The Impact of Concomitant Proton Pump Inhibitors Therapy on Clinical Outcome of Cancer Patients Treated with Immune Checkpoint Inhibitors: A Meta-analysis

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Abstract

Background: In patients with advanced cancer receiving immune checkpoint inhibitors (ICIs) therapy, there are conflict perspectives about the influence of concomitant use of proton pump inhibitors (PPIs). We are aimed at exploring the influence of concomitant PPIs exposure on clinical outcome among cancer patients receiving ICIs treatment. Methods: We searched relevant literatures in PubMed, EMBASE, and the Cochrane Library without language restrictions. We extracted the data from selected studies and calculated the pooled hazard ratios (HRs) with 95% confidence intervals (CIs) through professional software for overall survival (OS) and progression free survival (PFS) among cancer patients undergoing ICIs therapy exposed to PPIs. Results: Fourteen studies including 6716 advanced cancer patients receiving ICIs treatment were appropriate for analysis judging by pre-set inclusion and exclusion criteria. The result indicated that concomitant PPIs exposure was significantly related to shorter OS (HR 1.388; 95%CI:1.278-1.498, P<0.001) and PFS (HR 1.285;95%CI:1.193-1.384, P<0.001) among multiple cancer patients receiving ICIs therapy. Conclusions: Our meta-analysis showed that concomitant PPIs exposure had adverse impact on clinical outcome among patients receiving ICIs therapy. Clinical oncologists must be cautious of PPIs delivery during ICIs treatment.

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Results: Fourteen studies including 6716 advanced cancer patients receiving ICIs treatment were appropriate for analysis judging by pre-set inclusion and exclusion criteria. The result indicated that concomitant PPIs exposure was significantly related to shorter OS (HR 1.388; 95%CI:1.278-1.498, P<0.001) and PFS (HR 1.285;95%CI:1.193-1.384, P<0.001) among multiple cancer patients receiving ICIs therapy.

Conclusions: Our meta-analysis showed that concomitant PPIs exposure had adverse impact on clinical outcome among patients receiving ICIs therapy. Clinical oncologists must be cautious of PPIs delivery during ICIs treatment.

Keywords:meta-analysis, immune checkpoint inhibitors (ICIs),overall survival (OS), proton pump inhibitors (PPIs), progression free survival (PFS).

INTRODUCTION

During the past decade, immune checkpoint inhibitors (ICIs) have become a dazzling star in curing multiple advanced cancers for its breakthrough efficacy and manageable untoward effect(1, 2). Antibodies inhibiting Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and programmed death-1/ligand-1 (PD-1/PD- L1) are mostly and widely researched ICIs in the world(2, 3). Nevertheless, the gut microbiota has been verified by many researchers to be closely related to clinical outcome among patients receiving ICIs(4-7).Several medications that can alter the gut flora distribution are usually administered to patients along with ICIs thus have adverse or beneficial impact on the efficacy of ICIs, such as antibiotics (ATBs) use which have been confirmed to be related to shorter OS and PFS as well as overall response rates (ORR) compared to ATBs-unexposed cancer patients undergoing ICIs therapy(8-12).

Except for ATBs, proton pump inhibitors (PPIs), maybe one of the most commonly concomitant prescribed medication among cancer patients(13), can also significantly decrease the gut microbiota diversity by altering the PH of gastric acid and delaying gastric emptying(14, 15), thereby, affect the efficacy of ICIs. Nevertheless, the effect of PPIs exposure and clinical outcome in cancer patients undergoing ICIs therapy remains controversial according to current existing literature. Hence, we collect the relevant studies and perform a meta-analysis to investigate the relationship between PPIs exposure and efficacy of ICIs to get a better understanding of this issue.

