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Title

Acid suppressants reduce the therapeutic effect of immune checkpoint inhibitors and increase the risk of acute kidney injury: a meta-analysis

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Abstract

Background: Immune checkpoint inhibitors (ICIs) are used in cancer immunotherapy; however, they can lead to immune-related adverse events (irAEs) through immune function of patients. Therefore, this meta-analysis aimed to assess the concomitant effect of acid suppressants (ASs) on ICIs, including several subgroup analyses. **Methods:** We identified related studies and generated the forest plot. The primary endpoint was defined as the change in progression free survival (PFS) and overall survival (OS) with or without ASs administration. We also evaluated the effect of ASs on the incidence of irAEs. **Results:** The total hazard ratio (HR) of ASs on PFS with ICI treatment was 1.39 and the 95% confidence interval (95%CI) was 1.21–1.59 (Z: $p < 0.00001$). Moreover, the total HR of ASs on OS was 1.40 and the 95%CI was 1.21–1.61 (Z: $p < 0.00001$), suggesting that ASs reduced ICI's therapeutic effect. The total odds ratio (OR) for evaluating the effect of ASs on irAEs was 1.23 with a 95%CI of 0.81–1.88 (Z: $p = 0.34$). However, ASs significantly worsened acute kidney injury (AKI) (total OR, 2.10; 95%CI, 1.74–2.53 (Z, $p < 0.00001$)). Furthermore, although proton pump inhibitors (PPIs) reduced ICI's therapeutic effect, histamine H₂-receptor antagonists (H₂RAs) did not affect OS. **Conclusions:** It was shown that ASs, especially PPIs, reduced ICI's therapeutic effect, while H₂RAs had no effect, and ASs did not affect irAEs; however, it is a risk factor for ICIs-induced AKI.

1 **Keywords**

2 Immune checkpoint inhibitor; Acid suppressant; Proton pump inhibitor; Histamine

3 H2-receptor antagonist; Immune-related adverse events

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1 **Introduction**

2 Immune checkpoint inhibitors (ICIs) are used in cancer immunotherapy and are
3 effective against various carcinomas [1]. ICIs exert antitumor effects by inhibiting
4 programmed cell death 1 (PD-1), programmed cell death ligand 1 (PD-L1), or cytotoxic T-
5 lymphocyte associated antigen 4 (CTLA-4) signaling, leading to immune cells targeting and
6 attacking cancer cells [1]. ICI administration drastically has changed the treatment outcomes
7 in many types of cancers [2]. Cancer immunotherapy is not only used as monotherapy but by
8 combining ICIs or other anticancer drugs, such as cytotoxic agents or multikinase inhibitors
9 [3]. However, ICIs develop specific adverse events called immune-related adverse events
10 (irAEs). ICIs induce efficacy and irAEs through immune function of patients, and several
11 factors could affect them. The irAEs are caused by excessive activated immune cell reactions
12 and show profiles different from those of conventional anticancer drugs [4]. In addition, irAEs
13 involve multiple organs, such as the skin, endocrine systems, and gastrointestinal tract, but the
14 incidence of irAEs differs for each organ, and the timing of onset remains unclear [5]. When
15 irAEs become severe, ICIs treatment must be suspended or discontinued [6], and appropriate
16 irAEs management is necessary to maximize the benefits of cancer immunotherapy.

17 In recent years, studies on the interaction between ICIs and concomitant drugs have
18 been conducted [7,8], suggesting that acid suppressants (ASs) have negative effect on ICIs
19 treatment [9]. Although concomitant drugs such as antibiotics and ASs can potentially impact

the response to ICIs by altering the gut microbiota, the mechanisms underlying this effect remain unknown [10]. ASs are classified into proton pump inhibitors (PPIs) and histamine H2-receptor antagonists (H2RAs) [11]. They are widely used for reflux esophagitis and heartburn and are also used in chemotherapy. For example, approximately 40–70% of patients with digestive organ cancer use ASs [12]. Moreover, vonoprazan, an AS, is classified as a potassium-competitive acid blocker (P-CAB) that inhibits the proton pump by a mechanism different from that of PPIs [13]. Although reports on the relationship between ASs and ICIs are increasing, the types of ASs that influence ICIs treatments are not well understood.

Although some meta-analytical reports have evaluated the effects of ASs on the therapeutic effects of ICIs and suggested that their effectiveness is diminished by ASs [14,15], there has been a significant increase in clinical research after previous reports; therefore, updated research is warranted, including subgroup analyses such as those assessing different cancer or histological types. In addition, no integrative reports have evaluated the effects of ASs on irAEs. Therefore, in this study, we conducted a meta-analysis to evaluate studies reporting the effect of ASs on ICIs therapeutic efficacy and irAE development after treatment, with the aim of establishing optimal cancer immunotherapy.

Materials and methods

1. Data sources and search strategies

We identified related studies in the PubMed and Web of Science databases, and the following terms were used for the search: “immune checkpoint inhibitor concomitant” and “immune checkpoint inhibitor proton pump inhibitor” (the last search was performed on March 31, 2022). Thereafter, we selected clinical research articles written in English that evaluated the effect of ASs on progression free survival (PFS), overall survival (OS), and irAEs. Manuscript screening was conducted by two individuals (KO and YS).

2. Selection criteria

The selected articles satisfied the following criteria: 1) full-text articles, 2) reported hazard ratio (HR) for PFS and OS, 3) reported the number of patients experiencing irAEs with or without AS treatment, and 4) conducted comparisons between patients with and without ASs co-administration. Studies with the following conditions were not considered for selection: 1) no differentiation between ASs and other concomitant drugs, 2) case reports and review articles, and 3) studies designed using meta-analysis, pool analysis, or a database.

3. Data extraction

Two independent authors (KO and YS) extracted the following data according to the inclusion criteria: name of the first author, year of publication, primary endpoints, HR, number of patients exhibiting irAEs, types of ASs, monotherapy or combination therapy, and cancer type.

