# Concomitant of Proton Pump Inhibitors is Associated with Poor Clinical Outcomes in Patients Treated with Immune Checkpoint Inhibitors：An Up-to-date Systematic Review and Meta-analysis

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# Concomitant of proton pump inhibitors is associated with poor clinical outcomes in patients treated with immune checkpoint inhibitors：An up-to-date systematic review and meta-analysis

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**Background**: The emergence of immune checkpoint inhibitors has greatly changed the treatment outcome of advanced malignant tumors. The basic medication for patients with advanced solid tumors may affect the efficacy of immunotherapy. The use of proton pump inhibitors may change the acidic environment and inhibit intestinal flora, thereby affecting the efficacy of immunotherapy. To clarify the correlation between PPI administration and the prognosis of solid cancer patients treated with ICI, we conducted a meta-analysis.

**Method**: Before February 12th, 2021, PubMed, Cochrane Library, Web of Science and EMBASE databases were used to search for eligible documents. The association of PPI administration with overall survival (OS) and progression-free survival (PFS), hazard ratio (HR) and 95% confidence interval (CI) were determined.

**Results**: This study included 10 studies, a total of 4072 patients with solid cancer who received ICI treatment. Overall, the PPI administered with OS (HR=1.31 (1.11-1.52), P = 0.001) deteriorate significantly associated. In the subgroup analysis based on cancer type, PPI administration was associated with worsening of PFS in NSCLC, and better results of PFS in melanoma patients. In addition, between 30 days before the occurrence of ICI and 30 days after the occurrence of ICI, PPI administration may reduce the efficacy of ICI.

**Conclusion**: Patients with solid cancer receiving ICI should use PPI with caution. However, only poor statistical results are observed on the OS, and further verification is still essential.

This study was registered in PROSPERO with registration number CRD42021243707.

## Introduction

Immune checkpoint inhibitor (ICI) is an important progress in the treatment of advanced malignant tumors. Its representative drugs include Programmed cell death 1 (PD-1)/Programmed cell death ligand 1(PD-L1) inhibitor and cytotoxic drug T lymphocyte-associated antigen 4 antibody (CTLA - 4)[(1)]. Recently, it has been proposed in the literature that other basic medications accompanying ICI may have a negative impact on the clinical outcome of related patients [(2).]In addition to pharmacokinetic interactions, some drugs can play immunomodulatory roles in the systemic and tumor microenvironment, such as influencing the clinical efficacy of immunotherapy by inhibiting intestinal flora, which plays an important role in regulating human immune function [(3).]More and more people realize that changes in intestinal flora will have a negative impact on the systemic immune response and ICI efficacy[(3-6).]

Proton pump inhibitors (PPI) is one of the most commonly prescribed drugs, which by irreversibly inhibiting gastric parietal cells in the hydrogen / potassium pump ( H + / K + - ATP pump) so that inhibit gastric acid secretion , thus it is the drug of choice for gastroesophageal reflux disease and peptic ulcer disease [(7)]. Studies have shown that the use of PPI is related to significant changes in the gut microbiome of cancer patients [(8)]. Omeprazole has been shown to reduce the abundance of Akkermansia muciniphila in a mouse model [(9)], and we know that metagenomic studies of baseline fecal samples from patients prior to ICI have revealed a correlation between clinical response to ICI and the abundance of Aspergillus mucosa [(4)] . It has even been suggested that oral administration of Aspergillus mucus can restore the efficacy of PD-1 blockade by increasing the recruitment of T lymphocytes(4). The impact of PPI on human immunity is multifaceted. First , it affects the microbiota through a non-PH dependent pathways, induces hormone changes and interferes with nutrient absorption, and has the potential to change the pattern

of bacterial food substrates[10]. Secondly, studies have pointed out that the effect of PPI may not be completely harmful: preclinical evidence emphasizes the anti-tumor potential of this drug class because of their ability to neutralize the acidic tumor microenvironment[11] . Nguyen et al[12] in a retrospective study including 95 patients with mixed histological tumors (melanoma 47%, head and neck 24%, stomach 18%) showed that PPI was used concomitantly during the course of nivolumab single-agent immunotherapy although there is a difference in tumor response rate compared with the non-PP group, progression-free survival (PFS) and overall survival (OS) do not show statistical differences, but it should still be recommended Reduce unnecessary PPI prescriptions during immunotherapy. Recently a series of relevant clinical studies have shown the efficacy of PPI for ICI is an uncertain factor, which range from no difference to the negative effects [13-18] . Given the available evidence is mostly retrospective study, unable to infer the use of PPI reliable suggestions. Therefore, at the same time the use of PPI in the role of ICI treatment efficacy remains controversial, in order to solve the problems described, we conducted a meta-analysis, evaluating PPI use and ICI treatment of the relationship between the clinical outcome of patients.

## 2.Materials and methods

### 2.1. Search strategy

As shown in Figure 1, the system review is conducted in accordance with the PRISMA guidelines. PubMed, Cochrane Library, Web of Science and EMBASE (as of Feb. 12, 2021) were used to search the related research on the relationship between PPI administration and cancer immunotherapy. The search keywords are used as follows: “neoplasm”, “carcinoma”, “malignant neoplasm”,”avelumab”, “atezo-lizumab”, “camrelizumab”, “cetrelimab”, “nivolumab”, “pembrolizumab”, “bintrafusp alfa", "envafolimab", "cemiplimab", "sintilimab", "durvalumab", "pidilizumab", "toripalimab", "ipilimumab", "tislelizumab", "proton pump inhibitors", "omeprazole", "pantopra-zole ”, “lansoprazole”, “rabeprazole”, “esomeprazole”, “dexlansopra-zole” . In addition, since electronic search strategies may ignore original articles and reviews,these published literature is carefully sifted to identify other eligible studies.