MATERIALS AND METHODS

Search Method

This meta-analysis was conducted in term of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Updating guidance(16). This research was registered in PROSPERO and ID was CRD42021281619. Two researchers (xing cao and yafei wang) searched in PubMed, EMBASE, and Cochrane Library independently for related electronic literatures without language restrictions (updated in September 2021). The comprehensive search strategy combined Medical Subject Headings (MeSH) terms with Entry Terms. Take PubMed for example, Proton Pump Inhibitors is MeSH, the Entry Terms in PubMed included the following: “Inhibitors, Proton Pump,” “Proton Pump Inhibitor,” “Inhibitor, Proton Pump,” and “Pump Inhibitor, Proton.” The same search strategy was applied in immune checkpoint inhibitors and merged two results by “AND”. The detailed search formula was presented in supplementary due to its prolixity.

Eligible and Exclusion Criteria

Studies that match all the inclusion criteria listed below were selected:1. Population: cancer patients undergoing ICIs therapy alone or in combination;2. Interventions: PPIs were prescribed within a treatment window of 30days before, during or after the first dose of ICIs therapy;3. Comparison: containing an PPIs-exposed

group and a control group did not;4. Outcome: intact data that have enough information to calculate HR and their 95% CI for PFS and OS.

Exclusion criteria were as followings:1. Case reports, case series, comments, reviews, letters, editorials, animal models;2. Inappropriate or unknown PPIs treatment window;3. Insufficient information to calculate HRs with 95% CI of PFS or OS;4. Special populations such as veterans. Two authors (xing cao and yafei wang) screened the studies independently and conflicts among them were solved by consensus with a third author.

Quality Assessment

The Newcastle-Ottawa Quality Assessment Scale (NOS) was employed by two authors(xing cao and yafei wang) independently to assess each study quality since all selected research were retrospective (17).

Data Extraction

Two authors (xing cao and yafei wang) collected data separately from eligible studies. The information relevant to this analysis was extracted: 1. The primary endpoint of investigation were the HRs for PFS and OS (especially OS) among cancer patients receiving ICIs therapy exposed to PPIs or not.2. Secondary variables including the author names, year of publication, country, ICIs agents, tumor type, ICIs treatment line, data from single or multiple centers, PPIs treatment window, study endpoints and number of patients.

Statistical Analysis

All statistical analyses were carried out on Comprehensive Meta-Analysis software (version 3.3.070, Biostat Inc, New Jersey, USA). $P<0.05$ was considered statistically significant. The pooled HRs for PFS and OS were calculated to evaluate the effect of PPIs exposure on ICIs therapy compared to non-PPIs users. The pooled HR>1.0 indicated an adverse influence of PPIs exposure undergoing ICIs therapy. HR<1.0 denoted a beneficial influence of PPIs exposure undergoing ICIs therapy. The χ^2-based Q test and I^2 statistic were applied to detect and quantize heterogeneity (18, 19). I^2>50% (I^2 <25%: no heterogeneity; I^2 = 25–50%: moderate heterogeneity; I^2 >50%: large heterogeneity) and/or P <0.1 for Q test represented statistically significant heterogeneity, in this situation, the random model was used, in other cases, fixed models were applied. We use funnel plot and Egger's test as well as Begg's test to detect publication bias. Publication bias is suspected if $p<0.05$ for the Egger's and Begg's tests(20, 21). Sensitivity analysis were conducted using one study removed to assess stability of pooled outcome of HR.

RESULTS

Search results and study selection

385 researches were obtained from the original search,21 duplicate records were removed. Following screening title and abstract, 291 publications were excluded owing to case reports, case series, comments, reviews, letters, editorials, animal models. The remaining 46 records were obtained for full-text assessment. Whereafter,32 publications were removed according to the items of exclusion criteria after checking the full-text. Such as veteran studies were excluded for its very high male proportion (almost 100%) which may cause bias to the result. Besides, publications without enough data for calculating pooled HRs for PFS and OS were also excluded. Eventually, 14 studies were eligible for this meta-analysis. A PRISMA flow chart describing the process of study screen and selection was presented in Figure 1.

