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Effect of Acid Suppressants on Adverse Events of Immune Checkpoint

Inhibitors Using Real-world Databases

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Epidemiological study

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Abstract

Background/Aim: Immune checkpoint inhibitors (ICIs) cause immune-related adverse events (irAEs) in various organs. Although many studies have suggested that acid suppressants (ASs) may affect irAEs, limited sample sizes have hindered detailed evaluations. Therefore, this study aimed to assess the impact of ASs on individual irAEs using large real-world databases, the Japanese Adverse Drug Event Report database (JADER) and the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS). **Materials and Methods:** We analyzed adverse event (AE) reports from the JADER and FAERS databases to assess the impact of ASs on ICI-related AEs. Reporting odds ratios (RORs) and 95% confidence intervals (95%CI)

were calculated. Drug-drug interaction signals were defined by non-overlapping 95% CIs between ICIs alone and their combination use. **Results:** Co-administration with ASs or proton pump inhibitors (PPIs) was associated with an increased risk of acute kidney injury (AKI) in both datasets, while H2-receptor antagonists (H2RAs) showed weaker or no signals. The incidence of endocrine-related AEs tended to decrease with ASs. The colitis results differed between the two datasets, with a decreased incidence in the JADER and an increased incidence in FAERS. Other ICI-related AEs showed consistent trends across datasets. Subgroup analyses of individual PPIs revealed varying results for AKI and colitis between the JADER and FAERS databases, with no consistent trends across PPIs. **Conclusion:** ASs have diverse effects on ICI-induced AEs and their characteristics may differ between PPIs and H2RAs.

Introduction

Immune checkpoint inhibitors (ICIs), used in cancer immunotherapy, are effective against various carcinomas by blocking immune checkpoints such as programmed cell death 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) (1). However, ICIs are also associated with unique side effects known as immune-related adverse events (irAEs). These are

caused by excessively activated immune reactions and can affect a wide range of organs (2, 3). When irAEs become severe, ICI treatment must be suspended or discontinued (4).

Through meta-analysis, we previously assessed the impact of acid suppressants (ASs), including proton pump inhibitors (PPIs), histamine H₂-receptor antagonists (H₂RAs), and potassium-competitive acid blockers (P-CABs), on the efficacy and adverse events (AEs) of ICIs (5). While the use of ASs or PPIs did not significantly affect the risk of irAEs, subgroup analysis revealed that concomitant AS use was a risk factor for ICI-induced acute kidney injury (AKI). These findings suggest that to accurately assess the influence of ASs on irAEs, it is essential to perform analyses targeting individual AEs. However, because many irAEs have low incidence rates and there is a limited number of case reports, conducting detailed evaluations through clinical studies or meta-analyses remains difficult. Therefore, in this study, we aimed to investigate the impact of ASs on irAEs in greater detail by using two real-world AE databases, the Japanese Adverse Drug Event Report database (JADER) and the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS), which provide large volumes of data for analysis.

Materials and Methods

Study design. We downloaded the JADER (November 2023) and FAERS (December 2023), AE-reporting databases provided by the PMDA and FDA, respectively. The time periods selected for the analysis were July 2014 to October 2023 for JADER and July 2014 to September 2023 for FAERS. The dataset was organized as previously described (6). The following drugs were extracted as target medications: ICIs: nivolumab, pembrolizumab, durvalumab, avelumab, atezolizumab, cemiplimab, ipilimumab, and tremelimumab; ASs – PPIs: omeprazole, lansoprazole, rabeprazole, esomeprazole, and pantoprazole (FAERS only); H2RAs: cimetidine, famotidine, nizatidine, roxatidine, lafutidine, and ranitidine; and P-CABs: vonoprazan and tegoprazan (FAERS only). AEs caused by ICIs were defined using the Medical Dictionary for Regulatory Activities (MedDRA) ver. 26.1 (Supplemental Materials and Methods). ICI-related AEs were selected using preferred terms (PTs) and a Standardized MedDRA Queries code. PTs clearly unrelated to ICIs were excluded, and the selection was refined based on a previously published report (7).