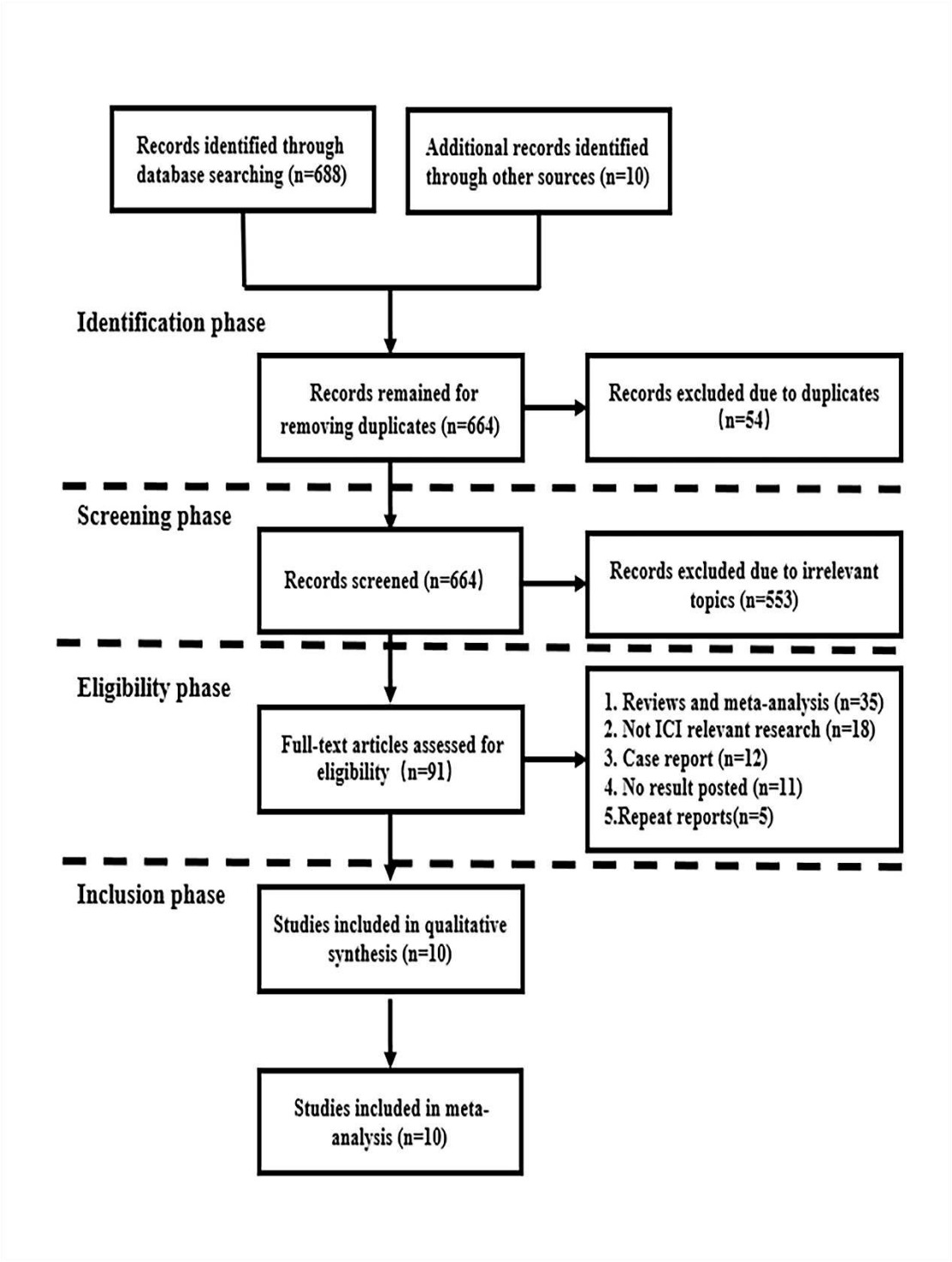


Fig.1 PRISMA flow diagram of articles identification and selection

The system literature search is shown in Figure 1. A total of 688 candidate articles were s elected from the electronic database using our search strategy, and 10 other articles were identi fied from other sources. After deleting duplicates, 664 entries remain. Then, due to irrelevant to pics (n=553), reviews or meta-analysis (n=35), non- ICI related studies (n=18), case reports (n=1 2), lack of relevant data (n=11), repeated study cohort (n=5). Finally, a total of 10 articles(19-2 8) were determined to meet the requirements of Meta-analysis.

### 2.2.Study selection

The inclusion criteria are as follows: (1) The literature focuses on the impact of PPI on cancer patients treated with ICI. (2) A patient diagnosed with a solid cancer and underwent treatment ICI, whether given alone or in combination with other anti-cancer treatment; (3) PPI was administered before and/or during ICI treatment, irrespective of time and dose. (4) Results including the OS and/or PFS, hazard ratio (Hazard ratio, HR), and 95 % confidence interval (Confidence Interval, CI).

The exclusion criteria are as follows:(1) Relevant literature or data duplication;(2) Animal or cell experiments; (3) Reviews and meta-analysis without original data;(4) Publication of literature in non-English languages. In addition, if several eligible duplicate studies are identified, we will choose to include only the most comprehensive publications to ensure the reliability and quality of the data.

### 2.3. Data extraction

Two researchers (LCX and YMX) independently extracted data from the study. The following information is collated from the selected articles: first author, publication year, research type, cancer type, region, age, sample size, ICI protocol, PPI use protocol and time window, follow-up time, OS and/or PFS and HR 95% confidence intervals for PPI use in immunotherapy patients. If both univariate and multivariate analyses were used to calculate HR for OS or PFS, the latter was preferred due to confounding adjustment. The data extraction was carried out by two independent researchers, and the disagreement was resolved through discussion or evaluation with the third researcher（YM）.

