Systematic Review

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A Meta-Analysis of the Impact of Proton Pump Inhibitors on Survival Outcomes in NSCLC Treated with Immunotherapy

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Background: It has recently been shown that concomitant medication, such as proton pump inhibitors (PPIs), can modulate the microbiome and has effect on the clinical outcome among advanced-stage cancer patients following immune checkpoint inhibitors (ICIs). Whether such relationship is associative or causative in advanced non-small cell lung cancer (NSCLC) is content of investigation. The current meta-analysis was conducted to explore the impact of proton pump inhibitors (PPIs) on ICIs treatment in NSCLC.

Methods and Materials: The electronic databases were searched until September, 2022. Researches investigating the predictive role of PPIs in NSCLC following ICIs were included. Then, the meta-analysis was aim to reveal the influence of PPI use on survival efficacy.

Results: 8 researches were finally included. For all interested outcomes, the between-study heterogeneity was low. Our results showed that the concomitant PPI use has a negative effect on the survival of NSCLC receiving ICIs. The pooled HRs of progression-free survival (PFS) and overall survival (OS) were HR = 1.33 (95% CI 1.21 to 1.46, $p < 0.00001$) and HR = 1.46 (95% CI 1.32 to 1.62, $p < 0.00001$) when compared to those without PPIs.

Conclusion: The impact of PPI use is related to poor survival efficacy and may attenuate the anti-cancer activity of ICI. The underlying biological mechanisms of the relation between PPI and the efficacy of ICI treatment should be elucidate through further researches.

Keywords: proton pump inhibitors; immune checkpoint inhibitors; NSCLC; meta-analysis

Introduction

Recently, immune checkpoint inhibitors (ICIs) have revolutionized the therapeutic management and have unprecedented effects on survival of solid cancer, including NSCLC [1]. The immune response has been shown to be effected by different elements, such as the expression level of PD-L1, history of smoking, TMB and radiotherapy [2,3]. In addition, it has been shown that concomitant medication exhibited effects on ICIs clinical efficacy [4–6].

Beyond the interaction between pharmacokinetic and pharmacodynamic, the putative tumoricidal activity of ICIs also influenced by the unbalancing of the intestinal microbiome [7] and the immune suppression associated with drug [8]. Taking the hypothesized relation between intestinal microbiota and impact of ICI into account, several researches have studied the influence of proton pump inhibitors (PPIs) on the clinical outcomes of patients with cancer [9–11].

PPIs have been found in the connection with gut dysbiosis, decreased richness of bacterial, and promotion of T-cell tolerance [12,13]. However, the results on the correlation between the use of PPI and the ICIs efficacy are scare, and this issue has not yet been explicated, especially in lung tumor. A pooled study from the OAK and POPLAR trials validated the impact of PPI use with negative prognostic features on survival outcome in NSCLC patients receiving atezolizumab [10]. While, Kaho Miura *et al*. [14] reported that the effectiveness of the ICIs, such as nivolumab and pembrolizumab, in NSCLC patients were not markedly influenced by PPIs.

Due to the conflicting results among those different articles, there has been controversy about the effect of the use of PPI in connection with the ICI therapeutic efficacy in the clinical settings. Our meta-analysis aims to systematically review the effect of the use of PPI on the survival outcomes of NSCLC receiving ICI therapy.

Methods and Materials

Search Strategy

The PubMed, Embase, and Medline databases were performed to conduct literature search until September, 2022. The Medical Subject Headings (MeSH) terms and following keywords were used: “Immunotherapy”, “PD-