Statistical analysis. The analysis method was partially modified from our previous reports (6, 8). For the evaluation of individual drugs, suspected drugs in JADER, as well as Primary Suspect (PS) and Secondary Suspect (SS) drugs in FAERS, were included. Concomitant drugs were included regardless of classification. The

disproportionate number of AE reports was analyzed using reporting odds ratios (RORs) and the corresponding 95% confidence intervals (95%CI) (9). The drug-drug interaction signal was defined as cases in which the 95%CI range of the ROR for ICIs with ASs or ASs alone did not overlap with that of ICIs alone. When multiple AEs occurred in a single individual, only reports of the target AE were included, and reports of other AEs were excluded. Data were analyzed using R software version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Analysis of effects of ASs on ICI-related AEs using JADER and FAERS. The results obtained using the JADER dataset are presented in Figure 1A and those obtained using the FAERS dataset are shown in Figure 1B. The detailed numerical data are provided in Supplemental Tables 1–10. In the FAERS dataset, data on P-CAB use were extremely limited (Supplemental Tables 1–10), and a few results were consistent with those from JADER. Therefore, the FAERS analysis focused only on ASs, PPIs, and H2RAs. In JADER, AKI associated with ICIs showed a trend toward an increased incidence with ASs and PPIs, while no signal was detected with H2RAs. These findings are consistent with those of our previous meta-analysis (5). In addition, no signals were detected for P-CABs concomitant likely H2RAs. In FAERS,

although a signal was detected for H2RAs concomitant, the ROR was lower than that of ASs and PPIs, which generally aligned with the findings from JADER. For endocrine-related AEs, such as adrenocortical insufficiency, hypopituitarism, type 1 diabetes mellitus, and thyroid dysfunction, a decreasing trend in incidence was observed with ASs use. In the case of colitis, ASs were associated with a decreased incidence in JADER, whereas the opposite trend was observed in FAERS. Similar results were observed for interstitial lung disease, immune-related hepatitis, myasthenia gravis, and severe cutaneous adverse reactions, in both JADER and FAERS.

Analysis of effects of each PPI on AKI induced by ICIs using JADER and

FAERS. Given that PPIs have been reported to cause AKI and that signals were detected for PPI monotherapy in the FAERS analysis (Supplemental Table 2) (10), a subgroup analysis was conducted for each PPI. In the FAERS dataset, all PPIs individually showed detectable signals in combination with ICIs (Figure 2, Supplemental Tables 11–12). In contrast, no consistent results were observed for PPIs in the JADER dataset.

Analysis of effects of each PPI on colitis induced by ICIs using JADER and

FAERS. As the impact of ASs or PPIs on ICI-induced colitis showed opposing results between the JADER and FAERS datasets, a subgroup analysis was performed for each PPI. The analysis revealed that all PPIs showed differing results between JADER and FAERS, and the trends also varied among individual PPIs (Figure 3, Supplemental Tables 13–14).

Discussion

In this study, we analyzed the impact of ASs on various AEs associated with ICIs using two real-world AE databases, JADER and FAERS. Although our previous meta-analysis was limited by an insufficient sample size for a detailed evaluation (5), the extensive data provided by these databases allowed for a more comprehensive investigation and identification of novel findings.

Our previous meta-analysis demonstrated that AS use is a risk factor for ICI-induced AKI (5), and similar findings were observed in this database analysis. While PPIs showed results consistent with ASs overall, H2RAs appeared to have a smaller impact on AKI than PPIs. These findings suggested that switching from PPIs to H2RAs may be a viable option when administering ICIs to elderly patients or patients with impaired renal function. In contrast, PPIs have been reported to cause kidney injury (10), which was also supported by our database analysis (Supplemental Tables

11–12). This study could not determine whether the increased frequency of AKI in patients receiving ICIs with PPIs was attributable to the PPIs themselves or to the synergistic effect of their co-administration with ICIs, and further detailed analysis is warranted.

