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Chemotherapy combined with immunotherapy in patients with gastric cancer: protocol for a systematic review

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ABSTRACT

Introduction The integration of chemotherapy and immunotherapy is continually making new advances in the field of gastric cancer treatment and has already become the new standard of care for the disease. However, few systematic reviews cover a wide array of immune checkpoint inhibitors (ICIs), antibody types and therapeutic modalities (perioperative or systemic) in this domain. Our aim is to incorporate the most recent clinical studies on combination therapy for the treatment of gastric cancer into a systematic review. This will comprehensively assess the benefits and drawbacks for patients with gastric cancer and will guide future research in this area. Ultimately, this will provide evidence-based support for patients with gastric cancer.

Methods and analysis This protocol for a systematic review adheres to the Preferred Reporting Items for Systematic Review and Meta-analysis – Protocols (PRISMA-P) guidelines. We will conduct a search of the MEDLINE, Embase, and CENTRAL databases from database inception, all retrieved literature will be screened by two authors in two rounds. Inclusion criteria will be randomised clinical trials, reported in English, that compare immunotherapy-combined therapy with chemotherapy alone in the perioperative and systematic first-line treatment of gastric cancer. The primary outcomes will be progression-free survival (PFS) and overall survival (OS). Secondary outcomes will include objective response rate (ORR), event-free survival (EFS), disease-free survival (DFS), pathologic complete response (pCR), major pathologic response (MPR), and the R0 resection rate. Heterogeneity and publication bias of included literature will be investigated. Where included literatures allow, we will conduct meta-analyses and subgroup analyses to further refine the pros and cons of combined therapy, providing evidence-based foundations for subsequent research.

Ethics and dissemination This work is a review based on existing literature and no ethical review is required. Dissemination of the results will occur via academic journal publication, conference presentations, and multiple media platforms.

PROSPERO registration number CRD42023477353.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The planned review will have a more extensive and comprehensive literature inclusion than previous studies, covering perioperative treatment and systemic treatment, as well as different types of immune checkpoint inhibitors (ICIs).
⇒ Inclusion criteria limited to randomised clinical trials (RCT), which can enhance the quality of the research and the validity of the conclusions.
⇒ It will include analysis of separate control groups for perioperative treatment and systemic treatment.
⇒ It will combine different types of ICIs with chemotherapy schemes may lead to higher heterogeneity.
⇒ Conclusions may be limited by the number and quality of included studies.

INTRODUCTION

Gastric cancer continues to pose a significant health challenge, ranking as the fifth most commonly diagnosed cancer globally, and the fourth leading cause of cancer-related mortality, responsible for 7.7% of deaths.[1 2] Combination therapy has become the standard approach in the current treatment of gastric cancer. CheckMate 649 is the first study to clearly define the survival benefits provided to gastric cancer patients by immunochemotherapy.[3 4] Related Studies, such as the ATTRACTION series, ORIENT series, and RATIONALE series for first line, and MATTERHORN, ATTRACTION-5 for perioperative treatment, were conducted synchronously or successively, bringing optimistic results.[5–7] Immunochemotherapies are now referenced by guidelines, firmly establishing them as a cornerstone in the contemporary management of gastric cancer.[8 9]

Several meta-analyses on this subject have previously been published. The work by Noori *et al*. (2022) suggests that first-line immunochemotherapy provides a survival benefit compared with chemotherapy alone (hazard ratio (HR) 0.76, 95% confidence interval (CI) 0.72 to 0.81), although with a higher incidence of adverse effects.[10] Later meta-analysis by Liu *et al*. (2023) incorporating four randomised controlled trials (RCTs), confirmed that pembrolizumab and nivolumab, when combined with

chemotherapy in patients with a combined positive score (CPS)>1, offers a survival benefit.[11] Li *et al.*, assessed the enhancement of pathological complete response (pCR) and major pathological response (MPR) in patients who received neoadjuvant immunochemotherapy treatment.[12] Several recent meta-analyses have further investigated the effects of immunochemotherapy in both neoadjuvant and first-line settings. These studies confirmed the significant benefits of immunochemotherapy in perioperative treatment or in patients with CPS>10, and concluded that it does not lead to an increase in treatment-related adverse events (TRAEs).[13–15] These studies further solidified the confidence of the combined therapies. However, these assessments often concentrate on one particular phase (adjuvant or systemic) with limited sample size or are restricted to programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) antibodies, without other types of immune checkpoint inhibitors (ICIs) like CTLA-4 or Dual ICI (e.g. cadonilimab). For the assessment of neoadjuvant treatment, included studies are mostly single-arm trials and often involve combination with a third therapy, leading to possible high heterogeneity. Additionally, recent updated study results such as KEYNOTE595, Orient-16 or the interim results of COMPASSION-15 are also worth incorporating into analyses.[6 16 17]