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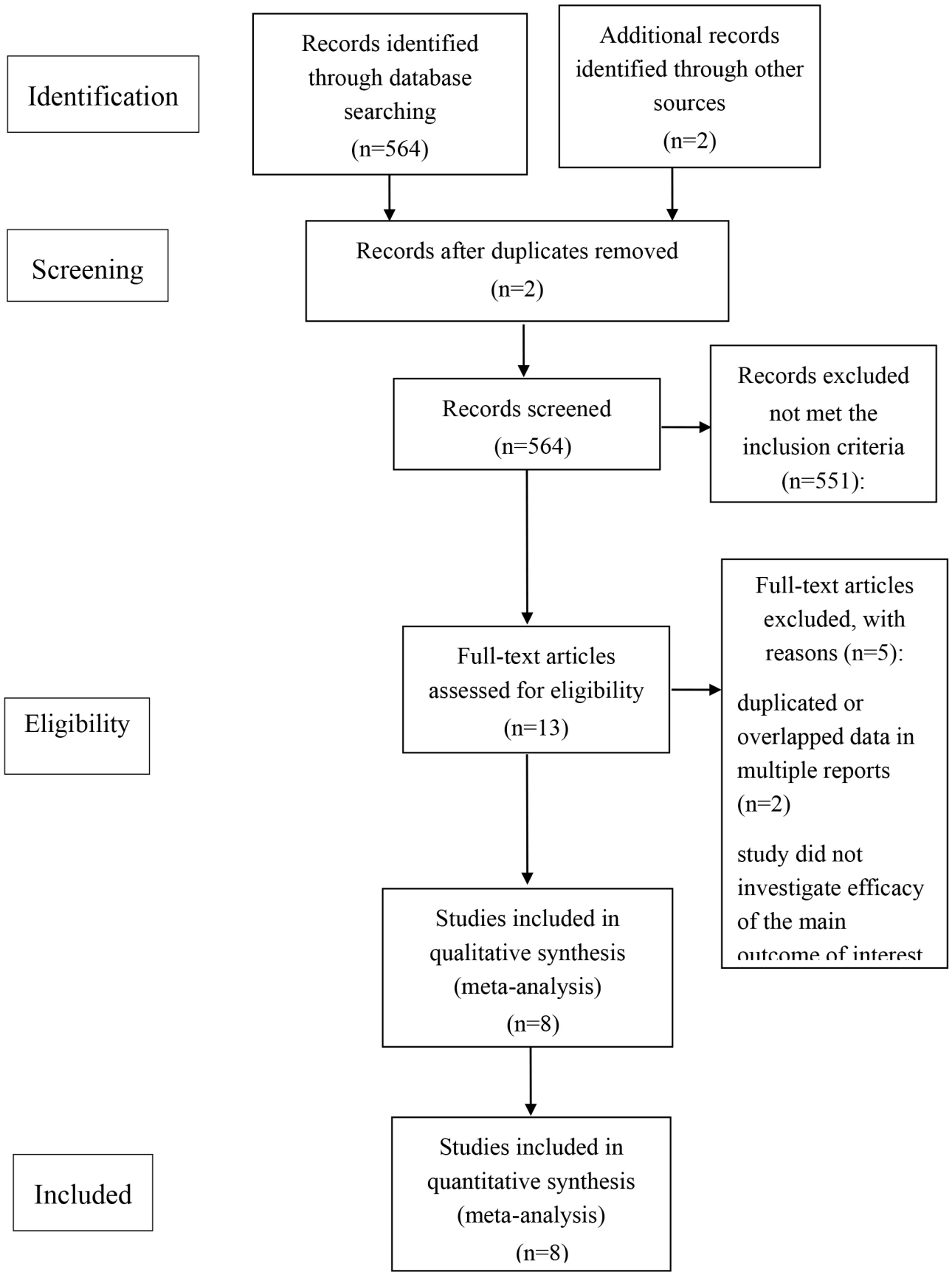

Fig. 1. PRISMA flow chart of selection process to identify studies eligible for pooling.