Patients developing irAEs have been reported to have better clinical outcomes than those without irAEs owing to the activation of the immune system (11). Moreover, our previous study showed that AS co-administration may reduce the therapeutic efficacy of ICIs (5). Therefore, it is highly plausible that the co-administration of ASs is associated with a reduced incidence of endocrine-related AEs, such as adrenocortical insufficiency, hypopituitarism, type 1 diabetes mellitus, and thyroid dysfunction. In contrast, AS use was associated with a higher incidence of AEs, such as interstitial lung disease and severe cutaneous adverse reactions, suggesting that the effects of ASs vary depending on the affected organ or pathological condition.

Interestingly, the effects of ASs on ICI-induced colitis showed markedly different trends in JADER and FAERS. JADER reflects AE reports from Japan, whereas FAERS includes reports from other countries. A higher proportion of Japanese individuals are poor metabolizers due to genetic polymorphisms in CYP2C19, an enzyme involved in the metabolism of PPIs (12). In addition, given that

the gut microbiota is closely linked to ICI efficacy and that ASs are known to alter the gut microbiota composition (13–15), the differences observed between JADER and FAERS may be influenced by racial or regional variations in microbiota and patient backgrounds.

Limitations. First, the definitions of ICI-related AEs used in this study may not completely correspond to the clinical understanding of irAEs. Second, due to the nature of the database analysis, detailed patient background information, such as performance status (16), was unavailable. Third, both the JADER and FAERS are based on spontaneous reporting, which may limit the reliability of the data. Fourth, differences in drug approval status and clinical practice across countries (e.g., P-CABs or pantoprazole in this study) may introduce bias. Further clinical research based on the findings of this study is necessary to overcome these limitations.

Conclusion

This study revealed that ASs exert diverse effects on ICI-induced AEs. It also demonstrated that the characteristics of PPIs and H2RAs may differ. In the future, more detailed clinical studies should be performed to examine the influence of ASs on irAEs as primary endpoints.

Conflicts of Interest

The Authors declare no conflicts of interest relevant to the contents of this article.

Authors' Contributions

Conceptualization: KO and MK; Investigation and Analysis: KO and JT;

Funding acquisition: KO; Writing – original draft: KO, JT, HU, KN, and MK.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

Supplementary Material

Supplementary Data can be accessed at the following link:

[https://drive.google.com/file/d/1WsYE_ih1oL_bavDf2JqcBNsy-UZJvdwG/view?usp=drive_link]

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Figure Legends

Figure 1. The effects of acid suppressants (ASs) on adverse events (AEs)

induced by immune checkpoint inhibitors (ICIs) in database analysis. The

analysis was conducted using (A) JADER and (B) FAERS. Open square indicates the

ROR for ICIs alone, circles represent the ROR for other groups, and closed circles

denote the presence of a detected drug-drug interaction signal. AKI: acute kidney

injury; ILD: interstitial lung disease; SCARs: severe cutaneous adverse reactions;

T1DM: type 1 diabetes mellitus.

Figure 2. The effects of each proton pump inhibitor (PPI) on acute kidney injury

(AKI) induced by immune checkpoint inhibitors (ICIs) in database analysis. The

analysis was conducted using JADER and FAERS. Open square indicates the ROR

for ICIs alone, circles represent the ROR for other groups, and closed circles denote

the presence of a detected drug-drug interaction signal.

Figure 3. The effects of each PPI on colitis induced by immune checkpoint inhibitors (ICIs) in database analysis. The analysis was conducted using JADER and FAERS. Open square indicates the ROR for ICIs alone, circles represent the ROR for other groups, and closed circles denote the presence of a detected drug-drug interaction signal.