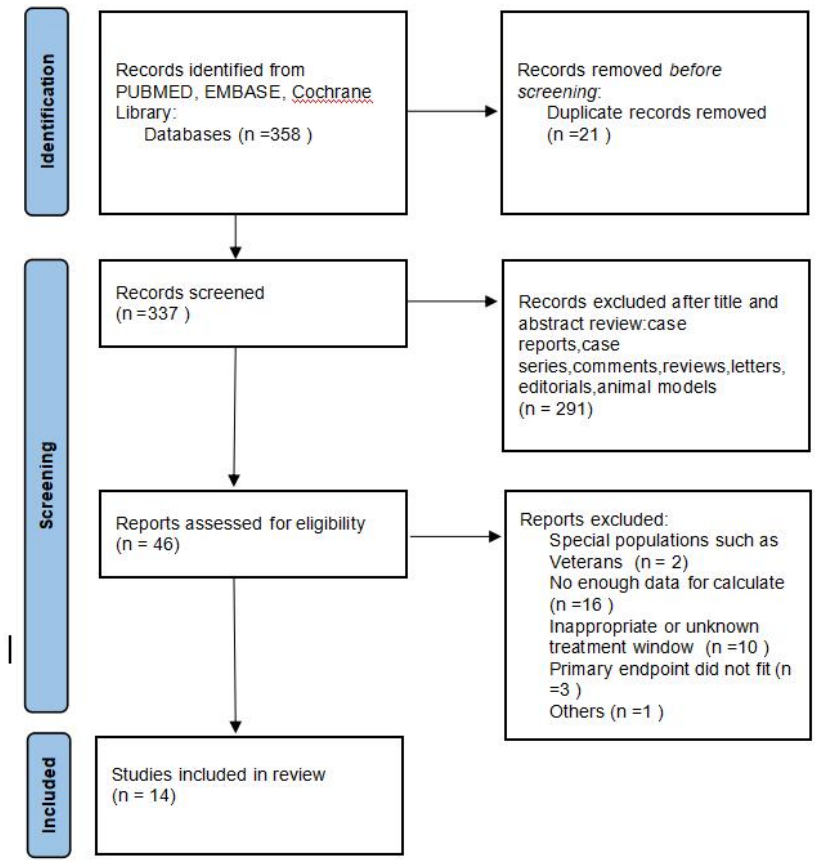


Figure. 1. The process of study identification and selection.

Study Characteristics

All the 14 records were retrospective studies. 6716 advanced cancer patients receiving ICIs treatment were included. Among the14 studies, 3 studies were conducted in USA(22-24), 7 studies were conducted in Europe(25-31),1 study was conducted in China(32), 3 studies were conducted worldwide(12, 33, 34). All the studies provided the relationship between PPIs exposure and OS, 9 of them offered the association between PPIs exposure and PFS. Table 1 summarized the basic information of the studies in this study. The NOS score evaluating quality of included studies were also presented in Table1.

Table 1 Study Characteristics in This Meta-analysis

Study	Year	Country	ICIs Type	Tumor Type
Afzal	2019	USA	Ipil/Pemb	Melanoma
Zhao	2019	China	Pemb/Nivo/SHR-1210	NSCLC
Chalabi	2020	worldwide	Atezo	NSCLC
Cortellini	2020	Italy	Pemb/Nivo/Atezo	NSCLC /Melanoma/RCC and others
Hopkins	2020	Worldwide	Atezo	advanced urothelial cancer
Santamaría	2020	Spain	Pemb/Nivo/Atezo/Ipil	NSCLC/RCC/Melanoma/bladder cancer
Svaton	2020	Czech	Nivo	NSCLC
Buti	2020	Italy	Pemb/Nivo	NSCLC, melanoma, renal cell carcinoma, others
Cortellini	2021	Italy and UK	Pemb	NSCLC