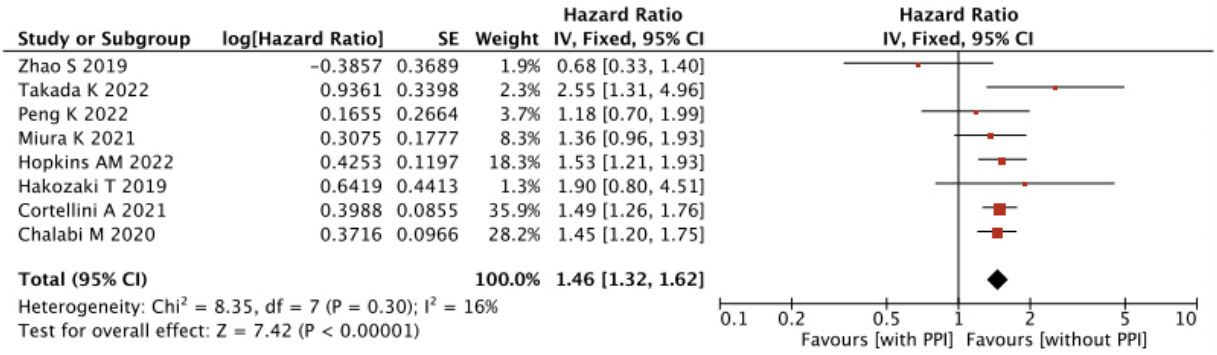

Fig. 2. Pooled analysis of efficacy between proton pump inhibitor (PPI) Use and overall survival (OS).

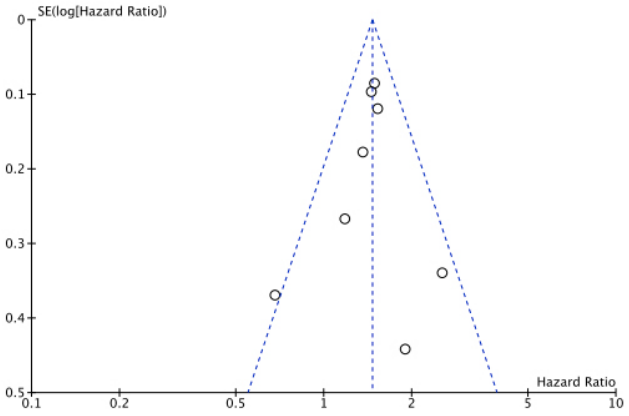

Fig. 3. Funnel plot of efficacy PPI Use and OS.

(L)1 inhibitor", "CTLA-4 inhibitor", "medication", "proton pump inhibitors", and "Non-small Cell Lung Cancer". The reference lists and materials were also conducted to search the extra literature.

Eligibility Criteria

The included articles should met the following conditions: (1) patients: studies that enrolled ICI treated with NSCLC patients; (2) interventions: studies that focused on the interaction between PPIs use and ICI efficacy; (3) outcomes: OS, PFS; (4) only full studies with most complete and latest data were included.

Quality Assessment

The Newcastle-Ottawa Quality Assessment Scale was performed to study the quality of the eligible articles [15]. The NOS method used three domains to assess the quality of cohort studies, which included selection of lung cancer patients, the comparability between two groups and the assessment of outcomes. According to the NOS method, 4 points, 2 points and 3 points were awarded to those three domains respectively. Studies with no less than 7 points were identified to have high quality, but those with 6 points or less were identified to have low quality. Two authors assessed the the quality of the included articles, independently and disputes were resolved via discussion.

Data Extraction

The information was extracted from each research by two reviewers, separately.

A consensus was achieved for any discrepancies through discussion. The following information included: the author name; the year of publication; date collection time; type of ICIs used; number of participants; and interested outcome.

Data Synthesis and Analysis

We used I^2 tests and Chi-squared to evaluate the heterogeneity of study and select the model for analysis [16]. Only when the included articles with low heterogeneity ($I^2 < 50\%$), the fixed-effects model was conducted to pool the HRs. Meanwhile, if there was moderate or high heterogeneity ($I^2 \geq 50\%$), the random-effects model was conducted [17]. Results with a p value < 0.05 were considered statistically significant. The Review Manager version 5.3 software (Revman; The Cochrane collaboration Oxford, United Kingdom) was performed for pooled analysis. The pooled results were demonstrated in forest plots.

Results

Overview of Literature Search and Study Characteristics

564 studies were included through the index procedure. 13 researches were preliminary assessed in more detail after screening the titles and abstracts, but 5 did not fulfill the criteria for inclusion. At last, a final total of 8 researches were included [10,14,18–23]. Fig. 1 showed the procedure of systematic search.