Figure 1A

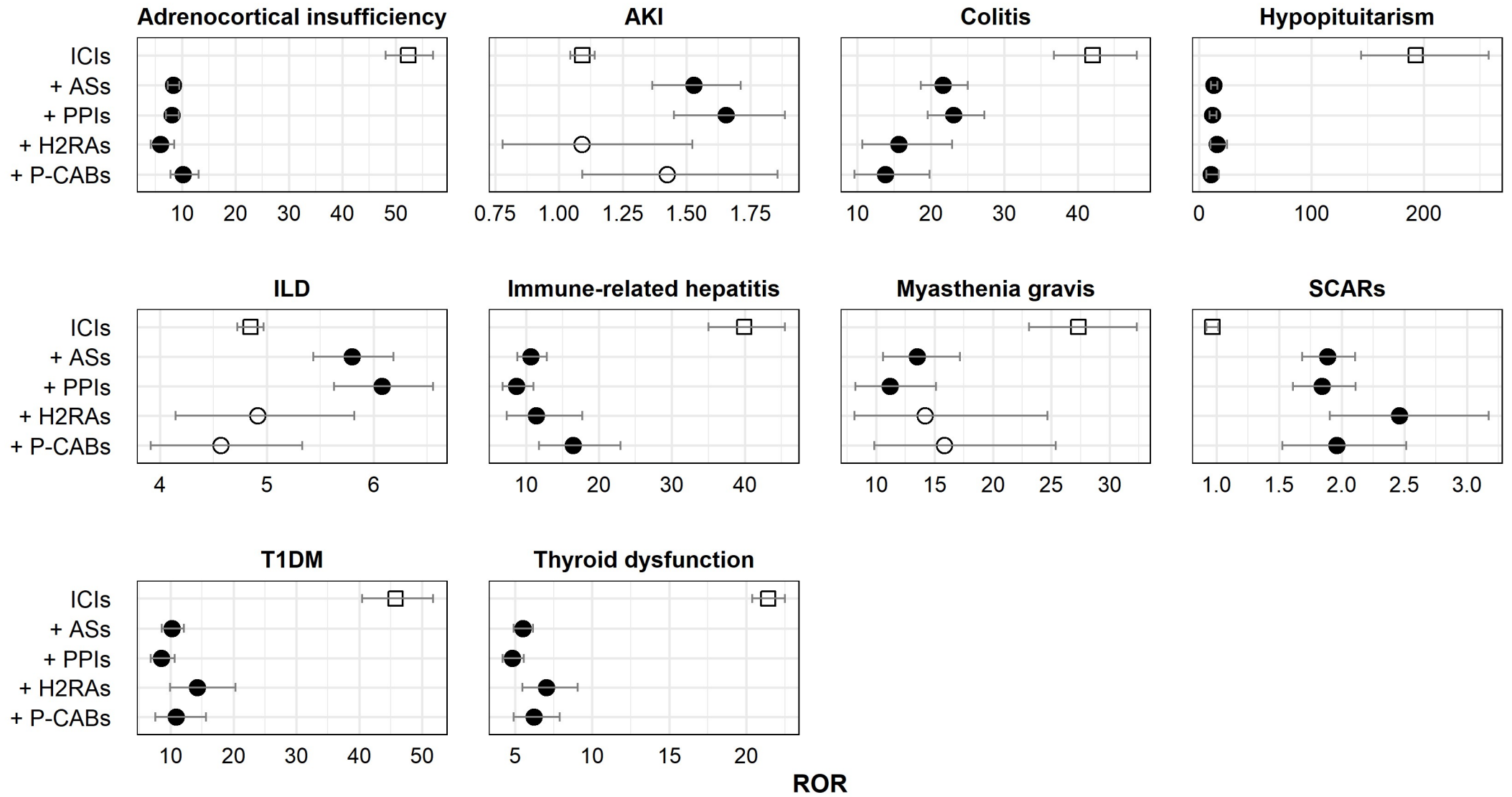