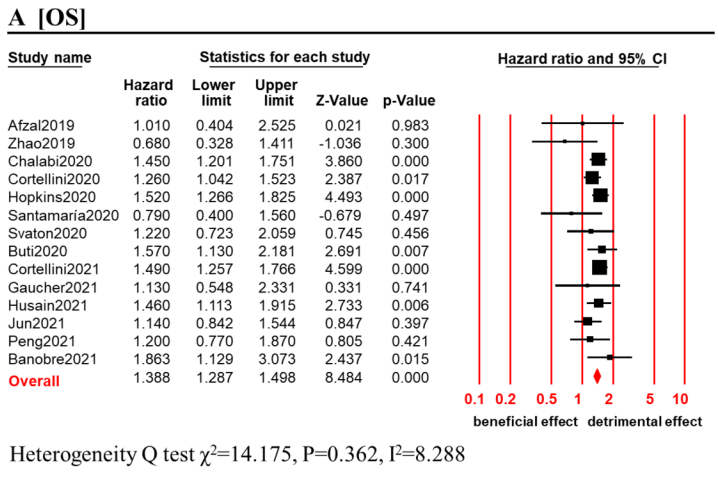
Study	Year	Country	ICIs Type	Tumor Type
Gaucher	2021	France	Ipil/Pemb/Nivo	Melanoma
Husain	2021	USA	PD1/L1/CTLA-4	NSCLC and Melanoma
Jun	2021	USA, Europe, and Asia	PD-1/CTLA-4	HCC
Peng	2021	USA	Nivo/Pemb	NSCLC, Melanoma, RCC, TCC, or HNSCC
Bañobre	2021	Spain	Atezo/Pemb/Nivo	metastatic urothelial carcinoma

Nivo: nivolumab; Pemb: pembrolizumab; Ipil: ipilimumab; Atezo: atezolizumab; NSCLC: non- small- cell-lung- cancer; TCC: transitional cell carcinoma; HCC: hepatocellular carcinoma; RCC: renal cell carcinoma; HNSCC: head and neck squamous cell carcinoma; PFS: progression free survival; DCR: disease control rate; ORR:overall response rates; OS: overall survival.

Main results

For OS, all 14 studies including 6716 cancer patients receiving ICIs treatment are analyzed for influence of concomitant PPIs exposure on OS. The fixed effect model was applied since no obvious heterogeneity existed (Q test P=0.362, I^2=8.288). The result demonstrated that concomitant PPIs use had significantly shorter OS among patients receiving ICIs therapy compared to PPIs-unexposed ones, the pooled HR for OS was 1.388 (95%CI:1.278-1.498, P<0.001) (Figure 2A).

Nine studies including 4866 patients undergoing ICIs therapy are available for analysis of effect of concomitant PPIs use on PFS. The fixed-effect model was applied since the heterogeneity was acceptable (Q test P=0.109, I^2=38.888). Similarly, the result indicated that PPIs use could also shorten PFS of cancer patients receiving ICIs treatment, the pooled HR for PFS was 1.285(95%CI:1.193-1.384, P<0.001) (Figure 2B).