### 2.4. Quality assessment

The Newcastle-Ottawa Quality Assessment Scale (NOS) is used to assess the quality of research. Two reviewers (LCX and YMX) graded the research from the following aspects: topic selection, comparability, and outcome evaluation. In the NOS system, the highest possible score is 9 points, and as long as the score is higher than 6 points, it can be considered as a high-quality research(29).Researches with a score lower than 6 points are considered relatively low quality and are excluded. Two investigators independently assessed the risk of bias and resolved their differences through discussions until they reached a consensus.

### 2.5. Statistical analysis

All statistical analyses were performed using Stata SE15.0 and RevMan5.3 software. Cochrane Q test and $I^2$ statistics were used to determine the heterogeneity between all studies. If P>0.1 and $I^2$ <50%, there was no heterogeneity between studies, and a fixed-effect model was used to analyze the results. On the contrary, if the heterogeneity between the research results is determined, and the random effects model is used for analysis. Sensitivity analysis is used to assess the stability of the results. The Begg and Egger test was used to assess publication bias. The observed HR>1 indicates that PPI administration is negatively correlated with OS or PFS, while the observed 95% CI>1 indicates that the correlation is statistically significant. For all analyses, P value of <0.05 was considered statistically significant.

## 3. Results

### 3.1. Search results and study characteristics

Table 1 summarizes the general clinical characteristics of the included studies. All studies were published from January 2016 to February 2021. Two of the studies were in Asian patients, two were in the United States, four were in Europe and two were worldwide. Four were diagnosed with non-small cell lung cancer and three with multiple cancers, two with malignant melanoma and one with urothelial carcinoma based on cancer type. Immunization therapy program comprising immunotherapy alone or in combination with chemotherapy/targeted therapy, immunotherapy drugs include PD-1/PD-L1 inhibitor and CTLA-4 antibody. All 10 studies provided an association between PPI use and OS, only 8 provides the use of PPI influence on PFS. Most patients received PPI treatment before and/or within immunotherapy, and the most commonly used PPI drug is Omeprazole. The available timing of PPI exposure from the included studies was provided in fig.2. a. The total number of people included in various ICI studies and the number of PPI users was provided in fig.2.b

**T**able 1 General information of included studies.

| Author | Year | Region | Cancer type | ICI treatment | PPI treatment | PPI | Patients | PPI exposure | Age | Evaluation criteria | Follow up time |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Afzal *et,al* | 2019 | America | Melanoma | CTLA-4 inhibitor or PD-1 inhibitor alone or in combination | Omeprazole(majority) | 29 | 120 | Taking PPI at the time of ICI initiation | 65 | NA | NA |
| Chalabi et,al | 2020 | Worldwide | NSCLC | PD-L1 inhibitor | omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole, dexlansoprazole | 234 | 757 | Within 30 days before or after the start of ICI | NA | RECIST 1.1 | 19.2m |
| Failing et,al | 2016 | America | Melanoma | CTLA-4 inhibitor | Omeprazole(majority) | 17 | 80 | At the start of ipilimumab treatment | 58 | RECIST 1.1 | 49m |
| Hakozaki et,al | 2019 | Asia | NSCLC | PD-1 inhibitor | NA | 47 | 90 | Within 30 days after the start of ICI | 67 | NA | NA |
| Iglesias-Santamaría et,al | 2019 | Spain | Multiple | PD-1 inhibitor or PD-L1 inhibitor or PD-1 inhibitor in combination with CTLA-4 inhibitor | NA | 76 | 103 | NA | 66 | 2017 iRECIST | 26m |
| Svaton et,al | 2020 | Europe | NSCLC | PD-1 inhibitor | Omeprazole, Pantoprazole, Lansoprazole | 64 | 204 | Within 30 days before or after the start of ICI | 67 | RECIST 1.1 | NA |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Zhao et,al | 2019 | Asia | NSCLC | PD-1 inhibitor | NA | 40 | 109 | Within 30 days before or after the start of ICI | 62 | RECIST 1.1 | 28m |
| Hopkins et,al | 2020 | Worldwide | Urothelial | Atezolizumab | omeprazole, pantoprazole, esomeprazole, lansoprazole, rabeprazole, dexlansoprazole | 471 | 1360 | Within 30 days before or after the start of ICI | NA | RECIST 1.1 | 11/17m |
| Cortellini et,al | 2020 | Europe | Multiple | PD-1 inhibit or PD-1 inhibitor | NA | 491 | 1012 | NA | 69 | RECIST 1.1 | 24.2m |
| Buti et,al | 2021 | Europe | Multiple | CTLA-4 or PD-1 or PD-L1 | NA | 104 | 217 | NA | 69 | RECIST 1.1 | 21.6m |

Abbreviations: NSCLC, non-small cell lung cancer; proton pump inhibitor (PPI) ; NA, not available; ICI, immune checkpoint inhibitor, CTLA-4, cytotoxic T-Lymphocyte-associated Antigen 4; PD-1, programmed cell death protein-1; PD-L1,programmed cell Death-Ligand 1;