Figure 1B

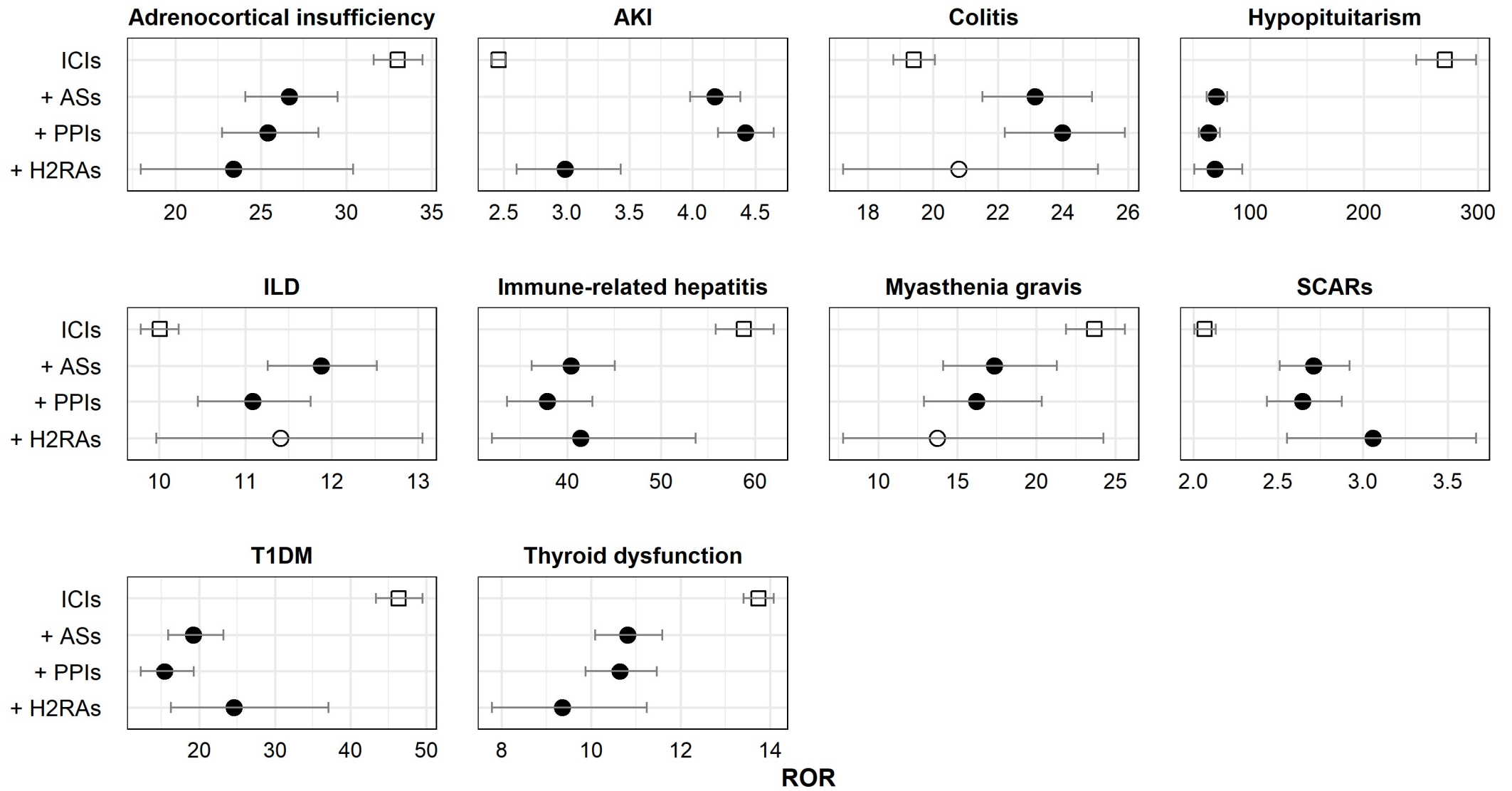