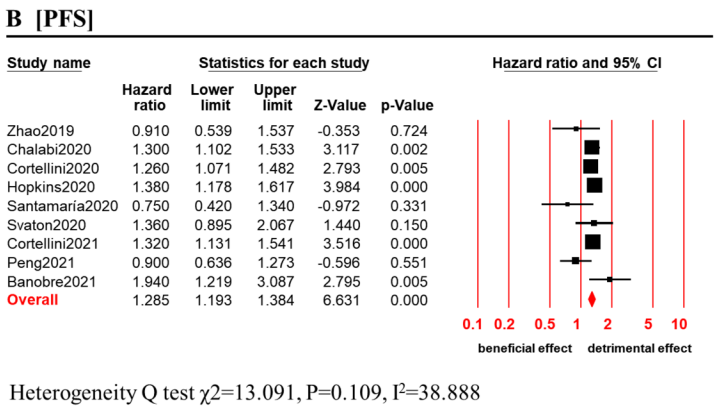
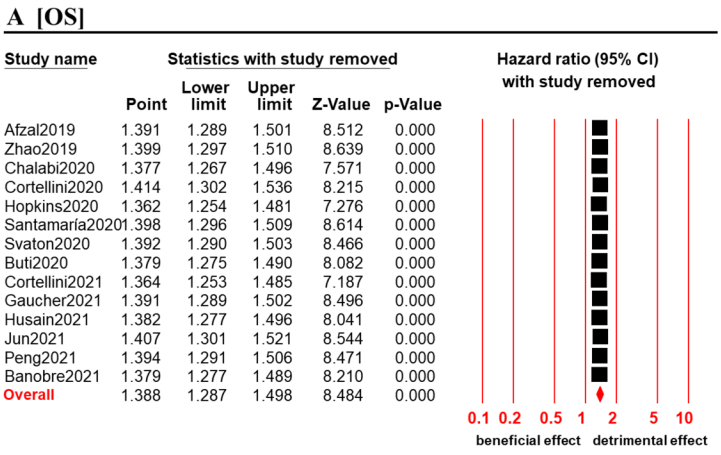


Figure 2 Pooled HRs of OS(A) and PFS(B) for PPIs exposed versus unexposed patients.

Sensitivity Analysis

Sensitivity analysis were conducted using one study removed method. The result showed that the pooled HR for OS did not significantly fluctuate after excluding studies one by one (Figure 3A). The result of PFS sensitivity analysis was consistent with OS (Figure 3B), demonstrating the stability of the pooled results.



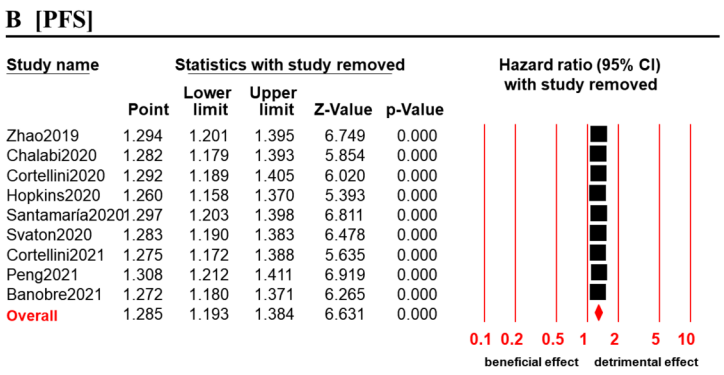


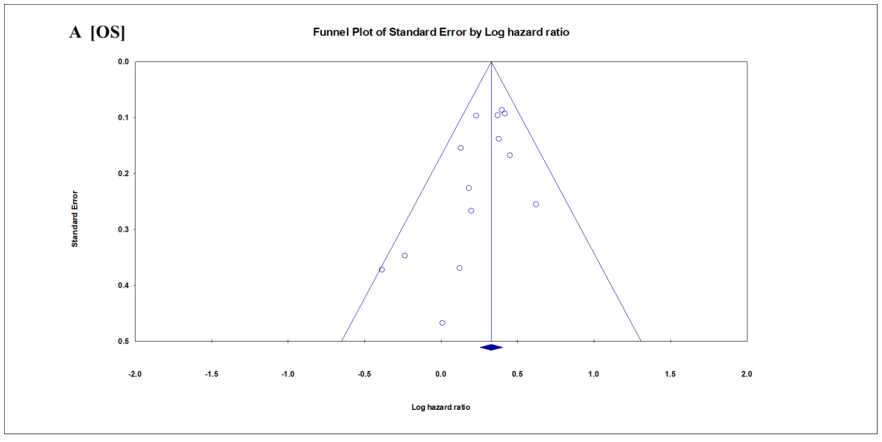
Figure3 Sensitivity analysis for OS(A) and PFS(B).