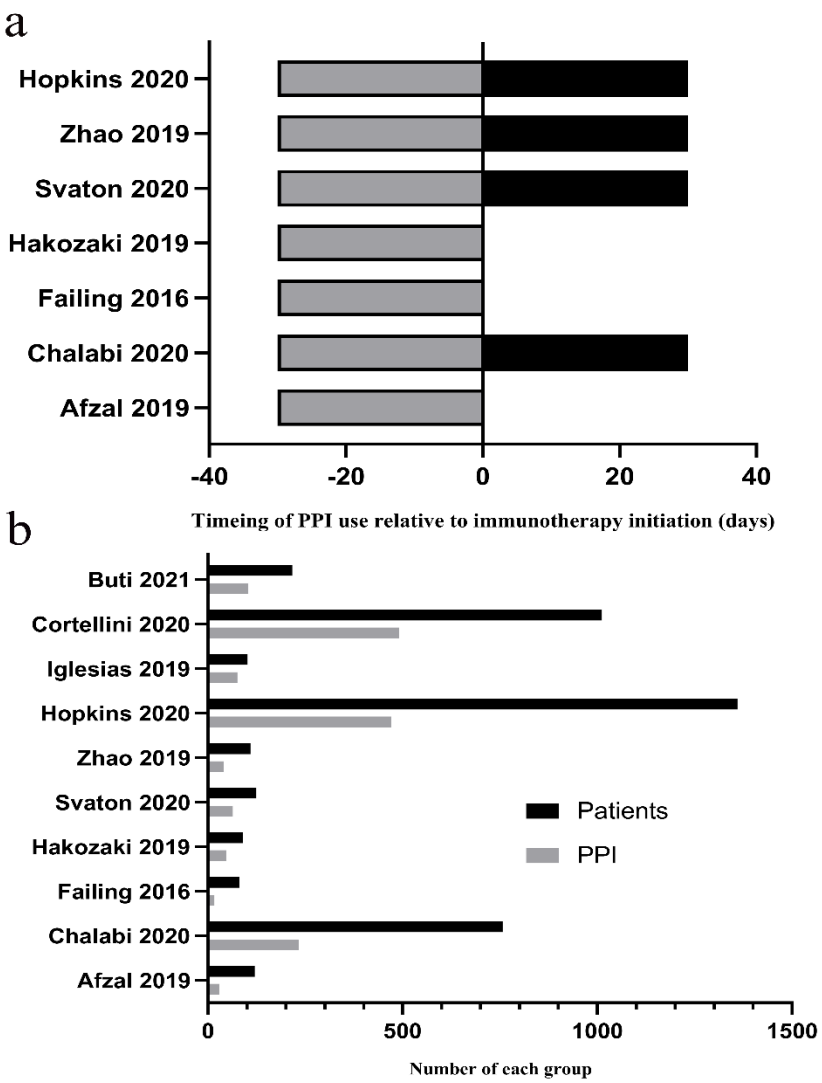


Fig.2. a. Summary graph of the timing for PPI administration in included studies. b. Summary graph of the total number of people included in various ICI studies and the number of PPI users

### 3.2. Quality assessment

Table 2 summarizes the prognostic information and quality assessment of the included studies. All studies were retrospective studies. A total of 8 studies reported OS and PFS and complete HR values. Seven studies used multivariate and one univariate analysis. It was found that 1 study had a NOS score of 6, 4 studies had a NOS score of 7, and 5 studies had a NOS score of 8. All studies met the inclusion criteria.

Table 2 Prognostic information and quality assessment of included studies

| Author | Year | Method | Outcome | HR (95% CI) for OS | HR (95% CI) for PFS | Analysis | NOS score |
|---|---|---|---|---|---|---|---|
| Afzal *et,al* | 2019 | RE | OS/PFS | 1.01 (0.40–2.55) | 0.30 (0.10–0.90) | M | 7 |
| Chalabi *et,al* | 2020 | RE | OS/PFS | 1.45 (1.20–1.75) | 1.30 (1.10–1.53) | NA | 8 |
| Failing *et,al* | 2016 | RE | OS/PFS | 0.44 (0.17–1.14) | 0.60 (0.34–1.06) | NA | 7 |
| Hakozaki *et,al* | 2019 | RE | OS | 1.90 (0.80–4.51) | NA | M | 6 |
| Iglesias-Santamaría *et,al* | 2019 | RE | OS/PFS | 0.79 (0.40–1.56) | 0.75 (0.42–1.34) | M | 7 |
| Svaton *et,al* | 2020 | RE | OS/PFS | 1.22 (0.72–2.05) | 1.36 (0.89–2.06) | M | 8 |
| Zhao *et,al* | 2019 | RE | OS/PFS | 0.68 (0.32–1.43 | 0.91 (0.54–1.53) | M | 8 |
| Hopkins *et,al* | 2020 | RE | OS/PFS | 1.52(1.27-1.82) | 1.38(1.18-1.62) | M | 8 |
| Cortellini *et,al* | 2020 | RE | OS/PFS | 1.26(1.04-1.52) | 1.26(1.07-1.48) | M | 8 |
| Buti *et,al* | 2021 | RE | OS | 1.57(1.13-2.18) | NA | U | 7 |

Abbreviations: RE, retrospective; OS, overall survival; PFS, progression-free survival; HR, Hazard ratio, CI: Confidence interval NA, not available; U, univariate; M, multivariate.

### 3.3. OS and PFS

As shown in Figure 3a, using a random-effects model (I2= 43%, P=0.07), we found a significant association between PPI administration and OS deterioration in cancer patients treated with ICI (HR=1.31 (1.11-1.52)), P=0.001). Using the same model (I2= 64%, P=0.008), we found that in cancer patients treated with ICI, PPI use and PFS showed a correlation between HR and deterioration, but the difference did not show a statistically significant association (HR=1.21 (0.93 - 1.34), P=0.22, Fig. 3b).