Therefore, in the planned study, we will utilise systematic review methodologies to thoroughly aggregate and synthesise the latest existing RCT research on combination therapies of gastric cancer, irrespective of the type of ICIs or their combined chemotherapy regimens. In this work, we aim to summarise the benefits and harms of current combination therapies in treating gastric cancer, offering an updated comprehensive descriptive review of the prevailing trends and providing a reference for future clinical practice.

METHODS AND ANALYSIS

This systematic review was prospectively registered at the Prospective Register of Systematic Reviews (PROSPERO) on 23 November 2023 (CRD42023477353). The present protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis–Protocols (PRISMA-P) 2015 Checklist.[18] The systematic review will follow the Cochrane Collaboration's standardised methodology and the results will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines.[19 20]

Eligibility criteria

This systematic review will include randomised controlled trials, reported in English, that focus on adult gastric cancer patients who received immunotherapy combined with chemotherapy simultaneously, including perioperative treatment and systemic treatment for advanced cancer. The Population, Intervention, Comparison and Outcomes (PICO) framework will be followed. Details of the inclusion criteria are listed below.

Type of participants (P)

Adult patients (aged over 18 years) with histologically confirmed gastric cancer will be included, despite the tumour stage or resectability.

Patients diagnosed with simultaneous primary malignancies in multiple organs, or metachronous metastasis from gastric cancer will be excluded.

Type of interventions and comparators (I, C)

This study will include clinical trials comparing solely chemotherapy with immunochemotherapy for the treatment of gastric cancer. The comparative groups will be divided based on treatment modalities into a perioperative treatment group and a systemic treatment group :

- Perioperative immunotherapy combined with chemotherapy vs chemotherapy alone.
- Systemic immunotherapy combined with chemotherapy vs chemotherapy alone.

Immunochemotherapy is defined as simultaneous use of chemotherapy and immunotherapy for gastric cancer, excluding drug therapies administered sequentially or in separate time intervals. Besides, combination therapy incorporating a third therapy (such as radiotherapy or targeted therapy) will not be included in the planed study.

Type of outcomes (O)

Primary outcomes:

- Progress-free survival (PFS).
- Overall survival (OS).

Secondary outcomes:

- Objective response rate (ORR).
- Event Free Survival (EFS).
- Disease Free Survival (DFS).
- Pathological complete responses (pCR) in neoadjuvant treatment setting.
- Major pathological response (MPR) in neoadjuvant treatment setting.
- R0 resection in neoadjuvant treatment setting.
- Safety outcomes, including adverse event (AE) rate and severe adverse event (SAE) rate.

Type of study design (S)

We will include only parallel design RCTs. Quasi-randomised trials will not be included. Studies published as full text or abstract only will be included together with unpublished data (such as interim study results and conference reports).

Information sources and search strategy

We will conduct systematic searches in the following databases, from database inception, to retrieve potentially eligible literature for initial screening:

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (the latest issue).

Table 1 Search strategy for MEDLINE (via Ovid)

Search	Search terms
1	exp Stomach Neoplasms/
2	(gastric or gastro or stomach).ab,ti.
3	(adenocarcinoma or cancer or carcinoma or neoplasm or tumour or tumour).ab,ti.
4	2 and 3
5	1 or 4
6	exp Immunotherapy/
7	(Immunotherapy or Immunotherapies or PD-1 or PD-L1 or CTLA-4).ab,ti.
8	(Retifanlimab or Tremelimumab or Pucotenlimab or Serplulimab or Envafolimab or Zimberelimab or Penpulimab or Tislelizumab or Camrelizumab or Sintilimab Durvalumab or Avelumab or Atezolizumab or Atezolizumab or Atezolizumab or Ipilimumab).ab,ti.
9	6 or 7 or 8
10	exp Drug Therapy/
11	(Chemotherapy or Drug Therapy or Pharmacotherapy or chemical therapy).ab,ti.
12	10 or 11
13	5 and 9 and 12
14	randomly.ab.
15	randomised controlled trial.pt.
16	controlled clinical trial.pt.
17	randomi?ed.ab.
18	placebo.ab.
19	clinical trials as topic.sh.
20	randomly.ab.
21	trial.ti.
22	or/14–21
23	exp animals/ not humans.sh.
24	22 not 23
25	13 and 24