4. Statistical analysis

Data were analyzed using Review Manager 5.4 software (The Cochrane Collaboration, Copenhagen, Denmark) and R software (R Foundation for Statistical Computing, Vienna, Austria). The primary endpoint was defined as the change in PFS and OS with or without ASs administration. Additionally, we evaluated the effect of ASs on the incidence of irAEs. The characteristics of the included studies were summarized using the HR, odds ratio (OR), and 95% confidence interval (95%CI). The forest plot was generated using the fixed-effects model, when there was low heterogeneity, and the random-effects model, when there was high heterogeneity, and a Z index p value < 0.05, was considered to indicate statistical significance. In the forest plot evaluating the OR, events indicate patients taking ASs or PPIs. The inverse variance (IV) and Mantel-Haenszel (M-H) methods were used for the HR and OR calculations, respectively. We evaluated heterogeneity among the studies using the Cochran Q test (χ^2) and the I^2 index; a χ^2 p value < 0.1 and I^2 > 50% correlated with high heterogeneity. Publication bias was examined using the funnel plot (visual inspection), Egger's test (linear regression) [16], and Begg's test (rank correlation) [17]. An asymmetric funnel plot and a p value < 0.1 correlated with a potential publication bias. When PPIs and H2RAs dosing were evaluated separately in the same study, they were incorporated into the analysis as separate data. Data were analyzed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [18].

Results

1. Data search

By conducting a literature search of the PubMed and Web of Science databases, 533 and 373 reports were found, respectively. After an in-depth evaluation, 13, 18, and 11 papers reporting PFS, OS, and irAEs, respectively, were extracted as candidates (Figure 1). Table 1 shows the characteristics of the eligible studies [7–10,19–37]. Some studies classified vonoprazan (a P-CAB) as a PPI.

2. The effect of ASs administration on the therapeutic efficacy of ICIs

The effect of ASs administration on the PFS of ICIs treatment was analyzed using 13 candidate articles, and the total HR was 1.39 and the 95%CI was 1.21–1.59 ($Z: p < 0.00001$) (Figure 2a), suggesting that the co-administration of ASs significantly shortened PFS in ICIs treated patients. Moreover, as a result of evaluating OS in ICIs-administrated patients using 18 candidate papers, the total HR was 1.40 and the 95%CI was 1.21–1.61 ($Z: p < 0.00001$) (Figure 2b), revealing that the concomitant administration of ASs significantly shortened OS as well as PFS. In addition, a funnel plot was created using the candidate reports used for PFS and OS evaluations (Figure 2c and 2d). The PFS plot was bilaterally symmetrical, whereas that of OS was slightly asymmetrical. However, Egger's test for PFS and OS was $p = 0.5519$ and 0.8672 , respectively, and Begg's test for PFS and OS was $p = 0.8695$ and 0.9278 , respectively, suggesting that the possibility of a large publication bias among these candidates

1 is low. Consequently, it was revealed that ASs reduced the therapeutic effects of ICIs.

2 3. The effect of ASs administration on irAEs

3 The effect of ASs on irAEs was evaluated using 11 candidate articles, revealing that
4 the total OR was 1.23 and the 95%CI was 0.81–1.88 ($Z: p = 0.34$), suggesting that ASs do not
5 affect irAEs (Figure 3a). Although the Egger's test was $p = 0.7388$ and the Begg's test was p
6 $= 0.8072$, I^2 was as high as 86%, and the funnel plot was distorted (Figure 3b), suggesting that
7 publication bias was present between papers. On the other hand, as a result of subgroup
8 analysis regarding acute kidney injury (AKI), the total OR was 2.10 and the 95%CI was 1.74–
9 2.53 ($Z: p = 0.00001$), indicating that ASs increased the risk of AKI incidence (Figure 3c).
10 Additionally, the variation in the funnel plot was more symmetrical (Figure 3d).

11 4. Subgroup analysis: effect of PPIs or H2RAs on ICIs treatment

12 To evaluate the types of ASs that influence ICIs treatment, we evaluated the studies
13 focusing on PPIs alone as a subgroup analysis. PPIs co-administration showed that the total
14 HR was 1.34 and the 95%CI was 1.13–1.1.58 ($Z: p < 0.0006$) for PFS, demonstrating that it
15 significantly shortened PFS, similar to the result of ASs co-administration (Figure 4a). In
16 addition, the total HR was 1.43 and the 95%CI was 1.21–1.69 ($Z: p < 0.0001$) for OS,
17 indicating that OS was significantly shortened (Figure 4b). Moreover, the effect of PPIs on
18 irAEs was assessed with a total OR of 1.51 and a 95%CI of 0.90–2.56 ($Z: p = 0.12$),
19 suggesting that PPIs do not affect irAEs, which is similar to the ASs result (Figure 4c). The

funnel plots are shown in Supplemental Figure 1. These results indicated that PPIs reduced the therapeutic effects of ICIs.

Furthermore, we examined the effect of H2RAs on OS in patients administered ICIs. The results showed that the total HR was 0.80, and the 95%CI was 0.38–1.67 (Z: $p = 0.55$), indicating that H2RAs did not affect OS in ICIs-administered patients (Figure 5).

5. Subgroup analysis: effect of ASs on ICIs monotherapy or each carcinoma type

To assess the effect of ASs on ICI monotherapy alone, a subgroup analysis was performed of candidate articles evaluating ICIs monotherapy alone. This subgroup analysis showed the same tendency as the effect of ASs on ICIs treatment (Table 2), indicating that the influence of ASs administration on ICIs treatment could be observed regardless of ICI monotherapy.

In addition, to evaluate whether the effect of ASs on PFS and OS differs depending on the carcinoma, we evaluated candidate articles focusing on non-small cell lung cancer (NSCLC) and urothelial carcinoma because subgroup analyses for these neoplasms were possible owing to accessibility. As a result, in both NSCLC and urothelial carcinoma, ASs showed similar results to the effect of ASs on ICIs treatment (Table 3), demonstrating that ASs affect ICIs efficacy regardless of cancer type.

Discussion

We evaluated the effect of ASs on the therapeutic effect of ICIs by meta-analysis in this study, which showed that ASs administration significantly shortened PFS and OS in ICIs-administered patients. Since most of the candidate studies evaluated PPIs, we performed a subgroup analysis regarding PPIs co-administration alone, resulting in similar outcomes. PPIs are widely used for the treatment of reflux esophagitis, stomach discomfort, and heartburn [11] and are also used in cancer treatment [12]. It has been reported that ASs reduce the absorption of gefitinib, an oral anticancer agent, and PPIs increase the blood concentration of methotrexate [38]. Similar to these cases, the present results suggest that PPIs administration should be used with caution in ICIs treatment.