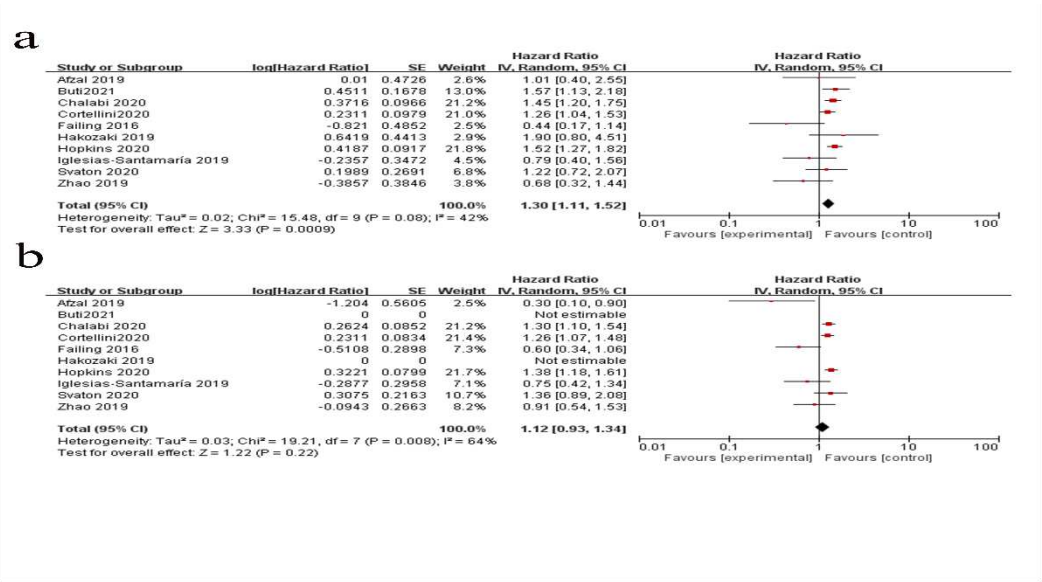

Fig. 3. Forest plots of HR for correlations of PPI administration with overall survival (a) and progression-free survival (b).

### 3.4. Subgroup analyses

In order to further study the effect of PPI administration on the prognosis of various specif ic patients, a subgroup analysis was conducted according to the region, cancer type, sample siz e, and PPI exposure time. As shown in Table 3 and Table 4. First, in the region subgroup, rese arch worldwide PPI administration significantly reduced the ICI patient the OS (HR 1.49 (1.30-1.6 9), P <0.00001), and PFS (H R 1.34 (1.20-1.51), P <0.00001). Subgroup studies in Europe were a lso related to poor OS (HR 1.28(1.07-1.54) p=0.007), while PFS (HR 1.19(0.92-1.52) p=0.18) had no statistical significance. North American patients OS (HR 0.67 (0.30-1.52) P = 0.34), PFS (HR 0.50 (0.28-0.91) P = 0.02) and Asian patients OS (HR 1.11 (0.40-3.04) P = 0.84), PFS (HR 0. 91 (0.54-1.53) P= 0.72) did not show statistical significance. Second, subgroup analysis of cancer types, in addition to a urothelial cancer research OS (HR 1.52 (1.27-1.82) P <0.00001 ) associated with poorer prognosis, NSCLC subgroup PFS (the HR 1.27 (1.09 -1.47) P = 0.002 ) has a poor pro gnosis , melanoma PFS ( HR ( 0.50 (0.28-0.91) P = 0.02 ) has a better prognosis , Other tumors ha d no statistically significant results in OS(HR 1.28(0.99-1.65)P= 0.06) and PFS(HR 1.05(0.65-1. 70) p=0.84). Thirdly, in the subgroup analysis of sample size, OS(HR1.42(1.29-1.58) P<0.00001) and PFS (HR 1.31(1.20-1.44) P<0.00001) of subgroups with sample size greater than 100 are all related to poor results. No statistically significant results were observed in the sample size of less than 100 OS (HR 0.94 (0.65-1.34) p = 0.72) PFS (HR 0.79 (0.53-1.20) p = 0.27). Fou rth, in the subgroup analysis of PPI exposure time, the 30 days before and after administration of ICI was found to be poor OS (HR 1.39 (1.16-1.67) P = 0.0004), PFS (HR 1.32 (1.19-1.47) P <0.00 001). No statistical significance was observed when ICI was administered at the same time or after administration of OS HR (0.96(0.42-2.21) p = 0.93), but PFS(HR0.50(0.28-0.91) P=0.02) was associated with better prognosis.

Table 3. Subgroup analysis for the association of PPI administration with overall survival

| Subgroup | No. of studies | OS Hazard ratios(95%CI) | P value | Heterogeneity | |
|---|---|---|---|---|---|
| | | | | I2 | P -value |
| Region | | | | | |
| Asia | 2 | 1.11(0.40-3.04) | 0.84 | 68% | 0.08 |
| America | 2 | 0.67(0.30-1.52) | 0.34 | 33% | 0.22 |
| Europe | 4 | 1.28(1.07-1.54) | 0.007 | 14% | 0.32 |
| Worldwide | 2 | 1.49(1.30-1.69) | <0.00001 | 0% | 0.72 |
| Cancer type | | | | | |
| NSCLC | 4 | 1.30(0.96-1.57) | 0.09 | 33% | 0.21 |
| Melanoma | 2 | 0.67(0.30-1.52) | 0.34 | 33% | 0.22 |
| Urothelial Carcinoma | 1 | 1.52(1.27-1.82) | <0.00001 | / | / |
| Multipe | 3 | 1.28(0.99-1.65) | 0.06 | 42% | 0.18 |
| Sample size | | | | | |
| <=100 | 6 | 0.94(0.65-1.34) | 0.72 | 28% | 0.23 |
| >100 | 4 | 1.42(1.29-1.58) | <0.00001 | 0% | 0.47 |
| PPI exposure | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| _30-30 | 4 | 1.39(1.16-1.67) | 0.0004 | 36% | 0.2 |
| 0_30 | 3 | 0.96(0.42-2.21) | 0.93 | 60% | 0.08 |