Available at: https://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=N&PAGE=main&SHAREDSEARCHID=2BBpcpHTBneNjrnp91EuoOc9oiH0Il rqYhPVaNLgOcJlaIIdcSweLe5cliJPme2gR.

- MEDLINE Ovid including In-Process & Other Non-Indexed Citations (from 1946 onwards).
- Embase Ovid (from 1974 onwards).

The search strategy for MEDLINE (via Ovid) is listed in table 1. In conclusion, the search will be conducted using the following keywords and their variations: "gastric cancer", "immunotherapy", "combination", "chemotherapy", "immunochemotherapy" together with possible ICI names such as "Sintilimab"," Durvalumab" and so on. There will be no restrictions of the searches by date of publication or study setting.

We will also use the WHO International Clinical Trials Registry Platform (apps.who.int/trialsearch) to explore ongoing clinical trials for potential inclusion.

Data extraction and management

All retrieved papers will be imported into the management software EndNote 21 and finish primary screen based on the title and abstract. Two authors (YH and WY) will finish this part of the study independently. The comparison of screening results and the resolution of conflicting opinions will be determined by a third author (ZC). Full-text screening will start after agreements and again, will be performed by two authors independently. The details of the workflow will be documented using a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram (figure 1), which includes information on the total number of papers retrieved, included, or excluded, and the reasons for their inclusion or exclusion.

For literature that meets the criteria and can be accessed in full text, the same two authors will individually perform data extraction managed using an Excel spreadsheet. The extraction panel will be arranged by PICO structure:

- Trial information: for example, trial participants, sample size, inclusion criteria, characteristics of participants (eg, age in average, gender, International Classification of Diseases (ICD) diagnosis, pathological diagnosis, tumour, node and metastasis (TNM) stage, combined positive score (CPS) if available).
- Intervention: for example, details of immunotherapy and chemotherapy regimens, treatment details, such as duration of medication usage and intervals, etc.
- Primary Outcome: OS, PFS.
- Secondary outcome: ORR, DFS, EFS, and safety outcomes (AE, SAE). pathological complete responses (pCR) and major pathological response (MPR) will be extracted from neoadjuvant trials.

General information such as article title, author, country, and publication date will be recorded. Additionally, details concerning study design, follow-up, dropout rates, and result analyses will be documented. Table 2 lists the items that will be extracted. Extracted data will undergo cross-validation by a third reviewer (ZC) to resolve any discrepancies. In cases where the required data are absent, efforts will be made to contact the original authors to obtain the missing information.

Assessment of risk of bias

Each of the included studies will undergo assessment using Cochrane's "Risk of Bias" tool,[21] the tool specifically designed for evaluating bias in RCTs within systematic reviews. Each study will be evaluated across seven dimensions and categorised as "low-", "medium-", or "high-" risk accordingly. The assessment results will be presented in chart format. Two authors (YH and WY) will independently conduct this assessment, with any disagreements resolved by a third reviewer (ZC).