Publication Bias and Cumulative Analysis

We use funnel plot and Egger's test as well as Begg's test to detect publication bias. For OS, the conventional funnel plot seems symmetric (Figure 4A), however, the result of Egger's test and Begg's test (Egger's test, P = 0.0407; Begg's test, P = 0.0487) implied that publication bias may exist. Furthermore, we made funnel plot of precision by log hazard ratio (Figure 4B), and the result showed some asymmetries. Hence, we suspect publication bias did exist for OS.

For PFS, the publication bias was not detected. Both conventional funnel plot and precise funnel plot were symmetric (Figure 4C and 4D). The result of Egger's test and Begg's test also support that (Egger's test, P = 0.272; Begg's test, P = 0.348).

We also made cumulative analysis presented in Figure5A and 5B, the result demonstrated the negative influence of PPIs use with the passage of time and appearance of more evidence.



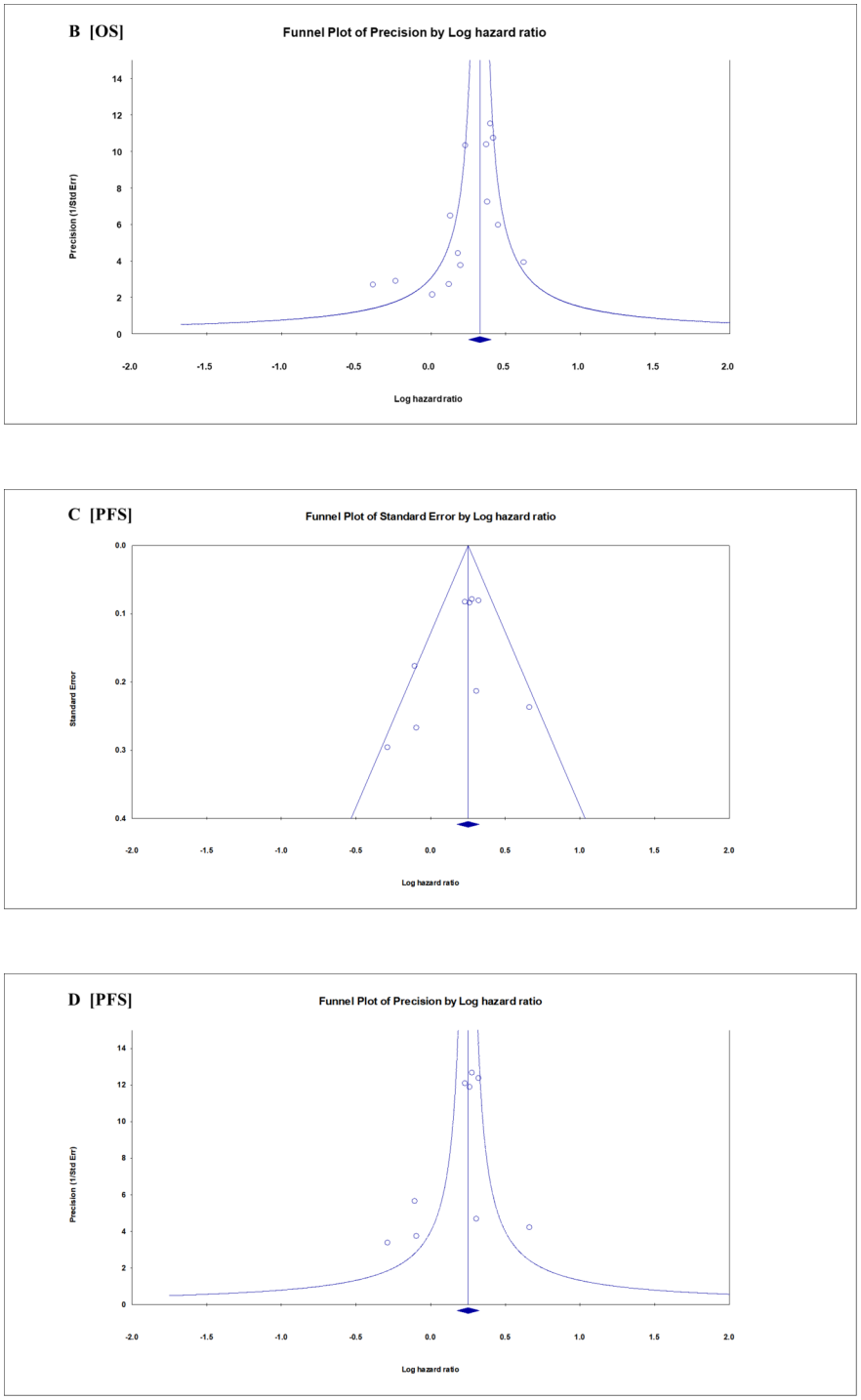
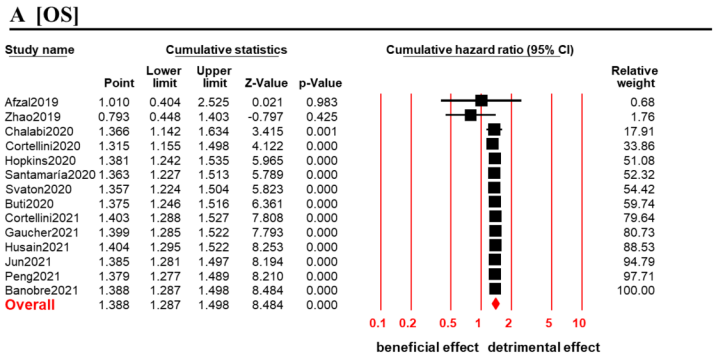