Abbreviations: NSCLC, non-small cell lung cancer; HR, Hazard ratio; OS, overall survival; CI; Confidence interval

Table 4. Subgroup analysis for the association of PPI administration with progression-free survival.

| Subgroup | No. of studies | PFS Hazard ratios(95%CI) | P value | Heterogeneity | |
|---|---|---|---|---|---|
| | | | | I2 | P -value |
| Region | | | | | |
| Asia | 2 | 0.91(0.54-1.53) | 0.72 | / | / |
| America | 2 | 0.50(0.28-0.91) | 0.02 | 17% | 0.27 |
| Europe | 4 | 1.19(0.92-1.52) | 0.18 | 35% | 0.21 |
| Worldwide | 2 | 1.34(1.20-1.51) | <0.00001 | 0% | 0.6 |
| Cancer type | | | | | |
| NSCLC | 4 | 1.27(1.09-1.47) | 0.002 | 0% | 0.41 |
| Melanoma | 2 | 0..50(0.28-0.91) | 0.02 | 17% | 0.27 |
| Urothelial Carcinoma | 1 | 1.38(1.18-1.62) | <0.0001 | / | / |
| Multipe | 3 | 1.05(0.65-1.70) | 0.84 | 65% | 0.09 |
| Sample size | | | | | |
| <=100 | 6 | 0.79(0.53-1.20) | 0.27 | 59% | 0.04 |
| >100 | 4 | 1.31(1.20-1.44) | <0.00001 | 0% | 0.71 |
| PPI exposure | | | | | |
| _30-30 | 4 | 1.32(1.19-1.47) | <0.00001 | 0% | 0.5 |
| 0_30 | 3 | 0.50(0.28-0.91) | 0.02 | 17% | 0.02 |

Abbreviations: NSCLC, non-small cell lung cancer; HR, Hazard ratio; PFS, progression-free survival: CI; Confidence interval

### 3.5. Publication bias and sensitivity analysis

As shown in Figure 4a-b, Funnel plots demonstrated slight asymmetry for HR of either O S or PFS. As shown in fig. 4c-d, sensitivity analyses were carried out by removing one single study could substantially affect the pooled HR, clarifying the pooled results were robust and s table. As shown in fig. 4e Egger and begg tests show that OS has no evidence of publication bias ($p = 0.059$). Due to the limited number of studies included in the PFS analysis and subgr oup analysis (less than 10), Egger and begg tests were not performed.