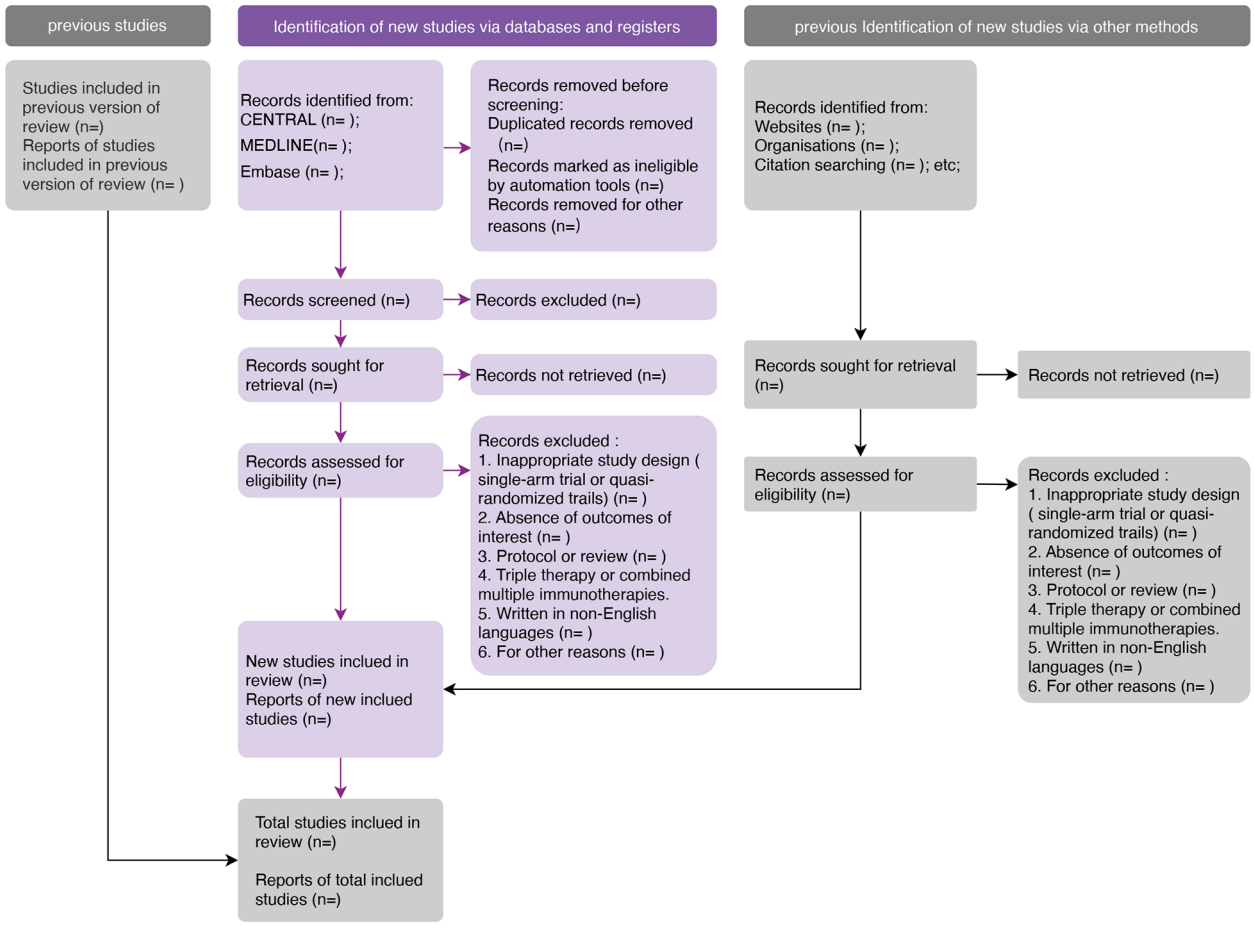

Figure 1 PRISMA flow diagram CENTRAL, Cochrane Central Register of Controlled Trials. MEDLINE, Medical Literature Analysis and Retrieval System Online.

Dealing with missing data

We will adhere to the recommendations outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* regarding the handling of missing data.[22] We will attempt to contact the authors of the studies to confirm essential study characteristics and acquire any missing numerical outcomes data whenever feasible (eg, the study is identified solely through abstract or when data for all participants are not available). In instances where obtaining this information is not feasible and the missing data are deemed to potentially introduce significant bias, we will assess the influence of including such studies on the overall result assessment through sensitivity analysis. Our handling of missing data, including any assumptions or imputations made, will be clearly elucidated and we will assess the impact of imputation through sensitivity analyses.

For binary outcomes (such as recurrence), the effect size will be determined using the total number of patients randomised in each group as the denominator.[22] For studies that do not report the HR and fail to provide results after 14 days of email correspondence with the

Table 2 Data extraction form

Content	Data items
Publication information	Title, authors, year of publication, country
Trial information	Study design, trial subjects, sample size, inclusion criteria, registration number, status
Participant characteristics	Age in average, gender, ICD diagnosis, pathological diagnosis, TNM stage, CPS score
Intervention	Treatment details (with dose information and duration)
Primary outcome	Overall survival, progression-free survival
Secondary outcome	Objective response rate, disease-free survival, event-free survival, pathological complete response, major pathological response, adverse event, serious adverse event, follow-up, dropout, and other available outcomes.