The mechanism by which PPIs co-administration affects ICIs response is still unclear. Currently, two main mechanisms are being considered. The first is that changes in the gut microbiota are caused by PPIs. It has been reported that changes in gut microbiota affects ICIs efficacy and antibiotics shorten OS in ICIs-administrated patients [10]. As PPIs alter the gut microbiota [39], they may work through a similar mechanism. Another potential mechanism is direct action on the immune system in the vicinity of the tumor tissue or indirect action by altering the pH of the tissue surrounding the cancer [40]. Although these hypotheses have been discussed in various studies, they have not yet been fully elucidated. Therefore, both clinical studies and basic research are required in the future.

We performed a subgroup analysis for the co-administration of PPIs and H2RAs on

1 the OS outcomes. As a result, H2RAs did not affect OS, which differed from PPIs, showing
2 that sufficient ICIs treatment can be performed by substituting H2RAs for PPIs, although the
3 number of reports on H2RAs co-administration was overwhelmingly small. H2RAs have been
4 reported to have different effects on the gut microbiota than PPIs [41]. Consequently, further
5 evaluation of the concomitant effects of H2RAs on ICIs is necessary. In addition, a meta-
6 analysis of the effect of H2RAs on PFS could not be performed, and only one candidate study
7 evaluated it with an HR of 1.33 and a 95%CI of 0.96–1.86 [7]. Unlike PFS, OS reflects not
8 only the effects of first-line treatment, but also the effects of second-line and subsequent
9 treatments. Therefore, the effect of H2RAs on PFS should be evaluated in future studies.

10 In addition to PPIs and H2RAs, vonoprazan, a P-CAB, targets proton pump as well
11 as PPIs but has a different mechanism from PPIs [13]. Although there are reports evaluating
12 the effect of P-CABs on ICIs by including PPIs [8,9], there has been no evaluation of P-CABs
13 alone. As PPIs and P-CABs have different detailed mechanisms of action, the importance of
14 evaluating P-CABs alone is high. In addition, P-CABs other than vonoprazan have been
15 approved in some countries [13]. Consequently, it is necessary to generate data to distinguish
16 between PPIs and P-CABs in the future.

17 Furthermore, in this study, the effect of ASs on irAEs was evaluated, which revealed
18 that ASs administration may not be associated with irAEs. To date, no meta-analysis has
19 evaluated the relationship between irAEs and ASs. In this evaluation, the problems of high

heterogeneity and large variability were identified. Three possible factors are considered. First, the evaluation of unspecified irAEs causes variability because each irAE appears at different times and frequencies [5]. Second, the frequency of irAEs varies among ICI drugs [3]. The third factor is the influence of concomitant or prior anticancer treatment. Moreover, some of the candidate papers did not strictly distinguish between irAEs and non-irAEs, and differences in the evaluation of side effects may also be a factor in the variability. In contrast, in a subgroup analysis of studies that evaluated only AKI as an irAE, these variations were suppressed. Therefore, it is necessary to conduct research to reduce imprecise evaluations in the future.

Subgroup analysis revealed that ASs were a risk factor for ICIs-induced AKI. ICIs-induced AKI is an irAE that occurs at a frequency of 1.4–4.9% and has recently attracted clinical attention [42]. PPIs have been suggested to exacerbate AKI because they induce acute interstitial nephritis [43]; however, the detailed mechanism is unknown. It has been reported that patients developing irAEs have better clinical outcomes than those without irAEs owing to the activation of the immune system [44]. However, since we found that ICIs efficacy was decreased by ASs, while it increased the risk of AKI in this study, the exacerbation of AKI by ASs may be caused by a mechanism different from the effect of ASs on the therapeutic effect of ICIs. In addition, irAEs persist for a long period and appear during extended treatment or after ICIs treatment in some cases [45]. To prevent the exacerbation of ICIs-induced AKI, the

1 period of administration and ASs initiation should be investigated in future studies.

2 Subgroup analysis revealed that ASs affected ICIs monotherapy. Cancer
3 immunotherapy using ICIs combination or other anticancer drugs reportedly enhances the
4 treatment efficacy and adverse events [3]. Therefore, it is possible that similar results can be
5 obtained in subgroup analyses that evaluated only ICIs combinations or use with other
6 anticancer drugs. We also assessed the effect on NSCLC and urothelial carcinoma in a
7 subgroup analysis. The main analysis suggests that the effects of ASs are not organ-specific.
8 However, two among the candidate reports evaluated the OS in patients with only melanoma;
9 one identified a total HR of 0.6 with a 95%CI of 0.34–1.06 ($p = 0.08$) [21], whereas the other
10 determined a total HR of 1.95 with a 95%CI of 1.41–2.71 ($p = 0.0001$) [34], suggesting
11 controversial results. Additional clinical studies focusing on only one cancer type will reveal
12 the relationship between ICIs and ASs in the treatment of other cancer types.

13 The objective response rate (ORR) was not assessed in this study because a previous
14 report indicated no correlation between the OS and ORR in ICIs treatment [46]. Moreover,
15 among the candidate reports, only three could have been used for a meta-analysis of ORR,
16 which would have been an insufficient number. This was probably because many reports
17 evaluated the effect of ASs as a secondary endpoint, without describing detailed data.

18 This study had some limitations. First, there was heterogeneity in patient
19 backgrounds, particularly inconsistencies in the duration and timing of ASs administration.

1 Second, the effects of other concomitant anticancer drugs and previous treatment were not
2 evaluated. Third, the criteria used for determining irAEs were not uniform.

3 In conclusion, our meta-analysis revealed that ASs, especially PPIs, decrease the
4 therapeutic effect of ICIs, whereas H2RAs have no effect. Moreover, it was also suggested
5 that ASs do not affect irAEs but are associated with ICIs-induced AKI. This study offers an
6 important finding that contributes to the performance of appropriate cancer immunotherapy
7 and provides basic outcomes for future studies.

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3

4 **Author contribution**

5 KO, YS, and AY participated in the study. KO and YS conducted the study and
6 performed the data analysis. KO, YS, AY, YT, and MS wrote or contributed to writing the
7 manuscript.