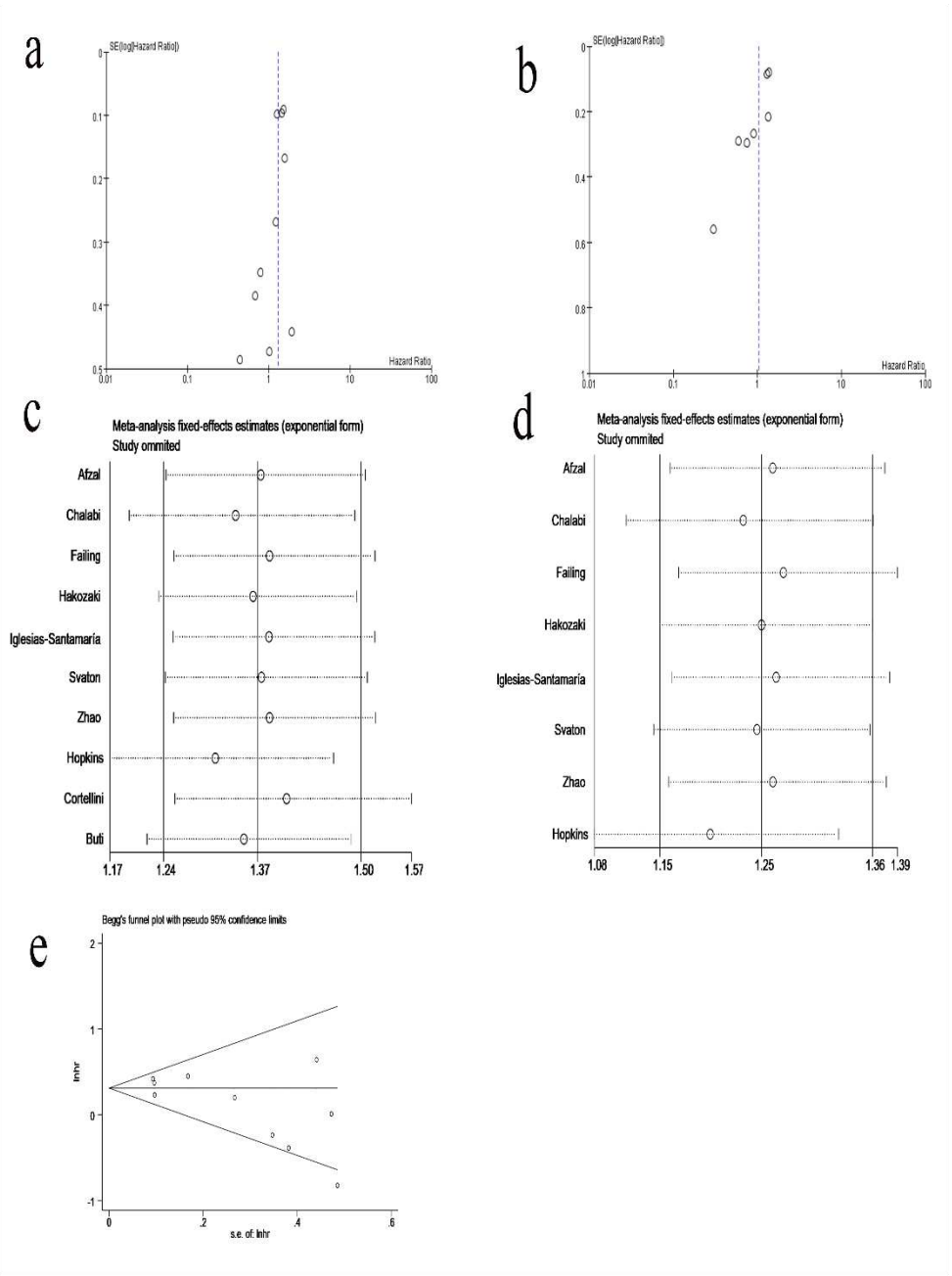


Fig. 4. Sensitivity analysis and publication bias. (a)Funnel plots of overall survival (OS). (b) Funnel plots of progression-free survival (PFS). (c) Sensitivity analysis of the studies assessing OS. (d) Sensitivity analysis of the studies assessing PFS. (e) Begg's funnel plots for evaluating publication bias of OS.

## Discussion

With the increasing popularity of immunotherapy in cancer treatment, more and more studies have focused on the potential factors that affect its efficacy. A large amount of evidence shows that the intestinal flora plays a key role(15) The intestinal microbiome can regulate systemic anti-tumor immune system and response to ICI treatment (30).PPI-driven hypochlorhydria can ca

use major changes in the composition of the intestinal flora. The use of PPI has been reported to be associated with decreased bacterial abundance, enteric malnutrition and T cell tolerance enhanced related. Hypochlorhydria also promotes the reduction of microbial diversity and growth of microorganisms with genotoxic potential, and at the same time increases the bacterial function of nitrate/nitrite reductase related to cancer development(31-33). PPI action is not only limited to the intestinal flora, but also that the tumor has been resistant to immunotherapy regenerate sensitive(34). During the preparation of our manuscript, we noticed that two meta-analyses were conducted last year to investigate the effect of PPI administration on the efficacy of cancer immunotherapy (35, 36). Manyu etc.(36) included 7 studies in first meta-analysis and showed that PPI use was not associated with OS and PFS in patients treated with ICI. However, concomitant PPI therapy had a negative effect on PFS in NSCLC patients and a positive effect on PFS in melanoma patients. The same of Li etc. (35) comprising 5 studies in another study meta-analysis, the table shown not found in cancer patients, using both PPI and ICI significant difference with the relevant OS or PFS. Compared with them, our current research includes more studies n= 10 , especially including several large-scale, multi-center latest retrospective studies(20, 23, 27) . And we did a more detailed subgroup analysis, and even reached some conclusions different from the previous two studies. Therefore, our research may provide some new insights for PPI in the immunotherapy of advanced malignant tumors.

Firstly, we used the random effect model and found that PPI administration was significantly related to the deterioration of OS(HR=1.31(1.11-1.52), P =0.001) and PFS(HR=1.21(0.93-1.34), P =0.22) in all patients receiving ICI, but PFS show no statistical significance may due to the lack of relevant data in two studies (20, 22). Sensitivity analysis and publication bias confirmed the reliability of our results. This is inconsistent with the previous two meta-analysis. In addition to directly changing the pH value of the stomach and delaying gastric emptying(17),the use of PPI has an important impact on the intestinal microbiome (37). It has also been shown to significantly reduce the diversity of the intestinal flora and induce the abundance of specific bacterial species in the intestine(31). Furthermore, Homicsko et.al (13)in an evaluation of pretreated serum samples from PD-1-treated melanoma patients showed changes in NCAM1/CD56 and CSF3R levels, both of which are expressed on neutrophils, in patients treated with PPI. Serum protein analysis of patients treated with PPI showed a significant increase in neutrophils at baseline, suggesting that these patients present with a proinflammatory state that affects the efficacy of ICI therapy. In addition, given the clinical heterogeneity between various cancers and individuals, we cannot definitively determine the negative effect of PPI on immunotherapy efficacy based on our overall analysis of all included cancers alone and further subgroup studies are required.

To further clarify PPI prognosis in cancer patients receiving immunotherapy right, were determined subgroup analysis by region, type of cancer, sample size, and time PPI administration. Because regional differences may lead to different genetic backgrounds and microbiota composition, we first found that PPI use was associated with poorer PFS in European studies, and similar results have been found in studies on global scale, suggesting that the adverse prognostic effect of PPI may not be related to regional differences. Then, we analyzed the prognostic impact of PPI in various cancer types and found that it was related to the poor prognosis of NSCLC and the better prognosis of melanoma. This is consistent with Manyu etc.(36) findings. Clinical studies have shown that there is an association between concomitant use of PPI and pneumoco