All eligible researches were represented moderate quality at least. Table 1 (Ref. [10,14,18–23]) described the main characteristics of the included researches in more detail, also presented the summary of the quality assessment process.

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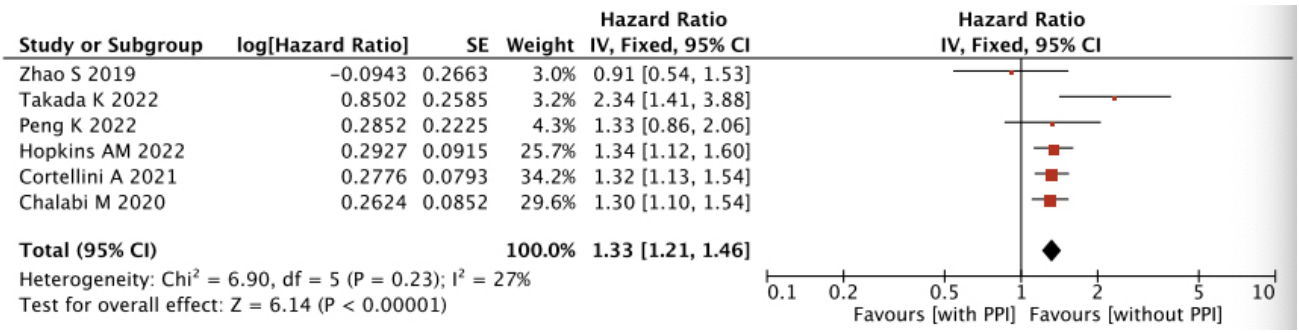

Fig. 4. Pooled analysis of efficacy between PPI Use and progression-free survival (PFS).

Table 1.

Study year	ICIs	Date Collection Time	Number of patients		NOS
			PPI+	PPI-	
Chalabi M 2020 [10]	atezolizumab	Aug 5, 2013–April 29, 2015	234	523	8
Hakozaki T 2019 [19]	nivolumab	January 2016–April 2017	47	43	6
Zhao S 2019 [20]	pembrolizumab, nivolumab or SHR-1210	January 2016–January 2018	40	69	7
Miura K 2021 [14]	nivolumab,pembrolizumab	January 2016–July 2018	/	/	6
Cortellini A 2021 [18]	pembrolizumab	January 2017–May 2020	474	476	8
Takada K 2022 [21]	pembrolizumab, nivolumab or atezolizumab	January 2016–December 2019	37	58	7
Peng K 2022 [22]	pembrolizumab, nivolumab, ipilimumab or atezolizumab	September 1, 2014–August 31, 2019	46	71	8
Hopkins AM 2022 [23]	Atezolizumab	March 31, 2015–Dec 30, 2016	441	761	8

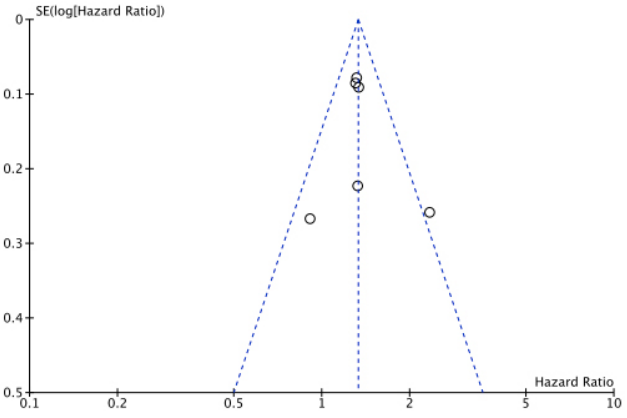

Fig. 5. Funnel plot of efficacy PPI Use and PFS.

Clinical and Methodological Heterogeneity

PPI Use and OS

Eight researches reported the influence of the using of concomitant PPI on OS in NSCLC treated with ICIs. Low heterogeneity was found in OS comparisons (Figs. 2,3). The pooled HR was 1.46 (95% CI 1.32 to 1.62), $p <$ 0.00001), representing that the PPI groups was related to the shorter OS compared to those without receiving PPIs groups.