8

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13 **Conflict of Interest Disclosure Statement**

14 Authors declare no competing interest.

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Table 1 Characteristics of eligible studies

Study	Primary endpoint	ICIs treatment endpoint			Evaluated irAEs	Type of AS	ICI monotherapy	Patient number	Cancer type
(Year)		PFS	OS	irAEs				ASs/Total	
Buti S <i>et al.</i> (2021) ^[19]	Efficacy		✓			PPI	✓	104/217	Several
Cortazar FB <i>et al.</i> (2020) ^[20]	Safety			✓	AKI	PPI		167/414	Several
Cortellini A <i>et al.</i> (2020) ^[7]	Efficacy	✓	✓			PPI, H2RA	✓	491/1,012 ^b , 56/1,012 ^c	Several
Failing JJ <i>et al.</i> (2016) ^[21]	Efficacy and safety	✓	✓	✓	Several	PPI, H2RA	✓	17/80 ^b , 2/80 ^c , 39/159 ^d	Melanoma
Fukuokaya W <i>et al.</i> (2022) ^[9]	Efficacy	✓	✓	✓	Several	PPI ^a	✓	86/227	Urothelial carcinoma
Gaucher L <i>et al.</i> (2021) ^[22]	Efficacy		✓			PPI		149/372	Several
Giordan Q <i>et al.</i> (2021) ^[10]	Efficacy	✓	✓	✓	Several	PPI		47/154	Several
Gupta S <i>et al.</i> (2021) ^[23]	Safety			✓	AKI	PPI		323/856	Several
Hopkins AM <i>et al.</i> (2022) ^[24]	Efficacy	✓	✓			PPI		290/802	NSCLC

Iglesias-Santamaría A (2020) ^[25]	Efficacy	✓	✓			PPI		76/102	Several
Jun T <i>et al.</i> (2021) ^[26]	Efficacy		✓			PPI, H2RA		85/314 ^b , 17/314 ^c	Hepatocellular carcinoma
Koks MS <i>et al.</i> (2021) ^[27]	Safety			✓	AKI	PPI		243/676	Several
Kostine M <i>et al.</i> (2021) ^[28]	Efficacy	✓	✓	✓	No notation	PPI		239/635, 239/632 ^d	Several
Miura K <i>et al.</i> (2021) ^[29]	Efficacy and safety		✓	✓	No notation	PPI ^a	✓	163/300	NSCLC
Mollica V <i>et al.</i> (2022) ^[30]	Efficacy	✓	✓			PPI		25/63	Renal cell carcinoma
Peng K <i>et al.</i> (2022) ^[31]	Efficacy	✓	✓			PPI		89/233	Several ^e
Ruiz-Bañobre J <i>et al.</i> (2021) ^[32]	Efficacy	✓	✓			PPI	✓	54/119	Urothelial carcinoma
Seethapathy H <i>et al.</i> (2019) ^[33]	Safety			✓	AKI	PPI, H2RA		630/1,046	Several
Stein C <i>et al.</i> (2021) ^[34]	Safety		✓	✓	AKI	PPI	✓	87/232	Melanoma
Takada K <i>et al.</i> (2022) ^[8]	Efficacy	✓	✓			PPI ^a		37/95	NSCLC
Tomisaki I <i>et al.</i> (2022) ^[35]	Efficacy	✓	✓			PPI	✓	15/40	Urothelial carcinoma

Yin J <i>et al.</i> (2022) ^[36]	Safety		✓	Colitis	PPI	104/176	Renal cell carcinoma
Zhao S <i>et al.</i> (2019) ^[37]	Efficacy	✓	✓		PPI	40/109	NSCLC

^a: including vonoprazan, ^b: evaluating PPI, ^c: evaluating H2RA, ^d: evaluating irAEs, ^e: including NSCLC AKI, acute kidney injury; AS, acid suppressant; H2RA, histamine H2-receptor antagonist; ICIs, immune checkpoint inhibitors; irAEs, immune-related adverse events; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression free survival; PPI, proton pump inhibitor.

Table 2 The subgroup analysis of ICIs monotherapy

Endpoint	Number of studies	HR or OR	95%CI	Z	I ²	Meta-analysis model
PFS	6	1.51	1.18–1.93	p = 0.0010	61%	Random-effects model
OS	10	1.50	1.23–1.84	p < 0.0001	60%	Random-effects model
irAEs	5	0.90	0.67–1.21	p = 0.48	46%	Fixed-effects model

95%CI, 95% confidence interval; HR, hazard ratio; ICIs, immune checkpoint inhibitors; irAEs, immune-related adverse events; OR, odds ratio;

OS, overall survival; PFS, progression free survival

Table 3 The subgroup analysis of type of cancer

Type of cancer	Endpoint	Number of studies	HR	95%CI	Z	I ²
Non-small cell lung cancer	PFS	4	1.38	1.19–1.59	p < 0.0001	0%
	OS	5	1.47	1.24–1.74	p < 0.00001	0%
Urothelial carcinoma	PFS	3	1.85	1.46–2.35	p < 0.00001	19%
	OS	3	1.99	1.48–2.66	p < 0.00001	31%

95%CI, 95% confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression free survival

