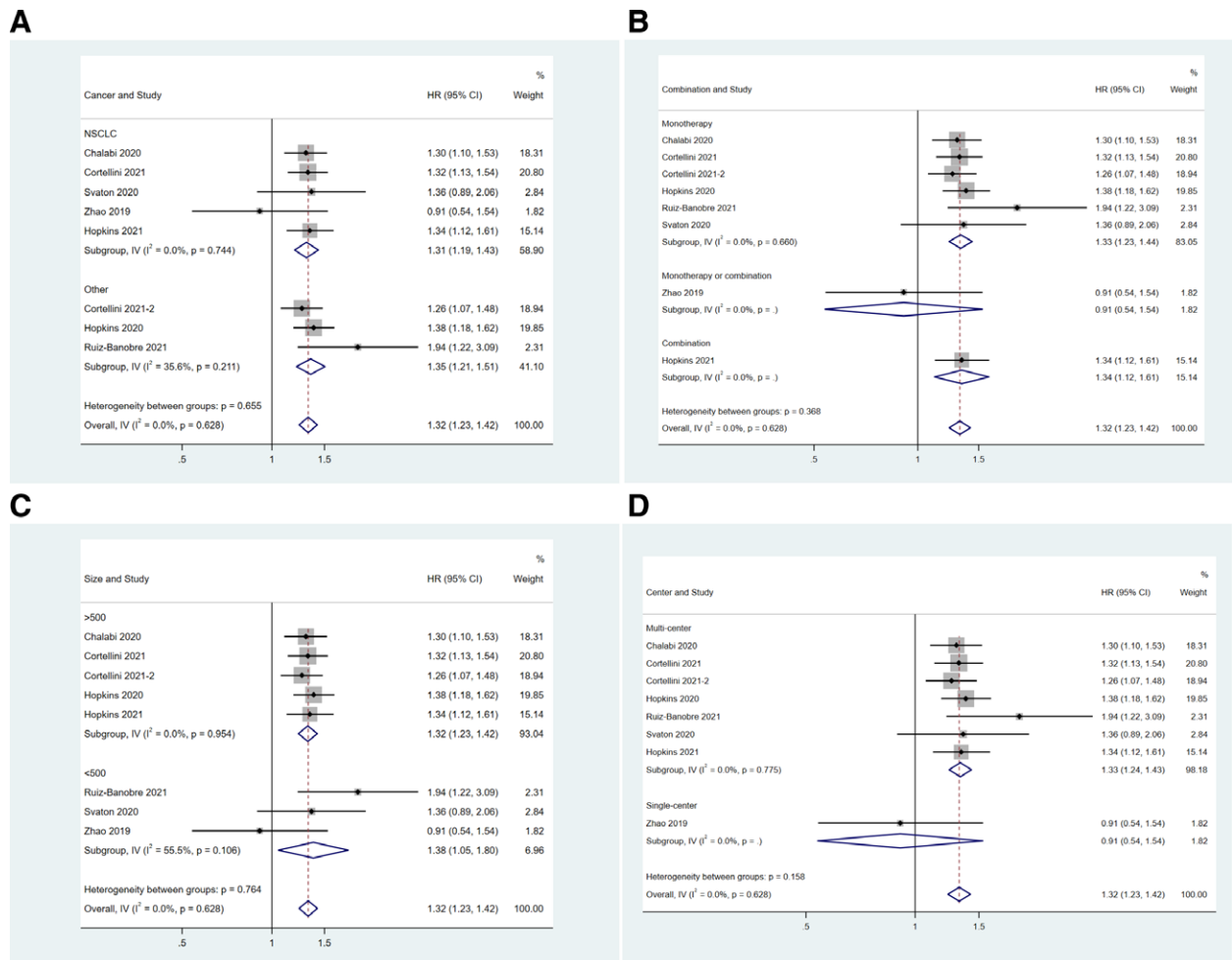

Figure 4. Associations between PPI use and PFS in cancer patients stratified by cancer type (A), treatment type (B), study size (C), and center number (D). PFS = progression free survival, PPI = proton–pump inhibitor.
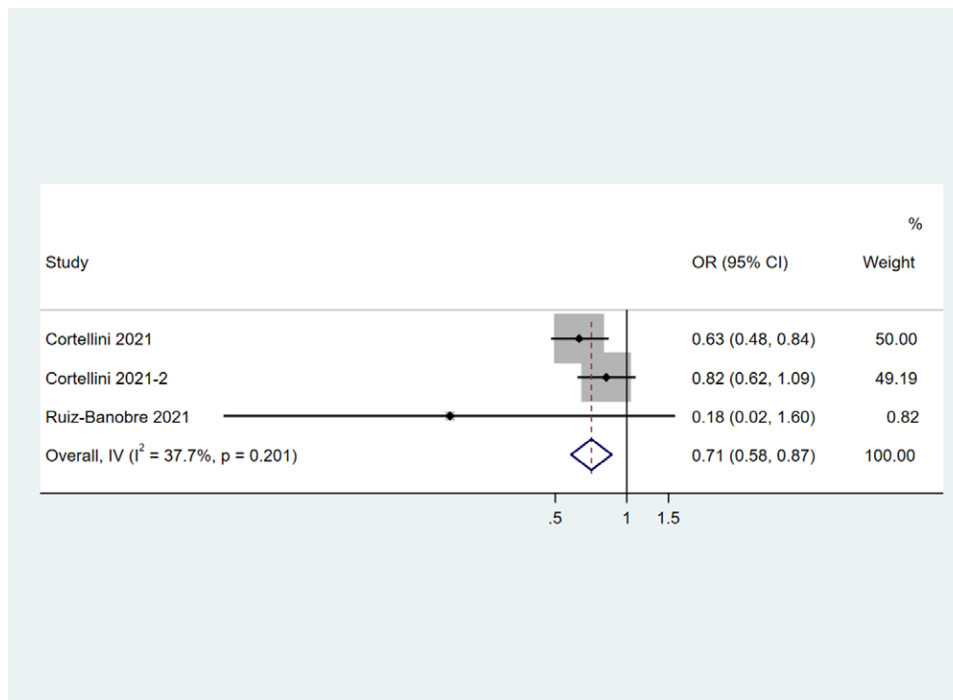