ccal pneumonia in the community(38)，so we have reason to suggest that the use of PPI has a n effect on human immunomodulatory function. Su et.al(39) also stated in a meta-analysis that in the population receiving immunotherapy, NSCLC patients are more susceptible to pneumonia than other types of cancer, leading to poor prognosis. Furthermore, it has been observed in basi c research that PPI reduces the α diversity of intestinal flora and increases the relative abunda nce of Actinomycetes, Micrococcaceae, Enterobacteriaceae and Streptococcus. (8, 31, 40-42) . N SCLC patients who benefited from ICI treatment were found to be rich in Ruminococcaceae bact eria(4). However, a significant reduction of Ruminococcaceae bacteria was found in the gut microbi ome of PPI users (31) . Therefore, the use of PPI may reduce the beneficial bacteria that are be neficial to the ICI reaction of the intestinal flora of NSCLC patients, leading to negative effects o f PFS in NSCLC patients. The changes of intestinal flora can also explain the positive effect of P PI on PFS in patients with melanoma. Matson et.al(5)report confirmed that patients with melano ma who responded to ICI treatment had more Bifidobacterium than those who did not. Basic r esearch and have found that tumor control subjects Bifidobacterium family members associated with increased immune-mediated and ICI related to the efficiency of treated mice(43) and found that Bifidobacterium PPI is used as a positive correlation (31). In a subgroup analysis found is gr eater than the amount in the sample 100 research and poor OS, PFS correlation, which further str ongly supported PPI use associated with poor prognosis. Finally, since previous studies have rais ed controversies about the time window of PPI administration in ICI treatment, we stratified the su bgroups according to the time before and/or after the initiation of ICI. As a result, we found t hat between 30 days before ICI initiation and 30 days after ICI initiation, the adverse prognosis of patients who received PPI was significant. However, in the subgroup where ICI was administered at the same time or after administration, we found that PFS (HR0.50 (0.28-0.91) P = 0.02) w as associated with a better prognosis. In a retrospective study of ipilimumab on patients with metastatic melanoma, Failing et al.(25) showed that patients with concurrent use of PPI are mo re likely to achieve complete or partial remission. Local tumor acidity plays an important role in malignant tumors. By changing the acidity of tumors, esomeprazole has been shown to inhi bit the proliferation of melanoma cells in human cell lines and mouse models, reduce tumor gr owth and improve survival (44). Another study in melanoma cell lines and mouse models foun d that lansoprazole pretreatment can induce tumor sensitivity to paclitaxel (even if the dose is insufficient), and has a synergistic effect(45). Therefore, we can speculate that the use of PPI after the start of immunotherapy will inhibit the growth of tumor cells by changing the local p H of the tumor. This explains why in our study, patients using PPI at the start of immunother apy have better PFS. The negative impact of PPI on immunotherapy within 30 days before an d after the start of immunotherapy may be due to the longer PPI administration window, whic h brings negative effects through more complex mechanisms such as affecting the intestinal flo ra. In the study of the time window of antibiotics for immunotherapy, some studies have show n that the prognostic effect of antibiotics may depend on the cumulative antibiotics exposure rat e , rather than some definite time frame(46). Similarly, PPI has been shown to affect the intesti nal microbiome through the direct action of gastric acid, which usually provides the main defe nse system against the influx of food and oral bacteria. Studies have shown that changes in the intestinal flora caused by PPI are more obvious than those caused by antibiotics (8, 31) · There fore, we have reason to infer that the effect of PPI has a certain relationship with the exposur e rate, which needs further verification in the future.

Meanwhile, there are several limitations in our research. First of all, all the publications included in this meta-analysis are retrospective studies and literature published in English. Although we have tried our best to collect information, many important details of the included studies are still incomplete, such as: PPI medication types, follow-up time. Secondly, a number of studies do not provide basic information calculation OS or PFS HR, and therefore excluded from these studies(13, 34) , which leads to some restrictions we further analyzed the possible presence of intrinsic limitations of selection bias . Third, in retrospective analysis, research heterogeneity is affected by various internal factors, such as patient choice, treatment method, and drug type dose. Including a larger number of studies may resolve this impact. Fourth, we failed to investigate the safety correlation between PPI administration and ICI. Our follow-up work should focus on this point. Fifth, in terms of cancer types, our current research is mainly focused on NSCLC, melanoma and urothelial cancer, so we should pay more attention to other solid tumors such as gastrointestinal or esophageal tumors in the future. Finally, the impact of using antitumor drugs other than ICI and other concomitant drugs other than PPI on patients was not considered. Therefore, it is necessary to conduct further prospective studies to identify which specific phenotype of intestinal flora may enhance or weaken the anti-tumor immune response due to the use of PPI. And the potential interaction between PPI and immunotherapy efficacy in different cancer types and underlying mechanisms. For example, the results of co-administration of PPI and ICI can be jointly evaluated from completed or ongoing randomized controlled trials.

## 5. Conclusion

Overall, our research shows that PPI administration is significantly associated with poor OS in solid cancer patients treated with ICI. During the period from 30 days before ICI initiation to 30 days after initiation, PPI administration may reduce the efficacy of ICI. These findings collectively indicate that PPI administration should be carefully considered in solid cancer patients receiving ICI treatment. When relevant clinical symptoms appear, it is recommended to use other drugs instead of $H_2$ antagonists. More clinical validation based on large samples is necessary, and experimental work should be carried out to further clarify the potential mechanism of the harmful effects of PPI-induced cancer immunotherapy.

## List of abbreviations

PPI: proton pump inhibitors

ICI: immune checkpoint inhibitors

OS: overall survival

PFS: progression-free survival

HR: hazard ratio

CI: Confidence interval

PD-1: Programmed cell death 1

PD-L1: Programmed cell death ligand 1inhibitor

CTLA – 4: cytotoxic drug T lymphocyte-associated antigen 4 antibody

NOS: Newcastle-Ottawa Scale

NSCLC: non-small cell lung cancer

## Declarations

### Ethics approval and consent to participate

Not applicable

### Consent for publication

Not applicable

### Availability of data and materials

All data generated or analyzed during this study are included in this published article.

### Competing interests

The authors declare that they have no competing interests.


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### Authors' contributions

Xuebing Yan and Jiandong Tong: Conceptualization and Methodology. Chaoxing Liu, Mengxue Yang, Haiyan Mao and Huaijuan Guo: Data Collection and Analysis, Writing-Original draft preparation. Xuebing Yan: Data Validation, Writing- Reviewing and Editing.


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