Fig. 1

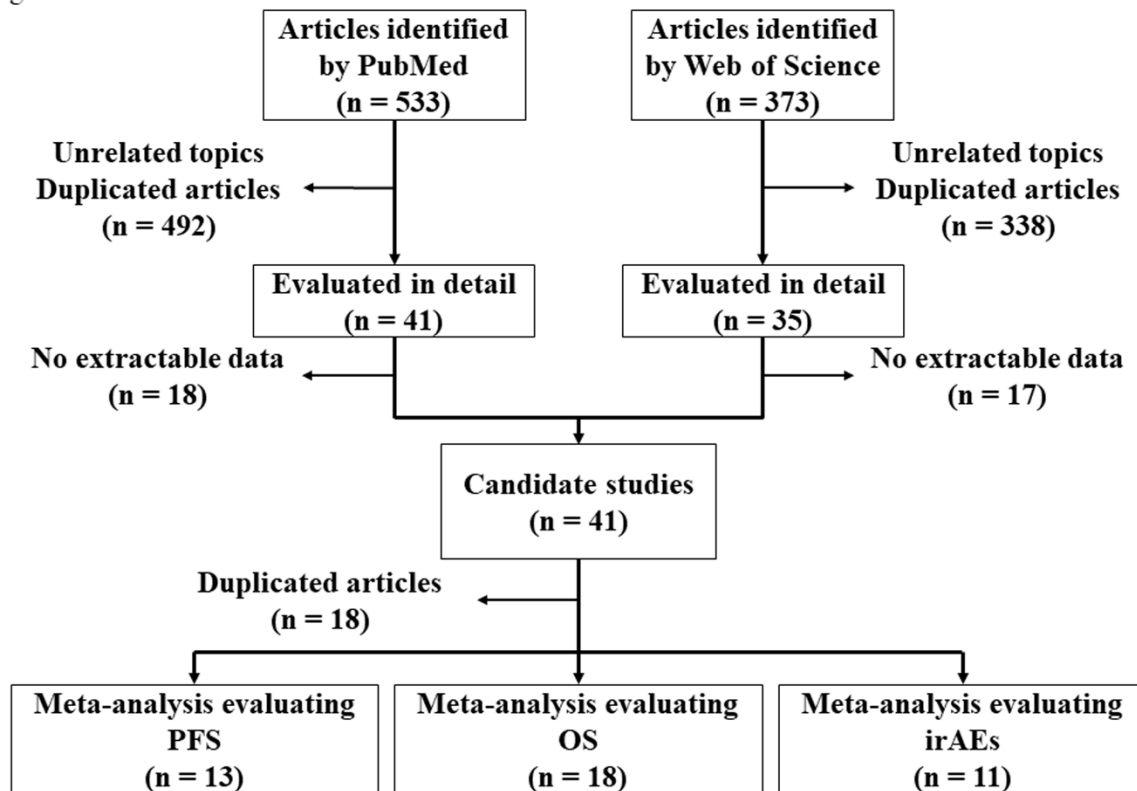


Fig. 1 Flow diagram of the study selection. There are duplicate studies among the last classifications.