Figure 5. Associations between PPI use and objective response rate in cancer patients treated with PD-1/L1 inhibitors. PPI = proton–pump inhibitor; PD-1/L1 = programmed death protein-1/ligand 1.
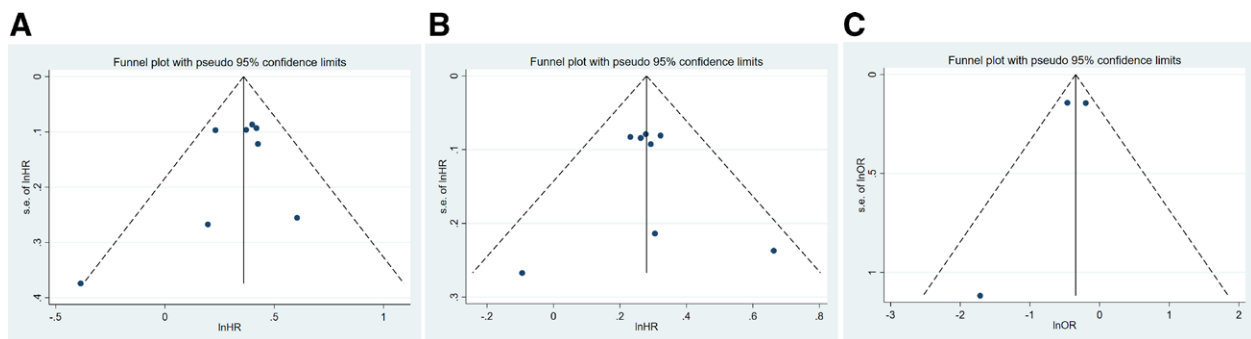

Figure 6. Publication bias analysis of OS (A) and PFS (B). OS = overall survival, PFS = progression free survival.