Figure4 funnel plot for OS(A), PFS(C) and precise funnel plot for OS(B), PFS(D)



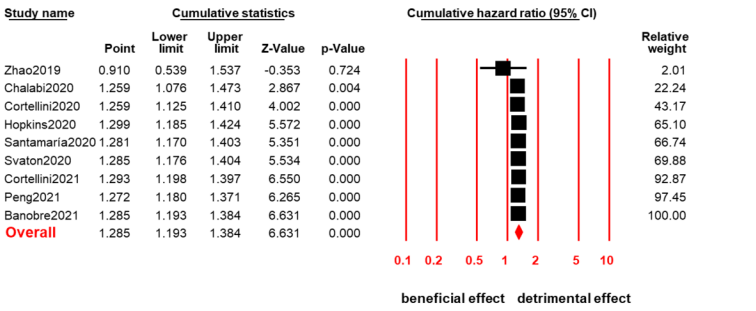


Figure5 cumulative analysis of OS(A) and PFS(B)

DISSCUSSION

Although immune checkpoint inhibitors (ICIs) have soon yield unusually brilliant results in oncotherapy and become the forefront treatment against various advanced cancer, its efficacy is not universal and affected by a number of factors, for instance, the level of PD-L1 expression in tumor(35) and tumor mutation burden(TMB)(36). The gut microbiota diversity has been recognized to have significantly influence on effectiveness of ICIs treatment in recently years(4-7, 37). Numerous studies have shown that antibiotics

(ATBs) have negative impact on PFS, OS and ORR of patients treated with ICIs(8-12). The molecular mechanisms below this phenomenon are not clear, the longstanding disturbance to the gut microbiota caused by ATBs might take the leading account(38).