Fig. 2a

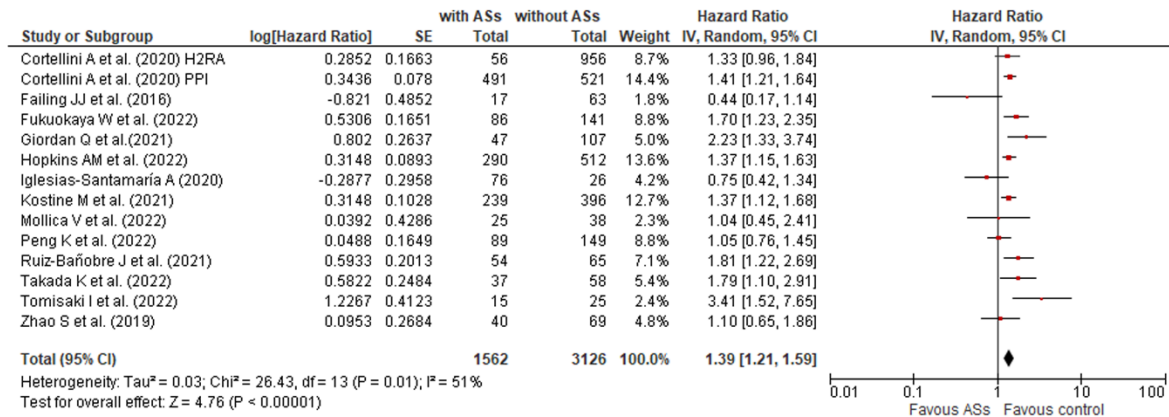


Fig. 2b

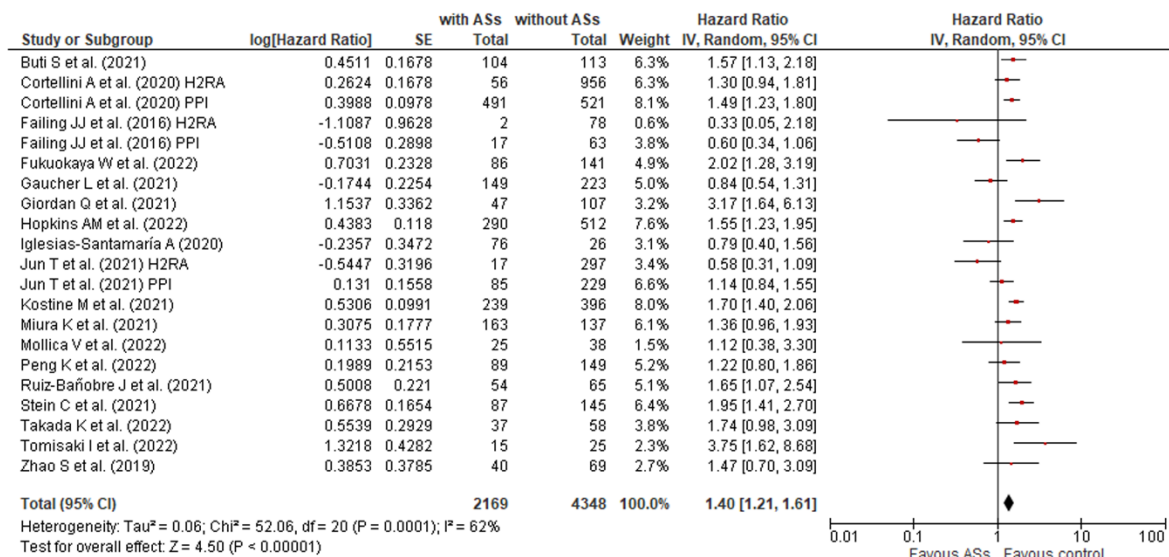


Fig. 2c

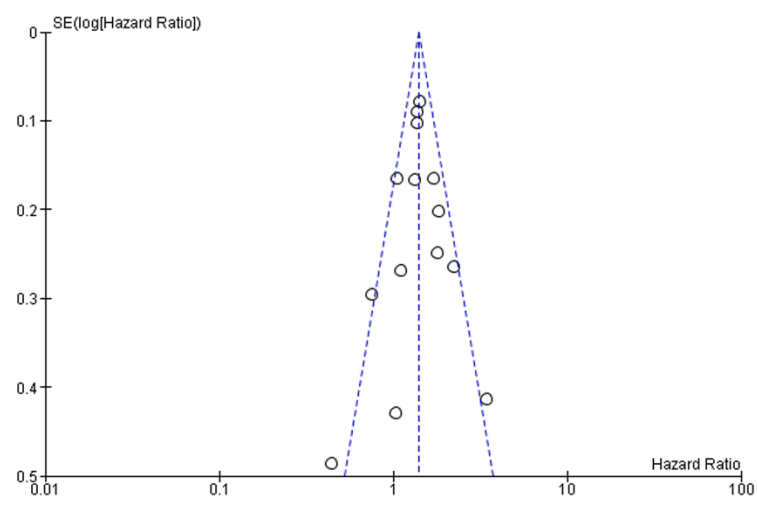


Fig. 2d

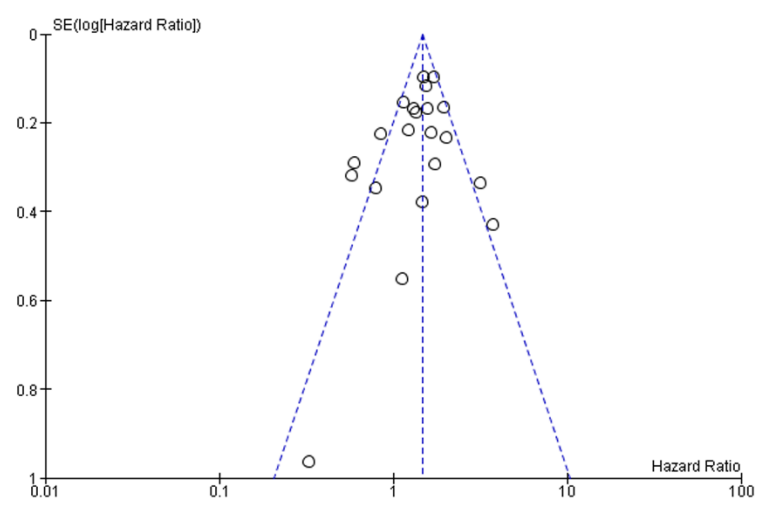


Fig. 2 The effect of ASs administration on PFS and OS of ICI-treated patients. Forrest plots assessed the effect of ASs on (a) PFS and (b) OS in ICIs-administrated patients. PPIs and H2RAs described in the figure as “Study or Subgroup” means that one study was divided into each group. Chi^2 and I^2 indicate heterogeneity. df: Degrees of freedom; Z: statistically significant. Funnel plots evaluated candidate studies on (c) PFS and (d) OS, respectively.