3.4. Objective response rate

Three studies reported ORR. The meta-analysis showed that PPI use was associated with a lower ORR. PPI use decreased the odd rate of response by 29% (odds ratio = 0.71, 95% CI 0.58–0.87) in solid cancer patients receiving PD-1/PD-L1 inhibitors (Fig. 5). There was not significantly heterogeneity among these studies (I^2 = 37.7%, Q test P = .201).

3.5. Publication bias and sensitivity

Egger test showed no publication bias among the 8 studies (P = .349 for OS; P = .883 for PFS, P = .521 for ORR, Fig. 6A, B, and C). Funnel plots demonstrated symmetry in the HR of either OS or PFS (Figure S2, Supplemental Digital Content 3, http://links.lww.com/MD/H299).

4. Discussion

Some concomitant drugs might affect the efficacy of PD-1/PD-L1 inhibitors. In this study, we revealed that PPI users had shorter OS and PFS than non-PPI users in advanced solid cancer patients receiving PD-1/PD-L1 inhibitors. Neither cancer type nor therapy type impacted the efficacies of concomitant PPIs on clinical outcomes.

Three meta-analyses have investigated the impacts of PPIs on immune checkpoint inhibitors (including PD-1/PD-L1 inhibitor and CTLA-4 inhibitor), but got different results.[8,19,20] Subgroup analysis has found that concomitant PPIs may have a positive effect on the prognosis of melanoma patients and a negative effect on the prognosis of NSCLC patients.[19] Further analysis found that melanoma patients mainly used CTLA-4 inhibitors, but NSCLC patients only used PD-1/PD-L1 inhibitors.[19] This might portend the different impact of PPI on effect of PD-1/PD-L1 inhibitors and CTLA-4 inhibitor. Hence, we focused on advanced cancer patients treated with PD-1/PD-L1 inhibitors and found that PPI use is associated with worse PFS or OS.

PPIs not only impact the gastrointestinal PH, but also the cancer/ immunity interface.[4] PPI have diverse effect, such as immune suppression via reducing the level of adhesion molecules expressed by inflammatory cells, and increasing the secretion of pro-inflammatory cytokines.[21] These effects may worsen the clinical outcomes of ICI treatment. PPIs can alter the

pH of gastrointestinal tract and further disrupt the composition of gastrointestinal microbiota.[19,22] This enhances the functions of nitrate/nitrite reductase which is involved in cancer development.[21,23,24] Besides, the alpha diversity of the gastrointestinal microbiota can be decreased by PPIs, which discounts the efficacy of immunotherapy.

But some basic research has obtained opposite conclusions. Solid tumors are characterized by a highly acidic microenvironment that may repress anti-cancer immunity. PPIs can neutralize the pH of the tumor microenvironment and indirectly affect the function of cytotoxic T lymphocytes, thus posing a positive impact on the clinical outcomes of immunotherapies.[25] Furthermore, *Helicobacter pylori* infection weakens the efficacy of cancer immunotherapies in preclinical animal models and NSCLC patients.[26] PPIs can inhibit the growth and reduce the viability of HP directly or indirectly by urase[27] or changing pH.[28] In this perspective, PPIs might improve the efficacy of immunotherapies in cancer patients with HP infection. Hence, basic studies are also needed to explore the possible mechanisms underlying the interaction between PPIs and PD-1/PD-L1 inhibitors.

There are some limitations in our study. First, only retrospective studies were included, which might bring about reporting and selection bias. Second, the effect of type, treatment timing, or the course of PPI was not analyzed due to incomplete data. Third, the impact of concomitant antitumor agents or other non-antitumor agents, other than PPIs, have not been evaluated due to the limited information.

5. Conclusion

In conclusion, our meta-analysis revealed that PPI use was associated with worse PFS and OS in advanced cancer patients treated by PD-1/PD-L1 inhibitors. This study provided evidence for the relation between PPI use and clinical outcomes of PD-1/PD-L1 inhibitors. However, the present study elucidated neither the causality between PPI use and efficacy of PD-1/PD-L1 inhibitors, nor the underlying mechanisms. Hence, larger prospective studies and basic research are needed to explain how PPI use changes the clinical outcomes of PD-1/PD-L1 inhibitors in solid cancer patients.

Author contributions

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Writing – review & editing: Xiaoqin Sun.

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