CPS, Combined Positive Score; ICD, International Classification of Diseases; TNM, Tumour Node Metastasis.

corresponding author, we will attempt to estimate the HR, including its logarithm (lnHR), the difference between observed and expected events as per the log-rank test (O-E), the log-rank test variance, and the variance of lnHR using indirect methods. In cases where these indirect approaches are not feasible, we will derive HR estimates from Kaplan–Meier curves.

Assessment of reporting bias

If this study is able to include more than 10 studies, we will use funnel plot testing to detect potential publication bias within the included literature pool. We will analyse and interpret the asymmetry of the funnel plot according to relevant recommendations from the *Cochrane Handbook for Systematic Reviews* and correlate it with the results of the review.[22]

Statistical analysis and data synthesis

When multiple study arms are reported within a single study, we will include only the relevant arms. If a study comprises more than two eligible intervention or control arms, we will describe all relevant study arms in the qualitative data synthesis. Risk ratios (RRs) or ORs will be utilised to describe dichotomous data, accompanied by 95% CIs. We will extract and report HRs (with 95% CIs) for time-to-event data if available.

We will use RevMan v5.4 for data synthesis. Considering the methodological differences between different treatment modalities (perioperative or systemic), the comparison groups in this study are predefined as two groups, as mentioned above. We will aggregate results by the comparison groups. Nevertheless, variations in monoclonal antibodies and different administration methods across studies may still lead to significant heterogeneity. Thus, initial qualitative assessments will be conducted separately for each comparison group to evaluate the suitability of these studies' results for meta-analysis aggregation. Meta-analysis will be considered only when clinical and methodological heterogeneity results are appropriate. In cases of high statistical heterogeneity in meta-analysis, subgroup analyses will be attempted separately to elucidate the causes of the heterogeneity.

We will employ a random-effects model as we anticipate some degree of heterogeneity among studies. We assume that not all studies estimate the same intervention effect, and this intervention effect follows a normal distribution across studies.

Sensitivity analysis

The leave-one-out sensitivity analysis will be performed to evaluate the robustness of the measure effects of primary outcomes in terms of risk of bias.

Confidence in cumulative evidence

Two review authors (YH and WY) will independently assess the certainty of each evidence, follow the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group approach,[23] which encompasses various dimensions such as study limitations, consistency of effect, imprecision, indirectness, and publication bias. The strength of the evidence will be categorised into four levels: very low (significant uncertainty about the estimate of effect); low (further research is highly likely to impact the confidence in the estimate and could lead to a change); moderate (further research may influence the confidence in the estimate and result in a change); and high (further research is highly unlikely to alter the confidence in the estimate of effect). Any decisions to downgrade or upgrade the certainty of evidence will be clearly explained in footnotes, providing readers with insights into the table and the underlying assessment process.

Patient and public involvement

None.

Ethics and dissemination

This work is a review based on existing literature and no ethical review is required. Dissemination of the results will occur via academic journal publication, conference presentations, and multiple media platforms.

Any protocol modifications made during the study will be fully documented in the final results manuscript and on the PROSPERO registration record (CRD42023477353).

DISCUSSION

Immunochemotherapy has emerged as one of the most critical treatments for gastric cancer. Several meta-analyses have provided valuable insights into the overall safety and effectiveness of immunochemotherapy in terms of survival benefits, side effects, and efficacy across different populations.[10 12–14 24 25] However, the discrepancy in studies focusing on perioperative vs late-stage first-line treatment highlights the need for a broader, more inclusive approach to analysis. Our planned updated systematic review aims to offer a more thorough and conclusive evaluation of immunochemotherapy for gastric cancer.

One of the challenges in this study will be the integration and analysis of data from neoadjuvant, adjuvant, and first-line therapies. We plan to conduct meta-analyses based on the characteristics of the included studies (eg, identical outcomes or acceptable levels of heterogeneity), while also employing a descriptive approach where necessary.

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Contributors YH, WY and YM conceptualised and designed this study, developing the eligibility criteria, search strategy, data extraction methods and data summary

plan. ZC and BZ provided methodological advice and statistical expertise. YH and WY drafted the manuscript. BZ supervised the work and revised the manuscript for important intellectual content. All authors reviewed and approved the final version of the manuscript. BZ is the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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