Fig. 3a

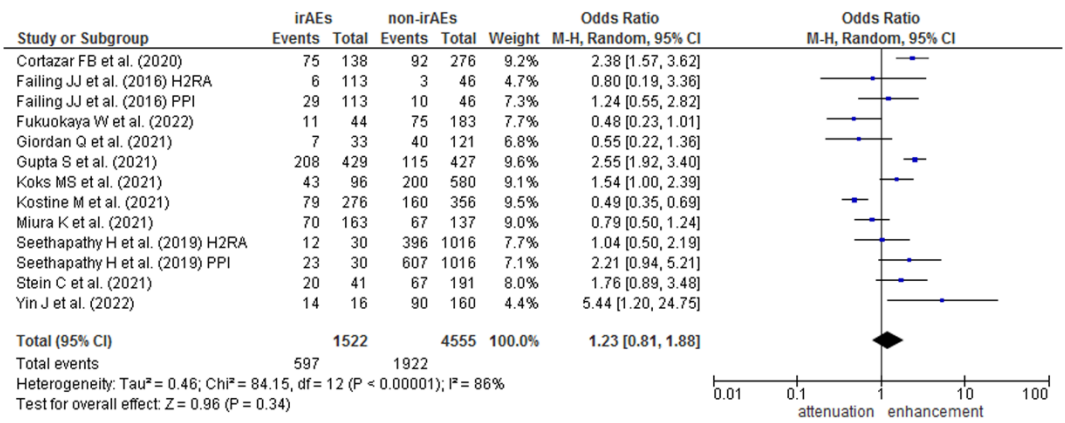


Fig. 3b

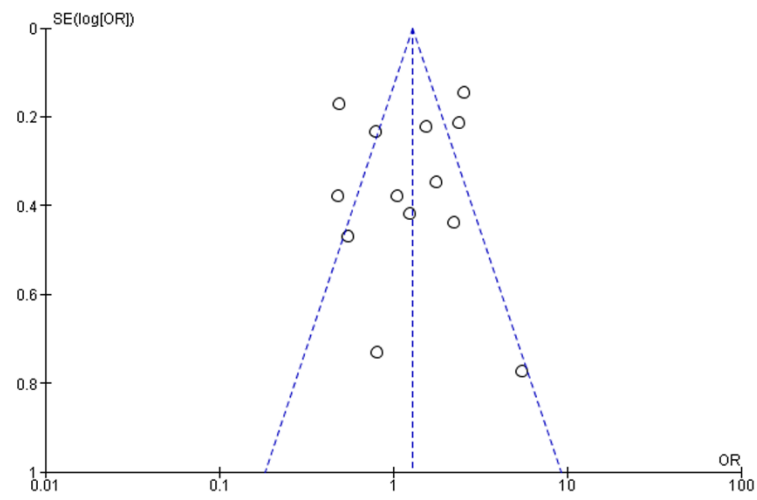


Fig. 3c

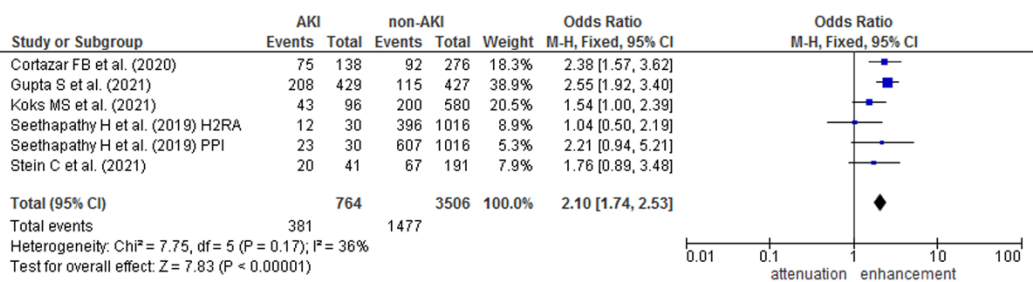


Fig. 3d

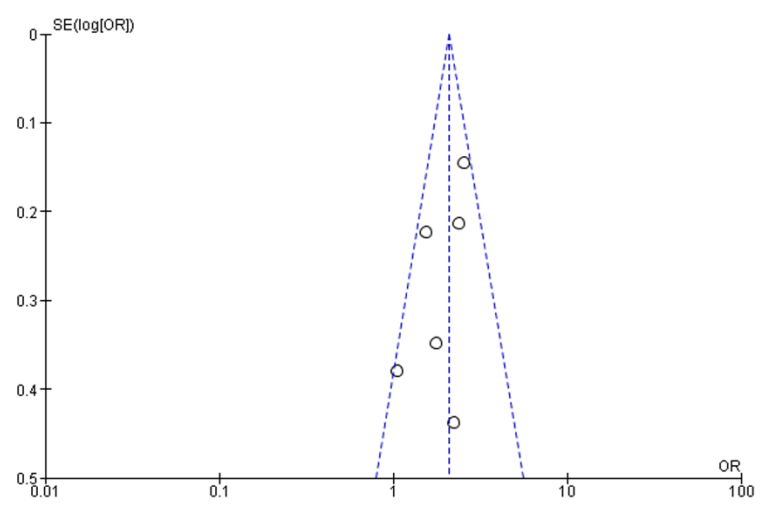


Fig. 3 The effect of ASs administration on irAEs and AKI (subgroup analysis) by ICIs.

Forrest plots assessed the effect of ASs on (a) irAEs and (c) AKI. Events group included patients that received ASs with ICIs and total means sum of patients with and without ASs. PPIs and H2RAs described in the figure as “Study or Subgroup” means that one study was divided into each group. Chi^2 and I^2 indicate heterogeneity. df: Degrees of freedom; Z: statistically significant. Funnel plot evaluated candidate studies on (b) irAEs and (d) AKI, respectively.

Fig. 4a

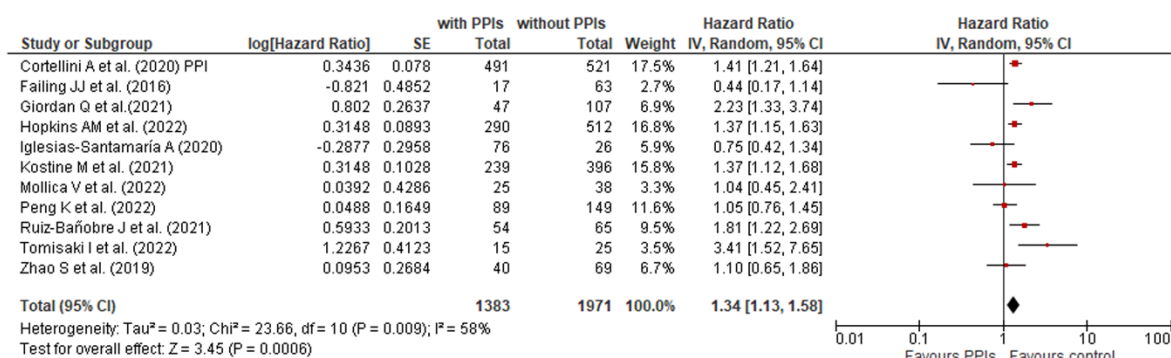


Fig. 4b

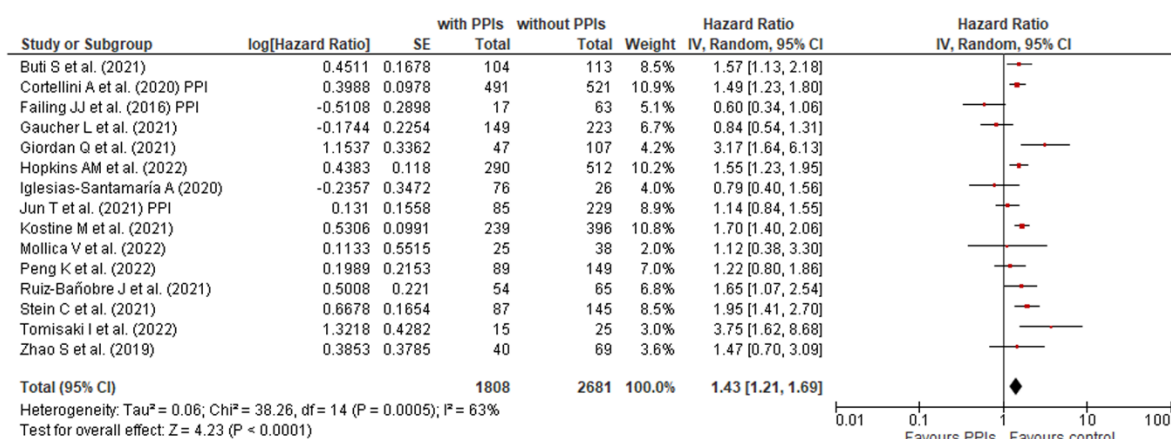


Fig. 4c

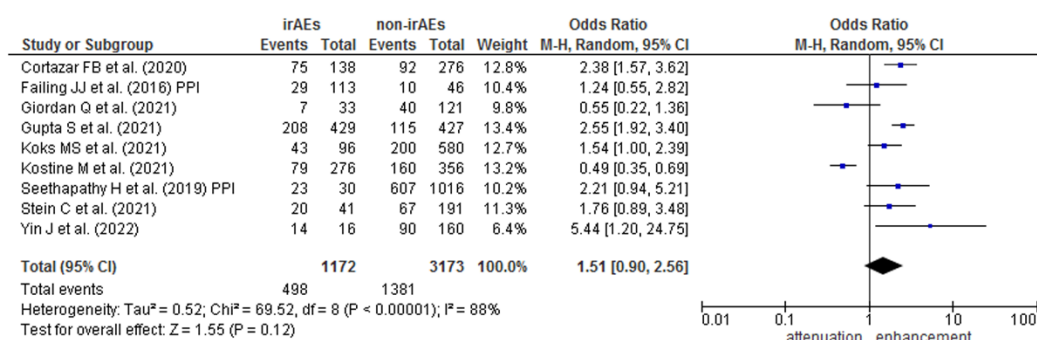


Fig. 4 Subgroup Analysis of the effect of PPIs administration on PFS, OS, and irAEs.

