INPLASY

Risk of Gastrointestinal Adverse Events in Cancer Patients on Immune Checkpoint Inhibitors: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ADMINISTRATIVE INFORMATION

Support - Not applicable.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202570093

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 July 2025 and was last updated on 23 July 2025.

INTRODUCTION

Review question / Objective This systematic review and meta-analysis aim to assess the risk of gastrointestinal adverse events associated with immune checkpoint inhibitors monotherapy based on randomized controlled trials.
Population: cancer patients (> 18 years old)
Intervention: immune checkpoint inhibitors monotherapy
Comparison: not applicable
Outcome: incidence of gastrointestinal adverse events, including diarrhea, nausea, vomiting, constipation, colitis, and abdominal pain
Study design: Phase III or IV randomized controlled trials.

Rationale Immune checkpoint inhibitors (ICIs), such as those targeting CTLA-4 and PD-1/PD-L1, have demonstrated remarkable efficacy in various cancers. However, ICIs are also associated with adverse events (AEs) affecting multiple systems, presenting challenges for cancer treatment. Gastrointestinal AEs are among the most common, and severe cases can lead to serious complications like intestinal obstruction or perforation. These AEs can limit ICI application, disrupt treatment, and potentially deny patients effective therapy. Therefore, there is a need for a comprehensive meta-analysis that evaluates the overall incidence of a broader range of gastrointestinal AEs associated with ICI monotherapy. This analysis will provide valuable insights into the safety profile of ICIs, aiding clinicians in managing treatment-related toxicities and optimizing patient outcomes.

Condition being studied Cancer is a leading threat to human health and life. Approximately 19.9 million new cancer cases occurred globally, resulting in 9.7 million deaths. Tumor cells employ a mechanism known as "immune evasion", which involves the abnormal expression of immune checkpoints that compromise the immune system's efficacy. Targeting these checkpoints with ICIs has garnered significant attention in cancer research due to their notable efficacy and the new

hope they offer for patients with advanced cancers. In clinical practice, ICIs primarily target CTLA-4, PD-1, and PD-L1. CTLA-4 inhibitors, such as ipilimumab, block the immunosuppressive effects of CTLA-4, activating T cells and leading to tumor destruction. Ipilimumab has been approved for the treatment of various cancers, benefiting approximately 10-20% of patients. PD-1/PD-L1 inhibitors, such as nivolumab, restore T cell-mediated cytotoxicity by blocking the PD-1/PD-L1 pathway, resulting in antitumor effects. Nivolumab has demonstrated significant survival benefits in melanoma patients. Overall, ICIs enhance the immune system's attack on tumors through different mechanisms, offering new hope for cancer treatment.

METHODS

Search strategy ("Immune Checkpoint Inhibitors" OR "Programmed Death-Ligand 1 Inhibitor" OR "Cytotoxic T Lymphocyte Associated Protein 4 Inhibitor" OR "Programmed Cell Death Protein 1 Inhibitor") AND ("Gastrointestinal adverse events" OR diarrhea OR nausea OR vomiting OR constipation OR colitis OR "abdominal pain") AND ("Phase III trials" OR "Phase IV trials").

Participant or population Cancer patients receiving ICIs monotherapy.

Intervention ICI monotherapy, such as CTLA-4 monotherapy, PD-1 monontherapy, or CTLA-4+PD-1 therapy.

Comparator Not applicable.

Study designs to be included Phase III or phase IV randomized controlled trials.

Eligibility criteria Inclusion criteria
1) Phase III or phase IV double-blinded RCTs involving adult cancer patients;
2) Participants receiving treatment exclusively with ICIs (including ICIs as neoadjuvant or adjuvant therapy), excluding those receiving any concomitant treatments such as placebo, chemotherapy, or radiotherapy;
3) Available data on gastrointestinal AEs, including diarrhea, nausea, vomiting, constipation, colitis, and abdominal pain, were required to cover any-grade, low-grade, or high-grade classifications. Any-grade refers to any severity level AEs (grades 1-5), low-grade includes mild to moderate AEs (grades 1-2), and high-grade encompasses severe AEs to life-threatening consequences or death (grades 3-5).
Exclusion criteria
1) Duplicated publications, abstracts, comments, reports, editorials, reviews, meta-analyses, case reports, unpublished studies, observational studies;
2) Studies lacking an assessment of gastrointestinal AEs in patients treated with ICIs;
3) Studies presenting only raw data without matching or adjustment.
4) Studies for which data extraction was impracticable.

Information sources PubMed, Embase, Web of Science, and Cochrane Library.

Main outcome(s) The overall incidence of low-grade (grades 1-2) and high-grade (grades 3-5) gastrointestinal AEs (diarrhea, nausea, vomiting, constipation, colitis, and abdominal pain) associated with ICI monotherapy.

Additional outcome(s) The incidence of these low-grade and high-grade gastrointestinal AEs within pre-defined subgroups.

Quality assessment / Risk of bias analysis Quality assessment was conducted using the Cochrane tool for assessing risk of bias in a randomized trial (RoB2, version 2), including 1) Bias from the randomization process; 2) Bias due to deviations from the intended interventions: assessing the effect of intervention allocation and intervention adherence; 3) Bias due to missing outcome data; 4) Bias in outcome measurement; and 5) Bias in selective reporting of results.

Strategy of data synthesis Data were analyzed using the R version 4.3.3, employing solely a random-effects model to assess the pooled incidences of gastrointestinal AEs across low-grade (grades 1-2) and high-grade (grades 3-5) classifications.

Subgroup analysis Subgroup analysis were performed based on geographical region, median publication year, CTCAE version, median sample size, study quality, cancer type, ICI type, treatment line, and median follow-up duration.

Sensitivity analysis Not applicable.

Language restriction English.

Country(ies) involved China.

Keywords Immune checkpoint inhibitor, gastrointestinal adverse events, colitis, diarrhea.

Contributions of each author

Author 1 - Zhongli Liao - Author 1 contributed to conceptualization, supervision, and original draft writing.
Author 2 - Xiaogang Hu - Author 2 contributed to data curation and formal analysis.
Author 3 - Shishi Yu - Author 3 contributed to data curation and formal analysis.
Author 4 - Jiong Wang - Author 4 contributed to methodology and validation.
Author 5 - Boweng Deng - Author 5 contributed to validation and visualization.
Author 6 - Fei Ao - Author 6 contributed to in visualization.
Author 7 - Jian Yang - Author 7 contributed to conceptualization, supervision, and manuscript editing.