PPI Use and PFS

A fixed-effects model was conducted to analysis the PFS, since the heterogeneity across the six articles was low. The pooled result revealed that the PPI use was associated with a significantly shorter PFS in NSCLC treated with immunotherapy (HR = 1.33 (95% CI 1.21 to 1.46), $p <$ 0.00001) (Figs. 4,5).

Discussion

Recently, the use of PPI is gradually being considered as taking an significant role in immunotherapy [12–14]. Several previous publications have indicated the reaction between PPI use and impact of ICIs.

A meta-analysis conducted by Li C *et al.* [24] investigating the effect of the use of PPI on the survival efficacy of cancer participants receiving ICI, demonstrating that no association was found between concomitant ICI-PPI therapy and ICI efficacy. Conversely, a recent systematic review suggested that PPI use increase the risk of survival progression with a shorter PFS and OS in advanced cancer patients treated with ICIs [25]. One possibility for this discrepancy is both the data has included various types of cancer.

As the therapeutic paradigm for NSCLC has radically evolved with the incorporation of ICIs, the effect of PPI use among lung cancer patients receiving ICI treatment is

no denying that this is an emerging area that needs to be focused on. Our systematic review aims to assess the relation between the use of PPI and response to ICIs among NSCLC patients.

The pooled result showed that that the use of PPI has been addressed as a detrimental predictor to ICIs therapy, in terms of the OS and PFS. Compared with previous meta-analysis, our study is the first published analysis suggesting that ICI-PPI therapy can impair the impact of ICIs in advanced NSCLC patients.

As is known, PPIs are widely used in cancer patients to prevent over secretion of gastric acid and indigestion. The underlying mechanisms of action has not reach a consensus.

It is becoming increasingly known that PPI may change the the levels of PH of the gut and alter the types of bacteria and reduce microbial diversity [13,26]. The gut microbiota palys a vital role in shaping systemic immunotherapy responses [27–29]. A serious of articles have reported that patients responding to the ICI therapy are those who have a more diverse gut microbiome. The gut microbiota alters the innate and adaptive immune system, interacting with PD-1/PD-L1 axis and CTL-associated protein 4 (CTLA-4), thereby influencing the ICIs efficacy [30,31]. Together, these data indicate that the reduce in variety of bacterial species following PPI may provide an explanation for the negatively influential on the efficacy of ICI in NSCLC.

These results indicated that a new therapeutic microbiota-based paradigm for increasing the ICIs efficacy or decreasing the irAEs [32,33]. Future investigation should focus on explaining the possible mechanisms for relation between ICI and PPI, and the role of the microbiome.

Limitations

Although the heterogeneity across the eligible articles was low, there are still some inherent limitations might have effect on the pooled results. First, various doses, different countries, types of PPIs and the ICI treatment regimens, which may lead to various interactions with the gut microbiome, potentially affecting the response to ICI. Due to the limited data of these covariates available to analysis. Further researches are needed to clarify this issue. Second, considering the retrospective nature of our analysis, resulting in imbalance between the PPI groups and those without receiving PPIs groups. More high-quality researches with further data are strongly in-needed to answer these questions. Third, the efficacy of PPIs on the biological processes of the gut microbiota and the potential mechanisms interaction with ICIs should be clarified through trials in further.

Conclusion

In conclusion, our study demonstrated a disadvantage effect of PPI on survival effect of ICI, regards to the OS and PFS. These results should be taken into account in clinical use, indicating that the PPI use should be restricted to strict indications in immunotherapy. Additionally, it should be stressed that our findings, as well as the previous reports, strengthen the potential the hypothesis of a potential link between ICI efficacy and microbiome diversity. Therefore, future focus on the experimental measures to control interactional factors with regard to the complex medications, and further articles are needed to confirm the findings of our meta-analysis.

Availability of Data and Materials

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

Author Contributions

LS carried out study concepts and design, definition of intellectual content; LS and XL contributed to literature research, data acquisition and analysis, manuscript preparation and editing; XL helped to manuscript review.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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