Forrest plots assessed the effect of PPIs on (a) PFS, (b) OS, and (c) irAEs. Events group included patients that received PPIs with ICIs and total means sum of patients with and without PPIs. PPIs described in the figure as “Study or Subgroup” means that only PPIs data were used in candidate study evaluating PPIs and H2RAs respectively. χ^2 and I^2 indicate heterogeneity. df: Degrees of freedom; Z: statistically significant.

Fig. 5

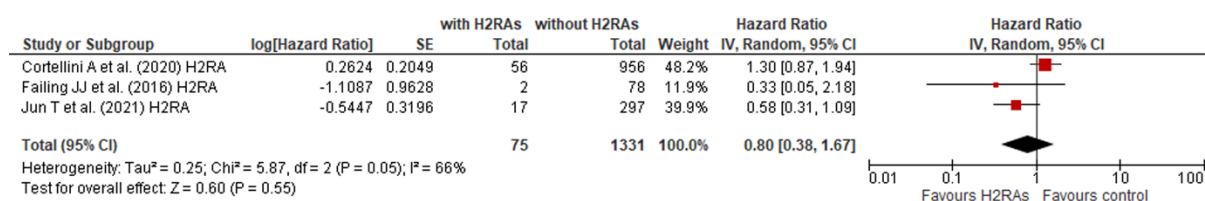
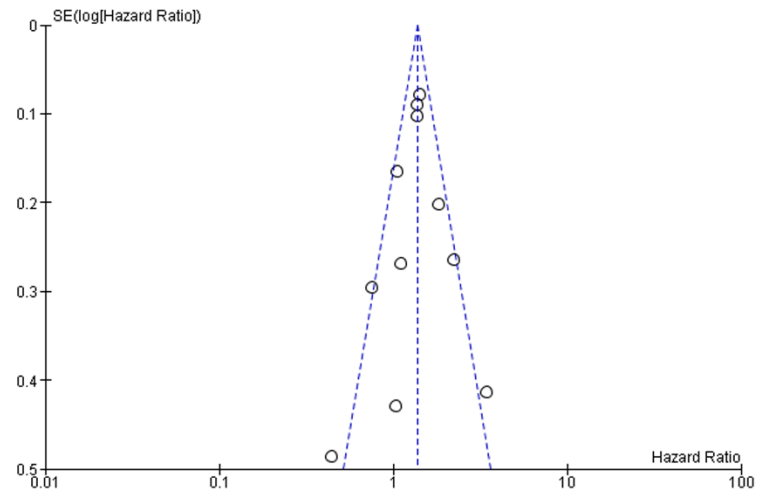
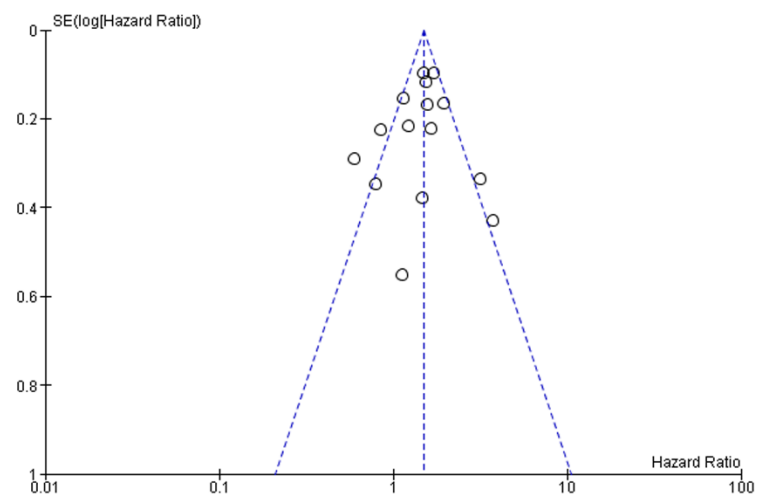


Fig. 5 Subgroup Analysis of the effect of H2RA administration on OS in ICIs-administrated patients. Forrest plots assessed the effect of H2RAs on OS. H2RAs described in the figure as “Study or Subgroup” means that only H2RA data were used in candidate study evaluating PPIs and H2RAs respectively. χ^2 and I^2 indicate heterogeneity. df: Degrees of freedom; Z: statistically significant.

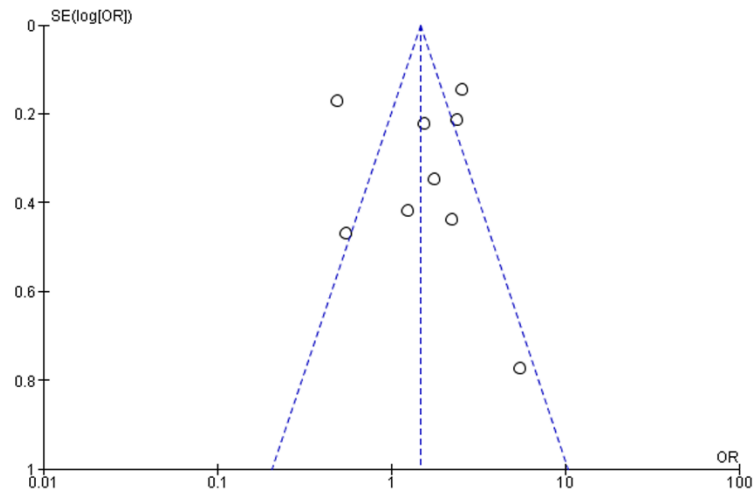
Supplemental Fig. 1a



Supplemental Fig. 1b



Supplemental Fig. 1c



Supplemental Fig. 1 Funnel plot for candidate studies evaluating the effect of PPIs administration on ICIs treatment. Funnel plot evaluated candidate studies on (a) PFS, (b) OS, and (c) irAEs, respectively.