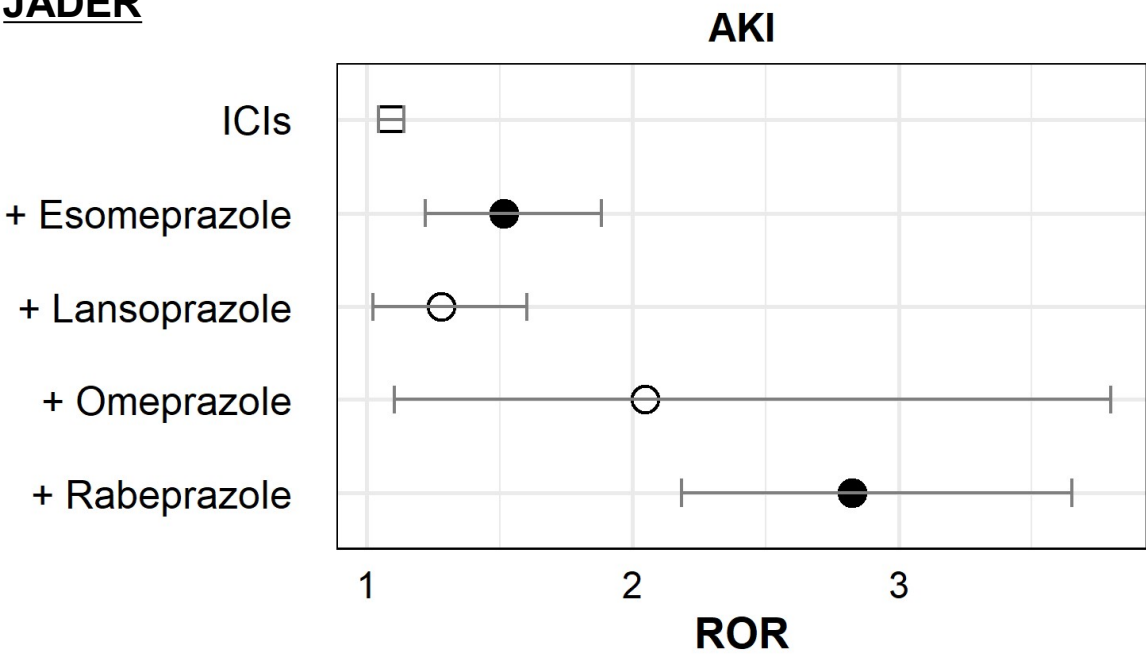