Unlike the directly kill and bacteria growth suppression of ATBs, PPIs influence the diversity of gut microbiota by sophisticated ways (38, 39) and theoretically influence ICIs efficacy. Drug–drug interactions have significant effect in anti-cancer treatment, the combination of different classes of cytotoxic medications can improve the clinical benefit by overcoming drug resistance. Since the pharmacokinetic of ICIs is stable and lesser influenced by concomitant therapies(8), PPIs may affect the efficacy of ICIs through indirect ways. PPIs can exert immunosuppressive properties by reducing the expression of adhesion molecules and altering neutrophil response(40). Homicsko et al. conducted retrospectively analysis in Checkmate 069 clinical trial, a rise of leukocyte and neutrophil levels was detected and pro-inflammatory status was established in PPIs users before ICIs initiated thus interferes with treatment efficacy(41). Hence, the causality between PPI use and ICIs efficacy cannot be deduced directly from present study. Routy et al. found that NSCLC patients who benefit from ICIs therapy was associated with significantly higher abundance of *Ruminococcus spp* in feces(5). However, Jackson et al. found a significantly lower abundance of *Ruminococcaceae* family among PPIs users(15). Besides, dozens of microbiota species altered after PPIs use which can enhance or weaken anti-PD-1 therapy by multiple ways(15, 42), which further illustrate the complexity of PPIs influence on gut microbiota and eventually affect the therapeutic effect of ICIs. Therefore, it is still controversial about the impact of concomitant PPIs exposure on clinical outcome of cancer patients undergoing ICIs therapy due to limited literatures. Numerous basic researches are urgently needed to elucidate the cellular and molecular mechanisms between PPIs use and ICIs efficacy.

The early studies did not support the adverse influence of PPIs on PFS and OS among patients undergoing ICIs therapy(22, 32, 43, 44) probably due to small sample size. Nevertheless, with accumulation of evidence, the tendency of detrimental effect of concomitant PPIs exposure on outcome of ICIs therapy became increasingly apparent(12, 25, 28, 30, 31, 33). It is worth mentioning that data from 4 randomized controlled trial were extracted retrospectively. The POPLAR and OAK trials explored the PFS and OS of PPIs use in NSCLC patients treated with atezolizumab(12),the result showed that PPIs users had poor outcome and PPIs exposure may affect the efficacy of atezolizumab. The IMvigor210 and IMvigor211 were conducted in advanced urothelial cancer patients undergoing atezolizumab treatment, their analysis indicated that PPIs users had significantly shorter PFS and OS(33).

Our meta-analysis consists of 14 studies including 6716 cancer patients receiving ICIs therapy indicated that concomitant PPIs exposure was significantly related to shorter OS and PFS, the pooled HR for OS and PFS were 1.388(95%CI:1.278-1.498, P<0.001) and 1.285(95%CI:1.193-1.384, P<0.001), respectively. PPIs are becoming one of the most frequently inappropriate prescribed and abused agents worldwide among cancer and other patients(45-48), and our findings raise concerns about PPIs use especially in cancer patients receiving ICIs therapy and remind of clinician be cautious of PPIs delivery during ICIs treatment. However, there are several drawbacks in our study, too. Firstly, all the included studies are retrospective and we did detect publication bias in this analysis. Secondly, there are no enough data to conduct subgroup analysis. The type of PPIs and dosage, ICIs type, cancer type, ICIs alone or in combination with others were variables and not all of them were homogeneous in every study, which demanded large randomized controlled clinical trials to validate the conclusion. Thirdly, we noticed that gastrointestinal cancer studies are not available in this study, most of the studies were concentrated on NSCLC and melanoma, which made the results to be limited. Further researches are needed to delve into the relationship between PPIs exposure and ICIs efficacy among gastrointestinal cancer patients.

Collectively, our findings indicate that concomitant PPIs exposure is significantly associated with shorter OS and PFS among patients undergoing ICIs therapy. Further randomized controlled trials are needed to confirm the findings. Clinical oncologists must take the detrimental effect of PPIs use into account when ICIs are given.

Conflict of Interest

The authors declare that the study was performed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

YhL designed the study and reviewed the manuscript. XC and YfW searched and extracted the data as well as drafted the manuscript. WH, PyL and CjG modified the article. XC drawed the table and did the computation part in software. All the authors contributed to the manuscript.

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