Figure 2

JADER



FAERS

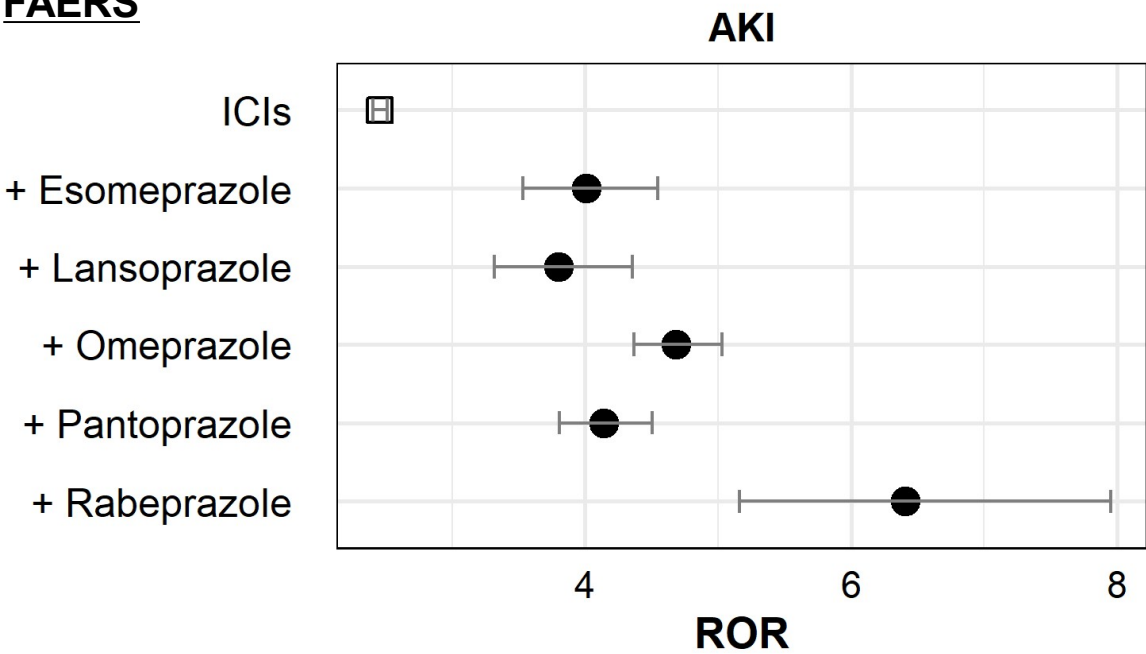
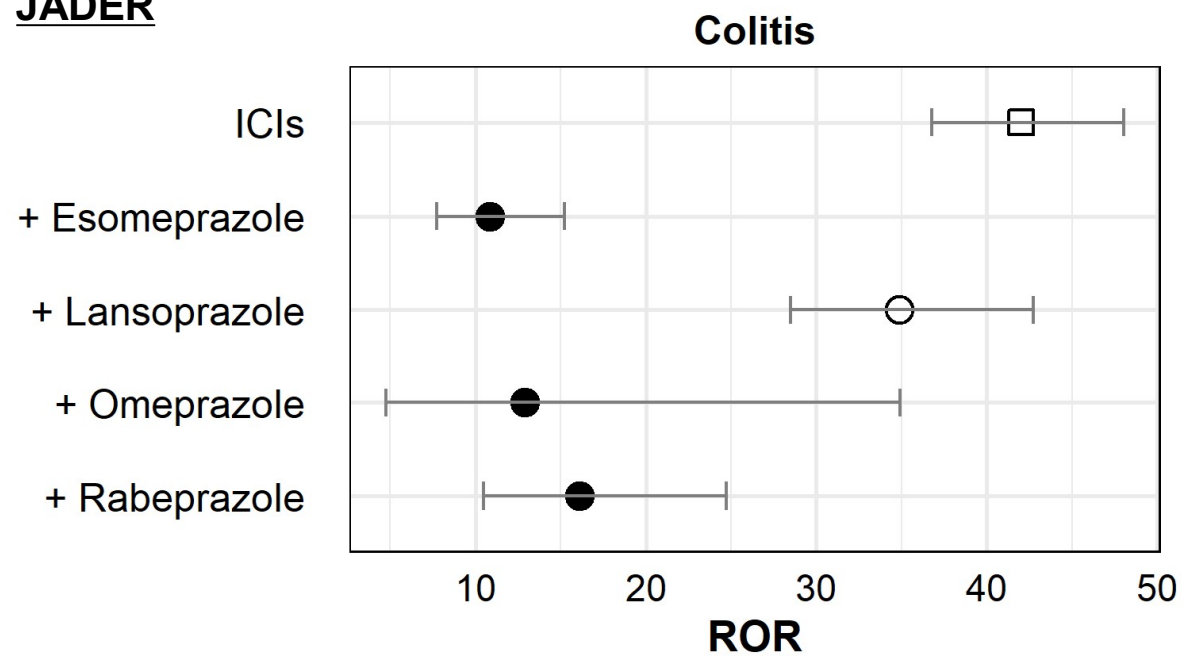


Figure 3

JADER



FAERS

